ORIGINAL ARTICLE

Cross-sectional study on patients' understanding and views of the informed consent procedure of a secondary stroke prevention trial

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Funding information
The authors received no specific funding for this work. SANO receives funding from the Innovationsfonds des Gemeinsamen Bundesausschusses (grant number 01NVF17032).

Abstract

Background and purpose: Improving understanding of study contents and procedures might enhance recruitment into studies and retention during follow-up. However, data in stroke patients on understanding of the informed consent (IC) procedure are sparse.

Methods: We conducted a cross-sectional study among ischemic stroke patients taking part in the IC procedure of an ongoing cluster-randomized secondary prevention trial. All aspects of the IC procedure were assessed in an interview using a standardized 20-item questionnaire. Responses were collected within 72 h after the IC procedure and analyzed quantitatively and qualitatively. Participants were also asked their main reasons for participation.

Results: A total of 146 stroke patients (65 ± 12 years old, 38% female) were enrolled. On average, patients recalled 66.4% (95% confidence interval = 65.2%–67.5%) of the content of the IC procedure. Most patients understood that participation was voluntary (99.3%) and that they had the right to withdraw consent (97.1%); 79.1% of the patients recalled the study duration and 56.1% the goal. Only 40.3% could clearly state a benefit of participation, and 28.8% knew their group allocation. Younger age, higher graduation, and allocation to the intervention group were associated with better understanding. Of all patients, 53% exclusively stated a personal and 22% an altruistic reason for participation.

Conclusions: Whereas understanding of patient rights was high, many patients were unable to recall other important aspects of study content and procedures. Increased attention to older and less educated patients may help to enhance understanding in this patient population. Actual recruitment and retention benefit of an improved IC procedure remains to be tested in a randomized trial.

KEYWORDS
comprehension, informed consent, interview, ischemic stroke, mixed methods

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INTRODUCTION

A major challenge in conducting patient-oriented studies throughout all study designs is recruiting the planned number of participants within the given timeframe and retaining the patients in the study over the trial course [1,2]. In a review from 2013 including 73 trials, only 55% of these trials met their recruitment targets [1]. Recruitment difficulties can have a significant negative impact on a trial by reducing its statistical power, elongating study duration, and increasing the total costs [3]. Reasons for low recruitment rates include structural misconceptions such as overestimation of the number of eligible participants, nonconsideration of actively recruiting competing studies, and underestimation of the time required for recruitment [4]. However, patient-centered aspects such as fear of negative consequences of participation and patients' lack of understanding of the study content and underlying procedures can also contribute to low recruitment [5–7]. Furthermore, valid consent requires sufficient understanding of study-related information. Insufficient understanding of informed consent (IC) therefore has practical, ethical, and legal implications for study conduct.

Lack of understanding might be especially relevant among stroke patients due to age-related comorbidities (e.g., poor eyesight and hearing) and stroke-related neurological deficits (e.g., neglect) or stroke sequelae (e.g., poststroke depression, cognitive impairment).

However, data on the understanding of the IC procedure are sparse for stroke patients. Previous studies have assessed which information of an IC procedure patients correctly understood and also could correctly reproduce [8–10]. Nonetheless, most studies were conducted with cancer patients, completely excluded stroke patients [9,11] or were conducted only in the hyperacute stroke setting [12,13]. However, to develop strategies to improve understanding of IC, study aspects that are generally difficult to understand for patients and relevant determinants that are associated with poor understanding need to be identified.

Therefore, the aim of the Cross-Sectional Study Investigating Contents Recalled From the IC Procedure Among Ischemic Stroke Patients (INA) was to investigate the understandability of an IC procedure of the interventional study Structured Ambulatory Poststroke Care Program (SANO). Furthermore, we aimed to identify factors associated with poor understanding in this patient group and potential measures that could improve understanding.

METHODS

Participants

Hospitalized first-ever ischemic stroke patients who took part in the IC procedure of the SANO trial were eligible for our trial, and the same inclusion and exclusion criteria were applied [14]. SANO is a cluster-randomized trial that assesses the effectiveness of a complex organizational and behavioral intervention in the context of stroke aftercare. Details regarding the design of the SANO trial have been published previously [14]. In brief, patients were recruited between January 2019 and December 2020 in 30 German stroke units. Intervention group patients had four personal follow-up visits, and both groups received a personal assessment after 12 months. Patients with first-ever and imaging-proven ischemic stroke had to be 18 years or older, be proficient in German, have a modified Rankin Scale of less than 3 on enrollment, and have no relevant aphasia. Patients were also eligible for the INA interview if they decided against participation in SANO after the IC procedure.

Two control and two intervention centers from the SANO trial participated in INA (Universitätsklinikum Würzburg, Rhön-Klinikum Campus Bad Neustadt an der Saale, Klinikum Ludwigshafen am Rhein, Leopoldina Krankenhaus Schweinfurt, Germany). Eligible patients were orally informed about the SANO trial and received written patient information (seven pages for intervention, five for control patients) and a flyer (two pages) depicting trial information in a visual manner. Readability of both documents was enhanced by reducing long sentences, and using large fonts and simple language. If patients decided to take part in the SANO study, they were asked to provide written IC. Subsequently, patients who decided to participate in SANO as well as those who were eligible for SANO but decided against participation were orally informed about the INA study. If patients agreed to participate, written IC was obtained for the INA study. The IC procedure was standardized at all study centers by providing a standard operating procedure (SOP) and standardized staff training.

The interviews were conducted by trained staff personally at three and due to logistical reasons via telephone interview at one study center (Bad Neustadt). Staff was encouraged to perform interviews within 72 h after the IC procedure while patients were still hospitalized. After the interview, patients were given the option to discuss content of the SANO trial they felt they had not properly understood. In this case, standardized explanations were given to reduce the likelihood of introducing information bias into SANO.

Study questionnaire

Based on international and national guidelines [2,15,16], various relevant aspects for an informed decision in nonpharmaceutical studies were identified. Through several discussions among a multidisciplinary team consisting of epidemiologists, psychologists, and neurologists, the topics were elaborated, adapted, and finally grouped into eight overarching themes (Figure 1). Subthemes assigned to each theme ranged from two to four. At least one question from each main category was included in the questionnaire depending on its applicability for INA; for example, from the main category "study methodology," the subtheme "group allocation" was applicable, whereas "principle of randomization" was not, as SANO was not

individually randomized. In addition, study-specific aspects were added to the questionnaire, resulting in 20 open questions (Figure 2, Table S1). To keep the interview time short, predefined answer options were provided in the questionnaire for the interviewer only. If a patient's response matched a predefined answer, the interviewer selected this answer. Otherwise, the answer was documented as free text. Multiple answers per question were allowed.
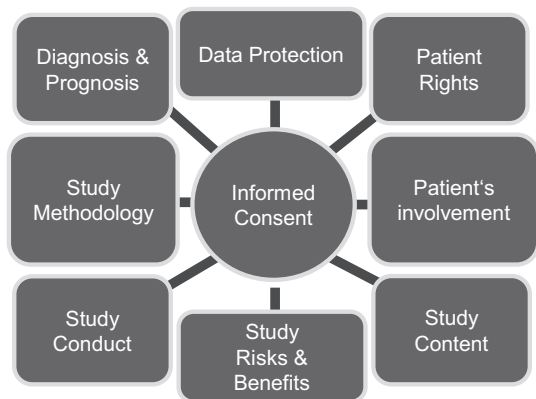

FIGURE 1 Overview of the eight categories relevant for general understanding of a research study

In addition, sociodemographic information (age, gender, highest education), stroke severity at admission (National Institutes of Health Stroke Scale [NIHSS]), IC-specific information (date and estimated duration of IC procedure, present partner during IC, interview time-point [before, during, or after baseline assessment of SANO]), and potential knowledge about stroke (first-degree relative with stroke, medical profession, reading of SANO study flyer and patient information) were collected. For patients who consented to merge their INA with their SANO data, neurological symptoms on hospital admission, history of silent strokes, and the Montreal Cognitive Assessment (MoCA) score measured during the SANO baseline assessment were collected.

Patients were asked for their reasons for (participants) or against (decliners) participation in SANO. The questionnaire was pretested in four ischemic stroke patients focusing on comprehensibility and time needed for completion.

Ethical approval

The INA study was approved by the Ethics Committee of University of Würzburg on 10 April 2019 (EC number 248/18).
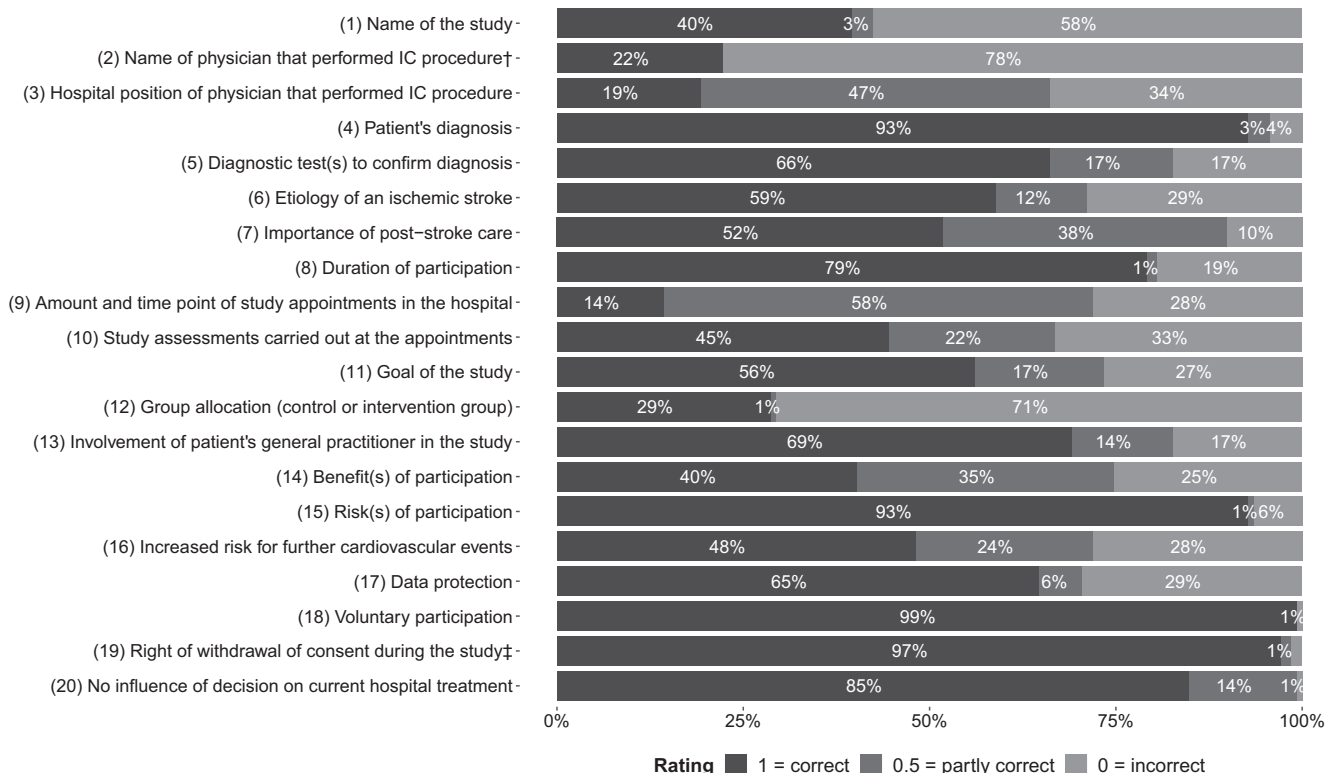

FIGURE 2 2 Overall understanding of the SANO (Structured Ambulatory Poststroke Care Program) study measured by 20 questions. Due to rounding, maximum can exceed 100%. IC, informed consent. †For privacy reason, this question was directly rated by the interviewer as correct or incorrect. ‡Incorrect answers, 1%

Sample size

Within SANO, total sample size was 2,790 patients (i.e., on average 93 patients per center). Based on the planned recruitment period of 8 months, it was estimated that 60–70 patients would be eligible per participating center. Assuming that 90% of eligible patients were approached for participation, a participation rate of 80%, and that 10% of willing participants could not be interviewed for other logistical reasons, the sample size for INA was estimated to be 150–180 participants. Based on the expected sample size of 150 patients, the simulated width of the 95% confidence interval (CI) was 5%–8% assuming standard deviations of 15.5%–25% (PASS 15.0.5) [17].

Data analysis

Responses to the 20 questionnaire items were rated by two researchers (F.A.E., J.M.R.) as correct (1 point), partly correct (0.5 points), or incorrect (0 points) based on a standardized scoring sheet [18]. A maximum of 20 points (corresponding to 100% of correct answers) could be reached. For testing interrater agreement, a random sample of 15 patients was drawn and rated by both raters. As agreement was satisfactory (Cohen κ = 0.85, 95% CI = 0.79–0.90), the rest of the dataset was randomly divided to both researchers. Uncertainties were dissolved by discussion.

Analysis of the outcome "percentage of correctly recalled information" was conducted using a weighted analysis for the following reasons: (i) adjustment for the number of questions included per main category was introduced; that is, questions from an overrepresented category received a smaller weight; (ii) bias resulting from the easier-to-answer yes/no questions was compensated for; and (iii) through weighting, we took into consideration that some aspects such as voluntarism are objectively more relevant than other aspects. Thus, each of the 20 questions received a weight through discussion between 0.25 and 1 in increments of 0.25 based on its relevance, question type, and the total number of questions included per main category (Table S1). Uncertainties were resolved together with a third researcher (P.U.H.). All of the following analysis applies to the weighted dataset if not stated otherwise.

All quantitative data were analyzed descriptively using summary statistics according to the parameters' distribution. To identify a simple combination of independent variables to predict the outcome "percentage of correctly recalled information," two prediction models were developed. The first model included only patient characteristics, stroke characteristics, and prior stroke knowledge variables. The second model additionally included IC and interview characteristics to assess the impact of the study-specific setting. Complete case analysis was performed, as the maximum number of missing values was one per patient and less than 1.5% for the whole dataset. Parameters were removed from the model using backward elimination based on the Akaike information criterion. A two-sided p-value of 0.05 was considered statistically significant. All analyses were performed using R version 3.5.0 (R core team, Vienna, Austria, 2018).

Structured content analysis was performed on the free-text answers that did not correspond to a pregiven answer option using an inductive approach and on the free-text reasons for participation using a deductive approach by two researchers (F.A.E., J.M.R.; for details, see Method S1) [19].

RESULTS

Participants

Recruitment took place between May 2019 and July 2020, and a total of 146 interviews were conducted (Figure S1). Anticipated recruitment was terminated slightly below the planned target, as two participating hospitals reached the target sample size of SANO and the COVID-19 pandemic resulted in a reduced capacity of hospital staff for conducting interviews. The expected width of the CI of the main outcome was simulated for N = 150 and N = 146 and revealed an estimated increase of 0.012%, considered sufficiently precise to justify dataset closure.

Of the 146 patients interviewed, 139 (95.2%) agreed and seven (4.8%) declined to participate in SANO. Mean age of INA participants who also participated in SANO was 65 ± 12 years, 38% were female, and median NIHSS at hospital admission was 2 (interquartile range [IQR] = 1–3; Table 1; for neurological characteristics on hospital admission, see Table S2). No statistically significant differences were observed between the two groups, although nonparticipants were older, with a mean age of 71 ± 11 years, and none of them had read the patient information in detail. Due to the low sample size of nonparticipants and as they were all sampled from one control center, it was decided to analyze these patients separately. The following results always refer to the 139 SANO participants unless stated otherwise.

Regarding study groups, significant differences were found for the NIHSS at admission (intervention centers 2 [IQR = 1–4] vs. control centers 1 [IQR = 0.25–1], p = 0.021), time between IC procedure and interview (≤12 h: intervention centers 58.9% vs. control centers 38.8%, p < 0.001), cognitive performance (MoCA: intervention centers 25 [IQR = 22–27] vs. control centers 27 [IQR = 24–29], p = 0.02, 17% missing), reading the study flyer (intervention centers 38.8% vs. controls centers 2.2%, p < 0.001), and close reading of the patient information (intervention centers 51.1% vs. control centers 22.4%, p < 0.01). In addition, no center-specific effects were observed, and the different methods of data collection (personal vs. telephone) did not distort data quality.

Understanding of study content

Overall understanding of study content was 67.9% (95% CI = 66.7%–69.1%). Results regarding each questionnaire item are depicted in Figure 2. Regarding study groups, 66.7% of intervention patients correctly stated the study goal compared to 36.7% of the control

TABLE 1 Baseline characteristics of INA participants who took part in the SANO trial

Characteristic	Participants, N = 139
Sociodemographics	
Age, years, mean (SD)	65 (12.1)
Sex, female, n (%)	53 (38.1)
Highest education, n (%)	
Primary/secondary education	84 (60.4)
Middle school	30 (21.6)
A-levels	25 (18.0)
NIHSS score, median (IQR)	2 (1–3)
Prior stroke knowledge, n (%)	
Stroke in first-degree relatives	57 (41.0)
Medical profession[a]	15 (10.8)
Flyer of SANO read[b]	21 (15.1)
Patient information read[b]	
(Rather) thoroughly	57 (41.0)
(Rather) not thoroughly	52 (37.4)
Not at all	30 (21.6)
Study-specific characteristics	
Group allocation, n (%)	
Control	49 (35.3)
Intervention	90 (64.7)
Interview time-point, n (%)[c]	
Before baseline assessment	32 (23)
During baseline assessment	13 (9)
After baseline assessment	94 (68)
Duration of SANO IC procedure, n (%)	
5–14 min	40 (29.0)
15–19 min	44 (31.9)
20–29 min	8 (5.8)
30–39 min	18 (13.0)
40–70 min	28 (20.3)
Time between IC procedure and interview, n (%)	
≤12 h	72 (51.8)
>12 h	67 (48.2)
Presence of partner during IC procedure, n (%)	19 (13.7)
Excitement during interview, median (IQR)[d]	2 (1–4)
Further characteristics	
Montreal Cognitive Assessment, median (IQR)[e]	26 (23–28)

Note: There was one missing value for the NIHSS and excitement (0.7%).

Abbreviations: IC, informed consent; INA, Cross-Sectional Study Investigating Contents Recalled From the IC Procedure Among Ischemic Stroke Patients; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SANO, Structured Ambulatory Poststroke Care Program.

[a]Defined as physician, nurse, physiotherapist, speech therapist, working in medical research, or similar profession.

[b]Patient-reported.

[c]First examination took place during hospitalization. Due to internal logistical reasons, some interviews were conducted before the examination, after several assessments had already been performed, or after all assessments had been completed.

[d]On a scale from 1 to 10.

[e]Missing values n = 23.

TABLE 2 Prediction model for the outcome overall percentage of understanding

Predictor	β	95% CI
Model 1		
Age, per 5 years	−0.018	−0.020 to −0.017
Graduation		
Primary/secondary	1	–
Middle school	0.062	0.006 to 0.120
A-levels	0.089	0.031 to 0.147
Model 2		
Age, per 5 years	−0.020	−0.022 to −0.018
Graduation		
Primary/secondary	1	–
Middle school	0.060	0.007 to 0.114
A-levels	0.102	0.047 to 0.157
Group		
Control	1	–
Intervention	0.089	0.047 to 0.132

Note: Model 1 includes sociodemographics and parameters depicting prior stroke knowledge. Model 2 includes sociodemographics, parameters depicting prior stroke knowledge, and study-specific parameters (see Table 1).

Abbreviation: CI, confidence interval.

patients. Of the control patients, 13.8% stated there was "no direct benefit," compared to 0% of the intervention patients. Only 14.3% of control patients reported receiving an additional assessment, although this applied to all patients.

Factors associated with understanding of study contents

In univariate analysis, lower age, higher education, intervention group allocation, reading of the patient information, an imaging-detected past nonsymptomatic infarction, and a higher MoCA score were significantly associated with the outcome "percentage of correctly recalled information" (data not shown). The β-coefficients and corresponding 95% CIs for the multivariate models are depicted in Table 2. The second model, including study specifics, explained 28.3% of the variation in our data (adjusted R^2). Sensitivity analyses including the patients' neurological characteristics on admission, the MoCA score, and the data of the seven nonparticipants in the SANO trial did not change these results substantially.

We explored whether differences of understanding were present between subgroups of older patients and patients with a lower educational degree. Patients with primary school diploma and age 71–80 years had 14.9% higher understanding, and patients aged 81–96 years had 24% higher understanding when they had read the patient information in detail. Furthermore, patients aged 71–80 years who had read the study flyer had a 14.7% higher understanding

compared to those who did not. However, this difference was not present when only the lowest educational group in this age group was considered.

Reasons for participation

Overall, 123 patients (88.5%) stated at least one personal and 59 (42.4%) at least one altruistic reason (Figure S2 and Table S3). The most common personal reasons were "personal benefit" (46.8% of all participants) and "learn more/get better understanding of my disease" (12.2%); the most common altruistic reasons were "help future patients" (28.8%) and "contribute to science" (26.6%). Multiple answers were possible.

Content analysis of free-text answers

Frameworks were developed for 11 questions, which provided a sufficient number of free-text answers. Per question, 16–110 codes were assigned (Tables S3–S14).

Content analysis revealed that it was difficult for some patients to distinguish between stroke diagnostics and study-specific examinations.

Furthermore, 11 patients incorrectly stated that "research on etiology" was the study goal.

On the other hand, it appeared that many patients had a basic understanding that their data are protected.

Analysis of nonparticipants

Of the seven nonparticipants, three fulfilled an exclusion criterion of the main trial. Among the remaining four participants, average understanding was 41.3% (95% CI = 20.2%–62.2%). Reasons against participation were "hospital too far away" (75%), "too time-consuming (50%), and "too cumbersome" (25%).

DISCUSSION

Our study revealed an overall good understanding of key aspects of the IC procedure in ischemic stroke patients. However, limited understanding was revealed, for example, for the concept of secondary prevention and the time-point and content of study assessments. Multivariate modeling showed a significant association of age, education, and group allocation with understanding of the SANO IC procedure. Addition of neurological characteristics on admission or the MoCA score did not further improve our model. Most of the patients reported taking part in the study for their perceived personal benefit.

Comparable studies have been conducted in different disease settings. In a study among healthy volunteers questioned about understanding of seven relevant study aspects 1 day after the IC procedure, average understanding was 64% [18]. In a Phase 2 randomized trial among tuberculosis patients, overall understanding of study-specific questions was 82% [20]. Lastly, a mean knowledge score of 76 of 100 was reported in a study assessing trial understanding among Phase 2 and 3 cancer trial participants [21]. Thus, the results of our study seem to fit well into the current literature. However, comparison of overall understanding between different studies is limited due to heterogeneous study populations, varying question types, heterogeneity of questions asked, and differing analysis strategies, among other reasons.

Therefore, it is at least as important to assess responses of individual questions. We observed that many stroke patients did not correctly understand whether a personal benefit might result from study participation. This is in contrast to a systematic review from 2015 that mostly included cancer trials and reported a pooled understanding of benefit in 74% of all patients [10]. Perceived personal benefit is a known and important aspect in the patient's decision-making process and was also stated as the dominant reason for participation in our study. In studies without payment, researchers should therefore identify other benefits that might be provided by study participation such as additional medical attention [22,23]. In our study, only about half of our patients were aware that they had an increased risk for further cardiovascular events. It is, however, extremely important that patients know their diagnosis and its consequences; only then are they able to put information about a research trial in the correct context and make an informed decision. Due to stroke-related neurological impairment, disease-specific information may be difficult to communicate compared to other patient populations. Physicians and scientists should be aware of this and should discuss the diagnosis and its consequences with the patient more than once.

On the other hand, our study revealed several encouraging results including high understanding of the right of withdrawal and voluntary participation. Understanding of these questions was about 20% higher compared to a systematic review including various disease conditions [10]. Moreover, it has previously been reported that patients sometimes felt obliged to take part in studies or anxious about their data not being well-protected [24]. Our results indicate a potential improvement of this view toward a more trusting attitude. However, our results might be slightly overestimated due to the dichotomous question type (yes/no question).

Within our study, we also assessed potential differences in the responses between participants and nonparticipants in the main trial. Another study among 183 cancer patients reported a high association between measured understanding of the study and consent to participate [25]. Unfortunately, very few patients received the full IC procedure and then decided against participation in SANO. Among these patients, we observed an extensively lower average understanding. This finding could imply that lower understanding is associated with lower willingness to participate in the study [25] However, given the cross-sectional design of our study, the increased age of these patients, and the low sample size, one should interpret these results with caution.

More research on this topic with sufficiently large sample sizes is advised.

The combination of old age and low educational level increased the likelihood of poor recall of the IC procedure in our study population. This is again in line with findings of previous reviews [9,26]. The observed group effect in INA might partly be explained by interviews being on average conducted after a shorter time period in the intervention compared to the control group. In addition, physicians in the intervention group might already pay increased attention to patient understanding, which could be considered a form of performance bias [27]. In addition, this effect might partly be explained by an underlying interviewer effect. However, interviewer effects could not be assessed in our study for data protection reasons. Overall, these results imply that when planning a study especially among stroke patients, recruiting physicians should be made aware that older and less educated patients are more likely to experience difficulties in understanding study-related information.

Current literature suggests a potential positive impact of extended discussions with potential study participants and in-depth testing of comprehension [10,28]. Although these measures also seem conceptually logical, feasibility in clinical practice is to some extend limited. We suggest the following approach instead. (i) Preselection of participants at high risk to have difficulties understanding study-related information should be performed. Preselection must be easy, fast, and feasible to perform by all study personnel. Age and educational level could be used according to INA. (ii) Preselected patients might benefit from reading the written patient information. Therefore, an attempt should be made to schedule the recruitment process to allow sufficient time between handing out the written study information and the oral discussion, including obtaining IC. (iii) Previous studies assessing the effectiveness of enhanced IC forms/written patient information have already shown promising results [10,28], but stroke patients remain a specific patient collective that might benefit from different interventions compared to other diseased populations that, for example, have a higher intrinsic motivation for research participation. It is therefore advisable to investigate an intervention tailored to this patient population in a randomized study, in particular with regard to the effect on willingness to participate.

Several limitations apply to our study. First, open answers were not sampled verbatim to reduce the time needed for the interview. Second, it was not assessed whether all questionnaire items were mentioned during an IC procedure by observation of an independent bystander. However, all study centers had received oral instructions and a written SOP for the conduct and content of the IC procedure. Third, information on patients' previous research experience was not sampled, which may influence willingness to participate in a study [29]. However, we assessed medical profession and stroke among first-degree relatives, which might actually have been better parameters to adjust for differences in prior stroke knowledge. Fourth, as this is a cross-sectional study,

residual confounding cannot be fully excluded. Fifth, the NIHSS on admission differed between the two groups. However, we regard this difference as not clinically relevant. Of note, only mildly affected patients were enrolled, and there was no trend that stroke severity on admission was associated with overall understanding. Lastly, results might be only partly generalizable to patients with intracranial bleeding or severe stroke, or interventional studies in the hyperacute phase of stroke.

To our knowledge, this is one of the few studies assessing IC comprehension among stroke patients and the first to assess comprehension after hyperacute treatment has already been performed. Our study therefore contributes valuable insights into the IC procedure and its understanding among stroke patients.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

A.G. reports a grant from the Federal Joint Committee (G-BA) within the Innovationfond. H.S. reports study grants from Bayer, Portola, Alfried Krupp Krankenhaus, and Bristol-Myers Squibb (ODEA-TIA Study), University of Göttingen (within Find-AF RANDOMIZED, supported by an unrestricted research grant to University of Göttingen from Boehringer Ingelheim), and University Hospital Heidelberg (within RASUNOA-Prime, supported by an unrestricted research grant to University Hospital Heidelberg from Bayer, BMS, Boehringer Ingelheim, and Daiichi Sankyo), and lecture fees from Bayer, BMS, and Daiichi Sankyo. K.G.H. reports study grants from Bayer and Sanofi-Aventis and lecture fees/advisory board fees from AstraZeneca, Bayer, BMS, Bristol-Myers Squibb, Boehringer Ingelheim, Biotronik, Daiichi Sankyo, W. L. Gore & Associates, Edwards Lifesciences, Sanofi-Aventis, Pfizer, and Medtronic. P.U.H. reports grants from the German Ministry of Research and Education, German Research Foundation, European Union, Federal Joint Committee (G-BA) within the Innovationfond, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert Koch Institute, German Heart Foundation, University of Göttingen (within Find-AF RANDOMIZED, supported by an unrestricted research grant to University of Göttingen from Boehringer Ingelheim), University Hospital Heidelberg (within RASUNOA-Prime, supported by an unrestricted research grant to University Hospital Heidelberg from Bayer, BMS, Boehringer Ingelheim, and Daiichi Sankyo), and Charité–Universitätsmedizin Berlin (within Mondafis, supported by an unrestricted research grant to the Charité from Bayer). None of the other authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Felizitas A. Eichner: Conceptualization (lead), data curation (lead), formal analysis (lead), methodology (equal), project administration (lead), validation (equal), visualization (lead), writing–original draft (lead). **Joschua M. Reis:** Formal analysis (equal), investigation (equal), project administration (equal), writing–review & editing (lead). **Joaquim Dores:** Investigation (lead), project administration (equal), resources (equal), supervision (equal), writing–review & editing (equal). **Vladimir Pavlovic:** Investigation (equal), project administration (equal), resources (equal), writing–review & editing (equal). **Luisa Kreß:** Investigation (equal), project administration (equal), supervision (equal), writing–review & editing (equal). **Naeimeh Daneshkhah:** Investigation (equal), project administration (supporting), resources (equal), writing–review & editing (supporting). **Renate Weinhardt:** Investigation (supporting), project administration (equal), supervision (equal), writing–review & editing (supporting). **Armin Grau:** Conceptualization (equal), methodology (equal), resources (equal), supervision (equal), writing–review & editing (equal). **Johannes Mühler:** Methodology (equal), resources (equal), supervision (equal), writing–review & editing (supporting). **Hassan Soda:** Methodology (equal), resources (equal), supervision (equal), writing–review & editing (supporting). **Christopher J. Schwarzbach:** Methodology (equal), project administration (equal), resources (equal), writing–review & editing (equal). **Michael Schuler:** Conceptualization (equal), methodology (equal), validation (equal), writing–review & editing (supporting). **Karl Georg Häusler:** Conceptualization (lead), methodology (lead), resources (equal), supervision (equal), validation (equal), writing–review & editing (equal). **Peter U. Heuschmann:** Conceptualization (lead), formal analysis (supporting), methodology (lead), supervision (equal), validation (equal), writing–review & editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author in its original language upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.