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ORIGINAL RESEARCH

Reasons for delayed admission after stroke: results of a qualitative and quantitative survey

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¹Department of Neurology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; ²Institute of Social Medicine & Epidemiology, Nursing Research Unit, University of Lübeck, Lübeck, Germany; ³Unit of Health Sciences and Education, MIN Faculty, University of Hamburg, Hamburg, Germany; ⁴Institute of Neuroimmunology and Multiple Sclerosis, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany **Background:** Acute stroke treatment shows time-dependent benefit to prevent disability. Public information campaigns and streamlining of emergency management have been performed, but still, only one-third of acute stroke patients are admitted >4.5 hrs after symptom onset.

Patients and methods: We interviewed 15 patients, presenting >4.5 hrs after symptom onset, regarding symptom recognition, emotions and their first action after symptom onset. Recorded interviews were analyzed by standardized descriptive analysis. Based on the results, a quantitative survey was developed. One hundred consecutive stroke unit patients surveyed to compare patients presenting within 4.5 hrs and more than 4.5 hrs of symptom onset.

Results: Patients predominantly noticed symptoms by themselves. The most commonly expressed feelings were uncertainty and shame. The most frequent action was waiting. Patients described moderate knowledge about stroke in general, but felt less informed regarding their stroke risk. Magazines (51%) were the most frequently indicated source of information, while general practitioners only accounted for 26%. Significantly better knowledge was shown in the answers on closed questions compared to open questions, although the same items were named.

Conclusion: Shame, uncertainty and insufficient individual risk knowledge about stroke were the most important factors delaying admission after stroke. Individual risk counseling could be investigated to close the gap between general stroke knowledge and recognition of own stroke risk.

Keywords: acute stroke, onset, admission, knowledge, risk factors, acute stroke treatment

Introduction

Stroke causes substantial disability and reduction of quality of life.¹ Acute reperfusion treatment with intravenous thrombolysis or endovascular stroke treatment improves stroke outcomes.^{2,3} However, reperfusion treatment is time dependent. Intravenous thrombolysis is licensed for treatment initiation within 4.5 hrs of symptom onset, and even within this time frame, the earlier treatment is started, the better the treatment effect.⁴

Only about one-third of acute stroke patients arrive at the hospital within 4.5 hrs after symptom onset. Interestingly this has not changed in the last 20 years.⁵⁻⁷

Factors negatively influencing the time to admission are living alone and milder stroke symptoms.⁶ Other factors as age, gender, risk factors (eg, diabetes, hypertension, ischemic heart disease, previous stroke) and type of stroke, did not show independent influence on admission time in previous studies.^{6,8} Also, previous

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© 2019 Alegiani et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms. work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission for Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial uses of the work are permitted without any further permission for Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial uses of the work are peragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php). stroke was not associated with a faster arrival at the hospital.⁹ Whereas patient transport with emergency medical service is associated with faster hospital arrival^{10–12} compared to self-transport, explained by an active role on the part of persons near the patient at the time of symptom onset.¹¹

Many studies have surveyed patients' and public knowledge of stroke symptoms, warning signs and their recognition. Repeatedly low levels of knowledge were shown.^{13,14} As a consequence public information campaigns about stroke and the necessity of early clinical presentation were established in the last years.¹⁵

Considering the event as serious, recognizing the stroke and not consulting a primary care physician are shown to be predictors of faster admission.^{8,11} Mackintosh et al¹⁶ concluded that factors influencing decisions to seek help are usually complex and that there is a need to improve recognition and increase knowledge of symptoms. Fear, denial and reticence to impose on others hinder the process of seeking help.¹⁶

Ritter et al¹⁷ found that symptom knowledge and action knowledge are not significantly associated with shorter pre-hospital times and concluded that good theoretical knowledge about stroke does not necessarily imply appropriate management in the emergency situation. Especially patients at risk have been described with limited awareness of their increased risk.¹⁸

The aim of this study was to better understand the reasons for late admissions and to define targets for improvement. We hypothesized that emotions like fear, denial and reticence still hinder the process of seeking help and interviewed patients with acute stroke who presented after >4.5 hrs since symptom onset. We also asked for patients' subjective and objective knowledge about stroke risk factors and symptoms. We hypothesized that the gap between theoretical knowledge and individual application might be a key factor leading to inappropriate stroke management.

Patients and methods

As a first step, we performed qualitative interviews questioning patients (01.-02.2014). Based on interview results, a survey was designed. All patients were recruited from one large university clinic in Hamburg, Germany (10.2014–03.2015). The study was approved by the Ethics Hamburg chamber of physicians (PV4980) and patients gave written informed consent. All data supporting the results are reported in Tables 1–5.

Qualitative interviews

Consecutive patients presenting later than 4.5 hrs after symptom onset to the hospital were surveyed within 24 hrs after admission. Inclusion criteria were the diagnosis of ischemic stroke, presenting later than 4.5 hrs after symptom onset, without history of previous stroke or speech disturbance, patients had to be conscious and oriented. We excluded patients with TIA and patients transferred from other hospitals. We recruited the patients consecutively without any dropouts. All patients gave written informed consent. The interview was half-standardized (predetermined questions and open answers) and patients were asked, in which situation symptoms appeared or were recognized and what emotions were noticed. The second question was, if they had reflected about possibly having a stroke. Further, they were asked for their initial emotional and cognitive reaction and why the emergency service was not called immediately. Interviews were audio recorded and analyzed by standardized descriptive interview analysis.¹⁹

Survey

Based on the interview results and prior experience,²⁰ we developed a multiple-choice questionnaire and surveyed 113 consecutive patients to prove and support the results of the qualitative analysis. We only included patients referred to our emergency room with ischemic stroke, who had full orientation and no speech disturbance. Six patients were excluded, because the diagnosis of stroke could not be verified by cerebral imaging. Two patients declined their participation due to speech barrier and five patients did not want to answer the questions in their situation of suffering acute stroke. Consecutive patients presenting to the hospital were surveyed within 24 hrs after admission during their stay at the hospital. We excluded patients with TIA and patients transferred from other hospitals. We separated patients into two groups by regarding the time frame from symptom onset to admission: \leq 4.5 hrs and >4.5 hrs.

Demographic parameters, National Institute of Health Stroke Scale (NIHSS)²¹ score on admission, symptom presentation on admission and time from symptom onset to admission were recorded. Patients were asked whether and how often they regularly visit a general practitioner and about the source of information they used to get information about stroke. Self-ratings of patients' knowledge about acute stroke treatment and about perceived stroke risk were performed by VAS, ranging from 0 to

10. Finally, we checked knowledge about risk factors and stroke symptoms by open and closed questions, according to a previous study.²⁰ Patients were asked to name stroke risk factors and symptoms using open questions and afterward to choose risk factors of stroke from a given list without the possibility to go back to the open questions.

Statistical analysis

Data were analyzed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). We predominantly performed descriptive analyses. To determine the dependency of the items on the time from onset to admission, odds ratios were calculated by logistic regression with Yates' correction for continuity for all items comparing the two groups of patients, presenting within 4.5 hrs or later than 4.5 hrs after symptom onset. All items were analyzed, items were not selected beforehand. Items in ordinal scales were dichotomized before calculating odds (details of categorization are given in Table 5). The cutoff *P*-value is <0.05.

Results

Interviews

We interviewed 15 patients with a first acute ischemic stroke. Seven patients were female. Median time from onset to admission was 44 hrs (range 5–166). Mean age was 56 years (range 37–84). Median NIHSS on admission was two (range 0–5). Eight patients stated to know some-one, who had had a stroke before, but had not been present when the stroke had occurred.

Twelve patients noticed the symptoms by themselves. The first association of the cause of symptoms was in three patients general weakness, in two patients stroke, in one patient stress and the other patients gave inhomogeneous answers as, for example, a peripheral nerve injury or hypertensive blood pressure.

The qualitative analysis (Table 1) showed that most patients did not expect to have a stroke. Frequently patients felt uncertainty and/or shame when symptoms appeared and mostly they waited for symptoms to disappear.

Survey

One hundred patients completed the questionnaire. The median time from onset to admission was 18 hrs. The median NIHSS on admission was two (range 0–19). Patients selected newspapers and magazine (51%), as well as television (38%) as more frequent sources of information about stroke, than the general practitioner

(26%) or the internet (19%). The self-rated knowledge about stroke was 4.9 in median (VAS 0-10). The self-rated risk of stroke was 3.3 in median (VAS 0-10) (see Table 2).

Most patients noticed the symptoms by themselves and 47% rated them as serious; 40% had realized the situation as urgent, but most of them experienced a feeling of uncertainty about the right classification of symptoms (70%). Although one-third of all patients were thinking of a stroke, the most common first reaction was to wait (70%) and 37% of patients did not expected having a stroke. Patients presenting within 4.5 hrs showed mostly the same perceptions, emotions and attributions of symptoms, but interpreted the symptoms more often as serious and urgent and the most common first reaction was to call a family member (see Table 3).

Results of answers on risk factors and stroke symptoms were different between open and closed questions. The most common additional answers regarding potential risk factors for stroke in the open questions were unhealthy lifestyle (90%), alcohol consumption (36%) and distress (33%). There were also only few additional answers when asking for possible stroke symptoms in an open format, the most common answer was cognitive deficits (17%). Significant better knowledge was shown in the answers on closed questions compared to open questions, although the same items were named. Especially risk factors like arterial hypertension, diabetes and atrial fibrillation were rarely named in open questions. Regarding symptoms, walking dysfunction and visual dysfunction were rarely named in open questions (see Table 4).

Logistic regression analysis identified symptoms like visual and walking dysfunction as predictors of delayed presentation (>4.5 hrs), while arm or leg paresis, facial paresis or speech disturbance were significantly associated with admission \leq 4.5 hrs. There was no significant association of risk factors, previous medication, living status, source of information, emotions, having a GP or knowledge to the time until presentation.

If patients called a family member as first reaction, and if symptoms were noticed by others, significantly more patients presented within 4.5 hrs after symptom onset.

If the symptoms were recognized as urgent or serious significantly more patients presented within 4.5 hrs after symptom onset. Patients having no idea of symptom cause, presented also significantly more often within 4.5 hrs after symptom onset (Table 5).

Table 1. Results of quality	ative semi-structured interviews
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Question	Category	Example
Symptom	Uncertainty/shame	"I was not sure what happened."
Recognition		"I noticed something is wrong, but felt a shame"
		"Not being able to speak normally."
		"I was not sure what happened, and asked the ophthalmologist/general practitioner."
	Sorrow	"I worried about the symptoms and thought it may be because of my back pain."
		"It may be because of my back pain."
		"I worried, but was not able to move and to seek help."
		"I worried and always thought about what could be happening."
	Fear	"I was afraid, but have to take care of my child and could not go to the hospital."
	Denial	"You think you're superman, you understand, and you hesitate."
		"Things like that have to get to me first"
Stroke perception?		"Yes, I thought that I may be having a stroke."
		"I noticed a weakness and thought it will disappear"
		"I had no idea, although I absolutely know stroke symptoms."
First reaction	Waiting,	
	for symptoms disappear	"I noticed the symptoms and thought they [would] disappear."
	avoiding the hospital	"My wife died in hospital, I did not want to go there."
	unable to move	"Because of the weakness and dizziness, I was unable to move to call for help."
	Contact GP	"My general practitioner thought it may be a stroke."

Discussion

We aimed to understand acute stroke patients' reasons for late admissions by a qualitative and subsequent quantitative survey. The survey showed a median time from symptom onset to admission of 39 hrs. Key finding of the qualitative interviews was that recognition of stroke symptoms is associated with uncertainty and shame. Most patients did not think they had a stroke and waiting was the most frequent first action. Patients declared to feel informed about stroke, but the association of the acute symptoms with stroke did not support a fast reaction.

The quantitative survey showed that symptoms were mostly recognized by patients themselves which is in line with other data, because living alone is an important factor delaying onset to admission time.⁶

The surveyed patients reported that their first reaction was waiting, despite one-third of patients were thinking about having a stroke. We found no significant influences on an earlier time to admission, if patients were thinking of a stroke or if they had suffered a stroke before. This has also been shown in earlier studies^{6,8,9} and might be explained by hindering emotions, for example, shame.²³ Indeed, our qualitative interviews offered evidence that emotions, like shame or fear hinder the early presentation. Denial or shame and a feeling of guilty are known to influence clinical encounters.²³ Patients often regard their illness as personal shortcoming,²³ which might have resulted in our patients' cohort late admissions instead of being prepared in case of stroke, knowing what to do and facing the consequences.

In contrast, patients declared to know that in case of a stroke a fast reaction is important and they felt informed about stroke, which emphasizes previous findings.¹⁶ We found a discrepancy between passive knowledge, which was significantly better, compared to active knowledge. Thus, the recognition of risk factors or symptoms from a list was relevantly more often correct than open questions for the same items. This observation might be due to information campaigns, which mostly address stroke symptoms and the need for a fast admission. However, patients who mentioned they did not expect, they might have a stroke, did not feel informed about their own stroke risk, although they felt informed about stroke and stroke risk in general. These results support the hypothesis that a good theoretical knowledge about stroke does not lead to faster reaction in the emergency situation.¹⁷

Regression analysis showed no significant positive influence of existing risk factors or previous medication on the time from symptom onset to admission. Another relevant finding is that patients indicated that they did

Table 2. Demographic data

Category	ltem	All patients	Admission ≤4.5 hrs	Admission >4.5 hrs
Patients (n)		100	30	70
Onset-to-admission time	(hrs)	18 (0,3–378)	1,5 (0,3-4,5)	24 (4,75–378)
Basic data Gender Age (years) NIHSS	Female	36 70,5 (29–89) 2 (0–19)	9 70,5 (29–89) 3 (0–19)	27 70,5 (46–87) 2 (0–9)
Symptoms				
	Walking dysfunction Aphasia or dysphasia Visual dysfunction Dizziness/nausea/headache Paresis Sensory deficit Facial paresis	50 (50%) 36 (36%) 35 (35%) 32 (32%) 30 (30%) 22 (22%) 19 (19%)	10 (20%) 16 (44%) 4 (11%) 9 (28%) 16 (53%) 3 (14%) 13 (68%)	40 (80%) 20 (56%) 31 (89%) 23 (72%) 14 (47%) 19 (86%) 6 (32%)
Risk factors				
Previous medication	Arterial hypertension Aicotin abuse Overweight Hypercholesterinemia Atrial fibrillation Diabetes Previous stroke Coronary artery disease Antihypertensive Platelet inhibitors Cholesterol lowering Antidiabetic Oral anticoagulation	61 (61%) 39 (39%) 35 (35%) 26 (26%) 6 (6%) 15 (15%) 12 (12%) 6 (6%) 52 (52%) 38 (38%) 16 (16%) 12 (12%) 3 (3%) 37 (37%) 61 (61%)	17 (28%) 10 (26%) 9 (26%) 8 (31%) 3 (50%) 3 (20%) 1 (8%) 4 (67%) 16 (31%) 15 (39%) 4 (25%) 2 (17%) 2 (67%) 11 (30%) 19 (31%)	44 (72%) 29 (74%) 26 (74%) 18 (69%) 3 (50%) 12 (80%) 11 (92%) 2 (33%) 36 (69%) 23 (61%) 12 (75%) 10 (83%) 1 (33%) 26 (70%) 42 (69%)
Health care	Not alone Nursing home	61 (61%) 2 (2%)	19 (31%) 0 (0%)	42 (69%) 2 (100%)
General practitioner, yes Visits (per year)		96 (96%) 3 (0–20)	30 (31%) 3 (0–12)	66 (69%) 3 (0–20)
Source of information				
About stroke risk	Newspaper/magazine Television General practitioner Internet K powledge	51 (51%) 38 (38%) 26 (26%) 19 (19%) 4 9 (0-10)	16 (31%) 13 (34%) 9 (35%) 7 (37%) 4 0 (0-10)	35 (69%) 25 (66%) 17 (65%) 12 (63%) 5.0 (0-10)
	Stroke risk	3.3 (0–10)	2.8 (0–10)	3.8 (0-10)

Notes: ^aVAS range: 0 (low) to 10 (high). Categorial variables shown as median (range); continuous variables shown as n or n (%). Abbreviations: NIHSS, National Institute of Health Stroke Scale; VAS, visual analog scale.

Questions	ltems	All patients	Admission ≤4.5 hrs	Admission >4.5 hrs
Who noticed the symptoms?	Patient	87 (87%)	21 (24%)	66 (76%)
	Other person	13 (13%)	9 (69%)	4 (41%)
Interpretation of symptoms	Serious	47 (47%)	19 (40%)	28 (60%)
	Not-serious	53 (53%)	11 (21%)	42 (79%)
Interpretation of situation	Urgent	38 (38%)	19 (50%)	19 (50%)
	Not-urgent	62 (62%)	(18%)	51 (82%)
Emotions	Uncertainty	69 (69%)	23 (33%)	46 (67%)
	Fear	41 (41%)	17 (41%)	24 (59%)
	Sorrow	19 (19%)	8 (42%)	II (58%)
	Anger	10 (10%)	4 (40%)	6 (60%)
	Shame	8 (8%)	l (I3%)	7 (87%)
	Frustration	2 (2%)	l (50%)	l (50%)
Attribution of symptoms	Stroke	32 (32%)	12 (38%)	20 (62%)
	General weakness	(%)	2 (18%)	9 (82%)
	Eye problems/disease	10 (10%)	3 (30%)	7 (70%)
	Nerve irritation	8 (8%)	l (13%)	7 (87%)
	No idea	7 (7%)	6 (86%)	(4%)
	Stress	6 (6%)	0 (0%)	6 (100%)
	Blood pressure	4 (4%)	2 (50%)	2 (50%)
	Cardiac dysfunction	5 (5%)	0 (0%)	5 (100%)
First action	Waiting because of	67 (67%)	3 (5%)	64 (95%)
	not suspecting stroke	37 (55%)	2 (5%)	35 (95%)
	negative experiences	9 (13%)	0 (0%)	9 (100%)
	call general practitioner	6 (9%)	l (17%)	5 (83%)
	other	15 (22%)	0 (0%)	15 (100%)
	Call family member	12 (12%)	12 (100%)	0 (0%)
	Call general practitioner	7 (7%)	6 (86%)	(4%)
	Call emergency	3 (3%)	3 (100%)	0 (0%)
	Medication intake	2 (2%)	0 (0%)	2 (100%)

Note: Values are absolute numbers (%).

receive stroke risk information from newspapers and television more often than from their doctors, despite regular GP visits. These results are remarkable as patients with a risk profile should have been informed about a potential stroke risk and about stroke symptoms. For example, known atrial fibrillation showed no influence on early presentation, although these patients have a high risk of stroke. Further, an existing cardiovascular medication, indicating a previously recognized risk, did not show an influence on presentation time. This is congruent with findings that patients on oral anticoagulation often are unable to say why drugs were prescribed.²²

If patients had no idea of symptom cause, they presented significantly more often within 4.5 hrs after symptom onset. The association with stroke did not support a fast reaction. Indeed, missing symptom attribution shortened the time to admission. The fact that the reaction was faster if the cause was unknown, leads to the hypothesis that a missing attribution to stroke ends up in a different risk attribution. Patients' ambivalence to seek medical help has already been suggested as an important factor resulting in delayed hospital admission.²⁴

Our data show a significant association of symptom presentation within 4.5 hrs in case of symptoms like facial paresis, hemiparesis, speech disturbance, visual or walking dysfunction and if symptoms were interpreted as urgent. These symptoms were associated with a significantly earlier presentation, potentially because of their relevant hindering effect as in case of a facial paresis.

We postulate that patients need to know their own risk to combine the recognition of their symptoms with their general stroke knowledge about the importance of a fast reaction. Against the background of hindering emotions, leading to a delay of presentation, patients need to know,

Table 4. Answers on	open and	closed	questions	for	risk	factors
and stroke symptoms						

Risk factors and stroke symptoms	Open question	Closed question
Risk factors		
	n=100	n=100
Arterial hypertension	22 (30%)	96 (96%)
Nicotine abuse	47 (64%)	95 (95%)
Overweight	16 (21%)	91 (91%)
Hypercholesterinemia	12 (16%)	86 (86%)
Atrial fibrillation	1 (1%)	47 (47%)
Diabetes	6 (8%)	64 (64%)
Stroke symptoms		
	n=100	n=100
Aphasia or dysphasia	50 (57%)	97 (97%)
Facial paresis	15 (17%)	95 (95%)
Paresis	78 (87%)	94 (94%)
Walking dysfunction	14 (16%)	92 (92%)
Hypesthesia	15 (17%)	90 (90%)
Visual dysfunction	22 (25%)	84 (84%)
Headache	7 (8%)	59 (59%)

Note: Values are absolute numbers (%).

why they should decide to react fast and what their possibilities and potential benefits are, if they present as early as possible in the hospital after stroke symptom onset. Profound knowledge and understanding of possible benefits of early treatment might reduce the psychological barrier to seek medical help, because of shame or denial.

There is evidence, that actively involving patients increases knowledge and satisfaction with the information.²⁵ But active involvement and/or counseling seems rarely implemented in stroke care with medical health staff not being able to act as an important source of information, as our data show. Potentially individual risk counseling could be a way to close the gap between general stroke knowledge and recognition of own stroke risk and possibly enables to overcome emotions like shame and denial. Emotions should be addressed in individual risk counseling to avoid negative influence.

As a limitation we did not perform a formal sample size calculation before and interviewed 15, respectively, surveyed 100 consecutive acute stroke patients, aiming to receive a representative data collection. However, the number of 15 patients is shown to be representative.²⁶

Conclusions

In conclusion, patients mostly notice stroke symptoms by themselves and only a minority presented in hospital

Table 5. Factors associa	ted with early	v time from syn	ptom onset
to admission (OR ≤4.5 ł	nrs)		

Factor	OR ^a ; OR	95% CI	P-value
Age (<65; >65) (years)	1.008; 0.426	2.382	0.986
Female	0.699; 0.284	1.72	0.436
NIHSS (0-4; 5-42)	0.37; 0.121	1.131	0.081
Symptoms			
Facial paresis	7.655; 2.614	22.418	<0.001
Hypesthesia	0.336; 0.098	1.148	0.082
Mono-/hemiparesis	4.434; 1.782	11.031	0.001
Walking dysfunction	0.386; 0.16	0.93	0.034
Dizziness/nausea/	0.893; 0.36	2.218	0.808
headache			
Aphasia or dysphasia	2.803; 1.172	6.708	0.021
Visual dysfunction	0.213; 0.071	0.642	0.006
Symptom notice			
Patient themselves	0.153; 0.045	0.52	0.003
Other person	6.53; 1.923	22.172	0.003
Symptom interpretation			
Serious	2.529; 1.06	6.033	0.035
Urgent	4.478; 1.828	10.97	0.001
Attribution of			
symptoms			
Stroke	1.664; 0.689	4.022	0.258
Weakness	0.568; 0.132	2.451	0.448
Eye problems or disease	1.078; 0.281	4.137	0.913
Nerve irritation	0.431; 0.071	2.622	0.361
No attribution	12.293; 1.964	76.947	0.007
Stress	0.195; 0.01	3.644	0.274
Blood pressure	2.404; 0.395	14.638	0.341
Cardiac dysfunction	0.195; 0.01	3.644	0.274
First action			
Waiting	0.013; 0.003	0.051	<0.001
Call family member	95.27; 5.387	1684.816	0.002
Call general	12.293; 1.964	76.947	0.007
practitioner			
Call emergency	17.945; 0.897	358.924	0.059
Medication intake	0.449; 0.021	9.639	0.609
Hospital	7.169; 0.284	181.122	0.232

Notes: ^aLogistic regression with Yates' correction for continuity. Factors with significant influence are highlighted in bold.

Abbreviation: NIHSS, National Institute of Health Stroke Scale.

within 4.5 hrs. Shame and insufficient individual risk knowledge about stroke were important factors for delayed admission. There is a clear need for individual risk counseling taking psychological factors into account. We postulate that information from the general practitioners and other health-care staff, especially for patients carrying risk factors, should include individual risk counseling. Combination of tailored risk counseling also addressing psychological factors as denial may

Ethics approval and consent to participate

The study was approved by the Ethics Hamburg Chamber of Physicians (PV4980) and all patients gave written informed consent.

Data availability

All data are available by contacting the corresponding author. There are no unpublished data from the study.

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Author contributions

All authors made substantial contributions to conception and design, gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. ACA, SA, and CH made substantial contributions to data acquisition and data analysis and interpretation. ACR, SK, and GT made substantial contributions to data interpretation. ACA and CH made substantial contributions to drafting the article and critically revising it for important intellectual content. SA, ACR, SK, and GT made substantial contributions to revising the article critically for important intellectual content.

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