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ORIGINAL RESEARCH ARTICLE

Non-invasive telemedical care in heart failure patients and stroke: post hoc analysis of TIM-HF and TIM-HF2 trials

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Abstract

Aims Patients with chronic heart failure (CHF) have an increased risk of ischaemic stroke. We aimed to identify the incidence rate and factors associated with ischaemic stroke or transient ischaemic attack (TIA) in CHF patients as well as the impact of non-invasive telemedical care (NITC) on acute stroke/TIA.

Methods and results We retrospectively analysed baseline characteristics of 2248 CHF patients enrolled to the prospective multicentre *Telemedical Interventional Monitoring in Heart Failure study* (TIM-HF) and *Telemedical Interventional Management in Heart Failure II study* (TIM-HF2), randomizing New York Heart Association (NYHA) II/III patients 1:1 to NITC or standard of care. Hospitalizations due to acute ischaemic stroke or TIA during a follow-up of 12 months were analysed. Old age, hyperlipidaemia, lower body mass index, and peripheral arterial occlusive disease (PAOD) were independently associated with present cerebrovascular disease on enrolment. The stroke/TIA rate was 1.5 per 100 patients-years within 12 months after randomization (n = 32, 1.4%). Rate of stroke/TIA within 12 months was in the intervention group similar compared with the control group (50.0% vs. 49.8%; P = 0.98) despite that the rate of newly detected atrial fibrillation (AF) was higher in the intervention group (14.1% vs. 1.6%; $P < 0.001$). A history of PAOD (OR 2.7, 95% CI 1.2–6.2; P = 0.02) and the highest tertile (OR 3.0, 95% CI 1.1–8.3) of N-terminal pro-brain natriuretic peptide (NT-proBNP) on enrolment were associated with stroke/TIA during follow-up. In patients who suffered acute stroke or TIA during follow-up, echocardiography was part of the diagnostic workup in only 56% after hospital admission.

Conclusions Annual rate of ischaemic stroke/TIA in NYHA II/III patients is low but higher in those with elevated NT-proBNP levels and history of PAOD at baseline. NITC showed no impact on the stroke rate during 1 year follow-up despite a significantly higher rate of newly detected AF. Irrespective of known CHF, echocardiography was often missing during in-hospital diagnostic workup after acute stroke/TIA.

Keywords Ischaemic stroke; Chronic heart failure; Telemedical Interventional Management in Heart Failure

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Introduction

Heart failure (HF) and ischaemic stroke share cardiovascular risk factors and have a high prevalence in the population. There is a twofold to threefold higher risk of ischaemic stroke and a higher risk of recurrent stroke in patients with chronic HF (CHF), compared with the general population.[1,2] There are several underlying pathophysiological mechanisms causing thromboembolism, that is, thrombus formation due to left ventricular hypokinesia, a hypercoagulable state due to increased aggregation of thrombocytes and reduced fibrinolysis. Furthermore, atrial fibrillation (AF) as a relevant risk factor for

stroke is more often found in CHF patients than in the general population, which further increases the risk of ischaemic stroke.[3]

CHF patients more often suffer severe stroke and have a poor clinical outcome than do stroke patients without CHF.[1] In the acute phase of ischaemic stroke, cardiac function may be reduced, indicating that the heart and the brain are connected with several feedback mechanisms.[4,5]

The *Telemedical Interventional Monitoring in Heart Failure* (TIM-HF) and *Telemedical Interventional Management in Heart Failure II studies* (TIM-HF2) investigated the impact of remote non-invasive telemedical care (NITC) on mortality and hospitalization in ambulatory CHF patients with New York Heart Association (NYHA) class II or III.[6,7] The TIM-HF study demonstrated that NITC in ambulatory CHF patients was not associated with a reduction in all-cause mortality if compared with usual care.[8] However, NITC was beneficial in the subgroup of patients with a *Patient Health Questionnaire* (PHQ-9) score < 10, a prior decompensation due to CHF within 12 months before randomization, and a left ventricular ejection fraction (LVEF) $\geq$ 25%, indicating that NITC may not appropriate for all CHF patients.[9] Considering these results, the main inclusion criteria and the amount of intervention of the TIM-HF2 study were adapted—given in detail in the Methods section—and study results showed that NITC leads to fewer days lost owing to unplanned cardiovascular hospitalizations and all-cause mortality.[10]

In this retrospective analysis of the pooled cohorts of the TIM-HF studies, we focus on incidence, aetiology, and independent predictors for acute ischaemic stroke/transient ischaemic attack (TIA) in the follow-up period of 12 months and the impact of NITC on the occurrence of acute ischaemic stroke/TIA. Furthermore, we highlight factors associated with known cerebrovascular disease at the time of randomization.

Methods

Ethics and study design

Both trials, TIM-HF and TIM-HF2 (clinicaltrails.gov identifier NCT00543881 and NCT01878630), were approved by the ethics board of the Charité – Universitätsmedizin Berlin (A1/052/07 and EA2/065/13). Detailed study design und results have been reported elsewhere.[6–10] In brief, the main common inclusion criteria in both studies were CHF NYHA II or III and ability to give informed consent. Randomization to intervention group NITC or usual care was 1:1 and stratified according to a central computerized randomization system.

NITC included daily measurements of blood pressure, body weight, electrocardiogram (ECG) (3 leads), SpO_2, and self-rated health status. Wireless data transfer was performed daily from the patients' home directly to the Telemedical Center (TMC) at the Charité – Universitätsmedizin Berlin, Germany.

The TMC served as a medical centre, not only collecting and monitoring data but also providing 24/7 physician-led personalized patient support and management following a holistic approach (medication changes; initiation of ambulatory assessment by home physician; or hospitalization). An HF nurse visited the patients once at home within seven working days after randomization to perform three tasks: (i) train patients on how to use the four non-invasive telemedical devices, (ii) perform a nursing assessment, and (iii) start an HF patient education programme, which was continued by monthly structured telephone interviews.

No recommendations were given to treating physicians of study patients, and no education programme was provided for the patients in the control group.

The inclusion criteria and endpoints of both studies were different to a certain extent: TIM-HF included patients with LVEF of $\leq$ 35% and at least one hospitalization due to decompensated HF within 24 months prior to randomization. In patients with LVEF $\leq$ 25% (as documented two times within 6 months prior to randomization), no previous hospitalization due to CHF was required. Referring to the results of TIM-HF study, the inclusion criteria of TIM-HF2 were adapted as follows: LVEF $\leq$ 45% or $>$45% with oral diuretics prescribed, hospitalization due to decompensated HF within 12 months prior to randomization, and depression score PHQ-9 $<$ 10. In TIM-HF, the primary outcome was all-cause mortality during follow-up (median 26 months). In TIM-HF2, the primary endpoint was modified as follows: percentage of days lost due to unplanned cardiovascular hospitalizations or death from any cause (follow-up time to a maximum of 393 days). In both studies, outpatient clinical visits were performed by a general practitioner or cardiologist at Months 3, 6, 9, and 12 (in TIM-HF as well in Months 18 and 24) after randomization. The following data were recorded (TIM-HF comparable with TIM-HF 2): vital signs, CHF symptomatic status, NYHA class, changes in medication, information related to death from any cause, hospitalization, and emergency room admissions. Echocardiography was not required in these follow-up visits. In both trials, a clinical endpoint committee, blinded to treatment allocation, classified all deaths and hospitalizations. For our investigation, prior cerebrovascular disease—including previous ischaemic and haemorrhagic stroke—was assessed at the time of enrolment. The presence of AF at the time of enrolment was assessed using the baseline 12-lead ECG. In addition, daily ECG recordings of patients in the intervention group of both studies as well as the follow-up visit ECGs after 12 months (in the intervention and the control group) were analysed in detail. Patients with no AF on the baseline study ECG but AF during daily recordings or ECG after 12 months and

naive to anticoagulation were considered as patients with newly detected AF.

Statistical analyses

Dichotomized and categorized characteristics were expressed as percentages. A two-sided Pearson χ^2 test was performed for univariate analyses comparing patients with or without prior cerebrovascular disease on enrolment as well as with or without acute ischaemic stroke or TIA during follow-up. Continuous data were presented as median and inter-quartile range (IQR), and the Mann–Whitney *U* test was applied for univariate analysis. All tests were two-tailed, and statistical significance was determined at an α level of 0.05. Multivariable logistic stepwise regression analyses were used to test for independent associations with cerebrovascular disease at enrolment or with ischaemic stroke or TIA in the follow-up period. Adjustment was made for variables associated with $P < 0.05$ in univariate comparisons. To prescribe the impact of serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) on stroke/TIA occurrence within 12 months and cerebrovascular disease at enrolment in more detail, we calculated three regression models: one with NT-proBNP as a continuous variable and two further models with NT-proBNP as an ordinal variable based on the tertiles and quartiles of the values. Statistical analyses were performed using SPSS software (version 24; SPSS, Chicago, Illinois) for Windows (Microsoft, Redmond, Washington).

Results

Factors related to cerebrovascular disease at baseline

At randomization, 240 (10.7%) out of 2248 CHF patients had a medical history of cerebrovascular disease. This rate was similar in both studies (10.6% in TIM-HF and 10.7% in TIM-HF2). There was no information about the time of onset of the cerebrovascular disease before randomization. Baseline characteristics of study patients with or without prior cerebrovascular disease are given in *Table 1*. According to the multivariate analysis, adjusting for all variables suggesting association of baseline recordings with a history of cerebrovascular disease at enrolment ($P < 0.05$) (*Table 1*), a history of hyperlipidaemia [odds ratio (OR) 2.0, 95% confidence interval (CI) 1.4–2.7; $P < 0.001$], peripheral arterial occlusive disease (PAOD) [OR 2.5, 95% CI 1.8–3.6; $P < 0.001$], body mass index (BMI) [OR per point 0.9, 95% CI 0.92–0.98; $P = 0.01$], and old age [OR 1.03 per year 95% CI 1.0–1.1; $P < 0.001$] were independently associated with a history of cerebrovascular disease at baseline, while NT-proBNP (as a continuous variable) was not [OR per point 1.00, 95% CI 1.00–1.00; $P = 0.81$]. With further sensitivity analysis using NT-proBNP as a categorical variable for the multivariate analysis, whether patients are in the highest tertile (2203–34 869 pg/mL) (OR 1.4, 95% CI 1.0–2.2; $P = 0.09$) or patients are in the highest quartile (2941–34 869 pg/mL) of NT-proBNP is independently associated with a cerebrovascular disease at randomization. In addition, we found no significant association of AF on ECG at randomization and cerebrovascular disease at baseline, while the time of onset

Table 1 Socio-demographic factors and presence of cardiovascular risk factors in TIM-HF and TIM-HF2 patients with or without a history of cerebrovascular disease on enrolment

	History of cerebrovascular disease[a]		*P*
	No $n = 1998$	Yes $n = 240$	χ^2 Pearson/ MWU
Socio-demographic factors			
Sex, female, % (*n*)	27.0 (539)	24.2 (58)	0.30
Age, years, median [IQR]	71 [62–77]	74 [67–78]	<0.001
Body mass index, kg/m^2, median [IQR]	28.6 [25.0–32.0]	26.7 [23.8–30.6]	<0.001
Randomized to telemedicine, % (*n*)	49.7 (993)	50.8 (122)	0.74
Cardiovascular risk factors			
Diabetes mellitus, % (*n*)	42.3 (863)	47.7 (114)	0.184
Hypertension, % (*n*)	76.2 (1516)	80.3 (192)	0.15
Hyperlipidaemia, % (*n*)	60.3 (1153)	76.8 (179)	<0.001
Current smoking, % (*n*)	10.8 (211)	6.0 (14)	0.02
Peripheral arterial occlusive disease, % (*n*)	9.8 (189)	24.9 (58)	<0.001
Medical history regarding to cardiologic diagnosis or findings			
Coronary heart disease, % (*n*)	59.7 (1170)	73.8 (172)	<0.001
Dilated cardiomyopathy, (*n*)	40.8 (807)	31.2 (74)	0.004
Left ventricular ejection fraction, median [IQR]	35 [25–45]	30 [25–50]	0.36
NT-proBNP, pg/mL, median [IQR]	1340 [579–2863]	1914 [988–3404]	<0.001
Mean arterial pressure, mmHg, median [IQR]	90.7 [83.3–98.3]	89.3 [80.0–96.7]	0.90
Atrial fibrillation on ECG at randomization, % (*n*)	31.5 (626)	33.8 (81)	0.47

MWU, Mann-Whitney-U-test; NT-proBNP, N-terminal pro brain natriuretic peptide.
[a]In 10 out of 2248 patients, there was no information about a history of cerebrovascular disease at enrolment.

of AF before randomization was unknown. There was an impact of prior cerebrovascular disease on all-cause death (13.8% vs. 8.2%; $P = 0.004$) or cardiovascular death (8.8% vs. 4.2%; $P = 0.001$) during follow-up.

Ischaemic stroke or transient ischaemic attack during follow-up

Within 12 months after randomization, 33 ischaemic stroke-related hospitalizations were reported. As one patient suffered from two strokes, 32 (1.4%) study patients were included into this analysis. Of these, 26 (81%) patients had an ischaemic stroke and six (19%) patients had a TIA. This corresponds to an ischaemic stroke rate of 1.2 per 100 patient-years, a TIA rate of 0.3 per 100 patient-years, and a total stroke/TIA rate of 1.5 per 100 patient-years of follow-up. Two additional patients were hospitalized owing to intracerebral haemorrhage during the follow-up period.

Baseline characteristics of study patients with or without ischaemic stroke/TIA during follow-up were given in *Table 2*. On admission, the median *National Institutes of Health Stroke Scale* score was 3 (IQR 2–6) points, indicating a moderate stroke-related deficit in the majority of patients. Based on medical records, the aetiology of ischaemic stroke/TIA was classified to be 'cardio-embolic' in 22 (69%) patients, microangiopathic in two (6%) patients, macroangiopathic in six (19%) patients, and cryptogenic in one (3%) patient according to *Trial of ORG 10172 in Acute Stroke Treatment* criteria.[11] The medical records of one patient with stroke/TIA in the follow-up period were incomplete. AF was present in 19 (59%) ischaemic stroke/TIA patients (including those with a history of paroxysmal AF); in 12 of these 19 patients, anticoagulation was established before the onset of acute stroke/TIA. Eighteen (56%) patients underwent echocardiography (14 transthoracic echo and four transthoracic and transesophageal echo) in the acute phase of ischaemic stroke/TIA (*Table 3*).

According to the univariate analysis, age [median 73 years, IQR (65–78) vs. 71, IQR (63–77); $P = 0.29$], AF (34.4% vs. 31.7%; $P = 0.75$), or prior cerebrovascular disease (18.8% vs. 10.6%; $P = 0.14$) showed no association with ischaemic stroke/TIA during the follow-up period. An association with ischaemic stroke/TIA during the follow-up period was given for PAOD and serum levels of NT-proBNP according to the univariate analysis. According to the multivariate analysis using backward selection, patients in the highest tertile (2203–34 869 pg/mL) (OR 3.4, 95% CI 1.1–8.3; $P = 0.03$) of NT-proBNP as well as patients with a history of PAOD (OR 2.7, 95% CI 1.2–6.2; $P = 0.02$) remained independently associated with ischaemic stroke/TIA during follow-up, while NT-proBNP as a continuous variable (OR per point 1.00, 95% CI 1.00-1.00; $P = 0.79$) was not. With the use of quartiles of serum levels of NT-proBNP on enrolment, the highest quartile (2941–34 869 pg/mL) was also independently associated with ischaemic stroke/TIA during follow-up (OR 3.7, 95% CI 1.04–13.3; $P = 0.04$). Patients with ischaemic stroke/TIA

Table 2 Univariate comparison of baseline variables of chronic heart failure patients with or without ischaemic stroke or transient ischaemic attack during study follow-up

	Ischaemic stroke or TIA		*P*
	Yes $n = 32$	No $n = 2216$	χ^2 Pearson/ MWU
Socio-demographic factors			
Sex, female, % (*n*)	37.5 (12)	26.6 (589)	0.69
Age, years, median [IQR]	73.0 [64.5–78.0]	71.0 [63.0–77.0]	0.29
Body mass index, kg/m^2, median [IQR]	26.6 [23.4–33.8]	28.4 [24.9–32.7]	0.27
Randomized to telemedicine, % (*n*)	50.0 (16)	49.8 (1103)	0.98
Cardiovascular risk factors			
Diabetes mellitus, % (*n*)	50.0 (16)	43.7 (967)	0.47
Hypertension, % (*n*)	75.0 (24)	76.8 (1694)	0.82
Hyperlipidaemia, % (*n*)	58.6 (17)	62.3 (1323)	0.69
Current smoking, % (*n*)	9.4 (3)	10.3 (222)	0.87
Peripheral arterial occlusive disease, % (*n*)	25.8 (8)	11.3 (241)	0.01
History of cerebrovascular disease, % (*n*)	18.8 (6)	10.6 (234)	0.14
Medical history regarding cardiologic diagnosis or findings			
Coronary heart disease, % (*n*)	70.0 (21)	61.1 (1327)	0.32
Dilated cardiomyopathy, % (*n*)	29.0 (9)	40.0 (878)	0.21
Left ventricular ejection fraction, median [IQR]	35 [25–50]	34 [25–45]	0.56
NT-proBNP[a] pg/mL, median [IQR]	2217 [1263–3804]	1385 [596–2920]	0.02
Mean arterial pressure, mmHg, median [IQR]	92.2 [78.6–100.0]	90.0 [83.3–98.3]	0.83
Atrial fibrillation on ECG at randomization, % (*n*)	34.4 (11)	31.7 (700)	0.75
Current medication			
Acetylsalicylic acid, % (*n*)	43.8 (14)	39.8 (883)	0.65
Other antithrombotic medication, % (*n*)	28.1 (9)	15.0 (332)	0.05
Anticoagulation, % (*n*)	53.1 (17)	56.9 (1260)	0.67

NT-proBNP, N-terminal pro brain natriuretic peptide.

Table 3 Data of in-hospital assessment in 33 TIM-HF or TIM-HF2 patients with acute ischaemic stroke or transient ischaemic attack during the follow-up period.

No.	Diagnosis	NIHSS on admission	Aetiology of ischaemic stroke/TIA	AF	Stroke prevention on admission	Stroke prevention at discharge	LVEF (%) at randomization	LVEF (%) at the time of stroke	Intracardiac thrombi
1	Stroke	10	Cardio-embolic	Yes	Unknown	LMH 1 × 60 mg (VKA r)	27	20	No
2	Stroke	2	Cardio-embolic	No	VKA	VKA	35	30	No
3	TIA	1	Cardio-embolic	Yes	VKA	VKA	20	Unknown	Unknown
4	Stroke	3	Cardio-embolic	Yes	VKA	VKA	20	22	Yes
5	Stroke	2	Cardio-embolic	Yes	unknown	VKA	25	Unknown	Unknown
6	Stroke	3	Cardio-embolic	No	ASA	CLP	25	20	no
7	Stroke	4	Microangiopathy	No	APA	APA	29	Unknown	Unknown
8	Stroke	5	Cardio-embolic	No	VKA	VKA	34	normal	No
9	Stroke	14	Cardio-embolic	Yes	none	CLP + ASS (VKA r)	20	Unknown	Unknown
10	Stroke	6	Cardio-embolic	No	ASA	ASA + APA	15	25	No
11	Stroke	6	Macroangiopathy	No	ASA	ASA	35	Unknown	Unknown
12	Stroke	5	Cardio-embolic	Yes	ASS	Eliquis	42	45	No
13	Stroke	6	Cardio-embolic	Yes	VKA	ASS + VKA	35	Unknown	Unknown
14	ZAV	1	Cardio-embolic	Yes	VKA	VKA	55	Unknown	Unknown
15	Stroke	18	Cardio-embolic	Yes	ASS	ASS	70	61	No
16	Stroke	4	Cardio-embolic	Yes	VKA	Eliquis	35	Unknown	Unknown
17	Stroke	3	Cardio-embolic	Yes	VKA	Eliquis	55	60	No
18	TIA	1	Microangiopathy	No	ASS	ASS	25	35	No
19	Stroke	2	Cardio-embolic	Yes	Eliquis	Eliquis	50	Unknown	Unknown
20	TIA	2	Cardio-embolic	Yes	VKA	Xarelto	63	71	no
21	Stroke	6	Cardio-embolic	Yes	Heparin, AC	n.a. exitus letalis	55	Unknown	Unknown
22	Stroke	5	Macroangiopathy	No	ASA	ASA	40	40	No
23	Stroke	8	Cardio-embolic	Yes	none	Eliquis	45	Slightly reduced	No
24	Stroke	4	Cardio-embolic (endocarditis)	Yes	VKA	VKA	50	Normal	No
25	Stroke	6	Cardio-embolic	Yes	Heparin, TP	Heparin, TP	44	36	No
26	Stroke	2	Cryptogenic	Yes	APA	APA	35	Unknown	Unknown
27	Stroke	3	Macroangiopathy	No	ASA	ASA+APA	41	37	No
28	TIA	2	Macroangiopathy	No	APA	APA	20	20	No
29	Stroke	3	Cardio-embolic	Yes	VKA	VKA	60	Normal	No
30	TIA	0	Macroangiopathy	No	VKA	VKA	40	Unknown	Unknown
31	TIA	0	Macroangiopathy	No	ASA	ASA	26	Unknown	Unknown
32	Stroke	Unknown	Unknown	No	Unknown	ASA	52	Unknown	Unknown

AF, atrial fibrillation; APA, anti-platelet agent other than ASA; ASA, acetylsalicylic acid; LMH, low molecular heparin; LVEF, left ventricular ejection fraction, patient died during intra-hospital stay; n.a., not applicable; NIHSS, National Institutes of Health Stroke Scale; r, recommended; TIA = transient ischaemic attack; VKA, Vit K antagonist.

during follow-up died significantly more often within 1 year after randomization than did patients without ischaemic stroke/TIA during follow-up (21.9% vs. 8.5%; $P = 0.008$). There was no statistically difference between both groups regarding cardiovascular death (6.2% vs. 4.5% $P = 0.66$).

We compared additionally baseline data of all patients randomized in both studies (*Table* S1, $n = 2248$) and of those with stroke/TIA within the analysed follow-up time period of 12 months (*Table* S2, $n = 32$) with regard to their randomization. However, there was no significant difference here.

Non-invasive telemedical care and ischaemic stroke/transient ischaemic attack

The stroke/TIA rate in the intervention group (1.4%) compared with the control group (1.4%; $P = 0.98$) was similar. AF was detected newly in 176 (7.8%) patients after randomization within the pooled cohort of the TIM-HF and TIM-HF2 studies. The rate of newly detected AF in the intervention group ($n = 158$) was significantly higher than in the control group ($n = 18$) (14.1% vs. 1.6%; $P < 0.001$). The summarized rate of established oral anticoagulation 12 months after randomization (43.3% vs. 38.8%; $P = 0.03$) was significantly higher in patients randomized to the intervention group than in the control group of TIM-HF or TIM-HF2.

Compared with study patients without stroke/TIA within 12 months after randomization, the summarized rate of newly detected AF (12.5% vs. 7.8%; $P = 0.32$) or the summarized rate of established oral anticoagulation at 12 months after randomization (40.6% vs. 41.1%; $P = 0.96$) was not different in study patients with stroke/TIA.

Discussion

This retrospective analysis of the prospective randomized TIM-HF and TIM-HF2 studies revealed a rather low annual rate of ischaemic stroke/TIA (1.5 per 100 person-years) in CHF patients with NYHA II or III. Elevated NT-proBNP levels and a history of PAOD at baseline were related to higher risk of stroke/TIA during follow-up. The aetiology of ischaemic stroke/TIA was predominantly assumed to be cardio-embolic, but diagnostic workup of ~44% of all patients did not include diagnostic echocardiography during the in-hospital stay after acute stroke/TIA.

Both studies, TIM-HF and TIM-HF2, were designed to investigate the impact of NITC on mortality and hospitalization in ambulatory CHF patients with NYHA class II or III. Taking into consideration that these studies were not designed to investigate the impact of NITC on ischaemic stroke/TIA, this analysis showed no benefit of NITC concerning prevention of stroke or TIA in CHF patients. The daily ECG analysis within the intervention group leads to a significantly higher rate of newly detected AF in comparison with that of the control group. Interestingly, neither AF on baseline ECG nor newly detected AF after randomization had an impact on stroke rate during follow-up in our analysis.

So far, the reported annual stroke rates in CHF patients range from 1.1 to 4.6 per 100 person-years.[4,12,13] As CHF severity and aetiology of HF may impact the incidence rate of ischaemic stroke/TIA[1,14] the exclusion of CHF patients with NYHA-IV and physical and mental disabilities in both studies according to inclusion criteria may have caused the comparably low incidence of ischaemic stroke/TIA. In TIM-HF and TIM-HF2, the main documented CHF aetiology was ischaemic cardiomyopathy, but we detected no impact of CHF aetiology on ischaemic stroke/TIA rate during the follow-up. AF detected on a 12-lead ECG on enrolment was known in 32% of all included patients. Published data reported even higher rates of AF in HF patients.[3] In addition, known risk factors for ischaemic stroke like a history of arterial hypertension, old age, prior stroke, or diabetes showed no impact in the present analysis including CHF patients.[15] According to the multivariate analysis, the highest tertile or the highest quartile of serum NT-proBNP on enrolment was an independent predictor for ischaemic stroke/TIA during follow-up, which is in line with reported results of a pooled analysis.[14] Also in accordance with other publications, CHF patients with ischaemic stroke/TIA during follow-up more often died than do CHF patients without ischaemic stroke/TIA.[1,4]

Detailed information regarding in-hospital diagnostic workup after acute ischaemic stroke/TIA is given in *Table 3*. Despite—or probably even of—known CHF, echocardiography was not performed in 44% of acute stroke patients. The presence of AF and the subsequent need of oral anticoagulation almost independent of echocardiographic findings may be an explanation, as AF was present in eight out of 13 stroke/TIA patients without echocardiography. In our mind, a transesophageal echocardiography is justified to rule out left atrial or left ventricular thrombi or valve vegetations.[5] Evidence of cardiac thrombus would result in an anticoagulation therapy even in patients without AF. Because of the observed diagnostic shortcomings, we are limited to describe the impact of acute ischaemic stroke on cardiac function in detail (e.g. stroke-induced HF).[4] Not surprisingly, stroke aetiology was most often assumed to be cardio-embolic in CHF patients.[9]

The pooled analysis of TIM-HF cohorts revealed that a history of cerebrovascular disease—including previous ischaemic and/or haemorrhagic stroke—on enrolment was related to old age, a history of hyperlipidaemia, history of PAOD, or presence of lower BMI. Body weight loss is a common observed condition after acute and chronic stroke. A stroke-related metabolic imbalance and ongoing systematic inflammation in chronic stroke as some explanatory approaches are under

discussion.[16] All other variables associated with the presence of cerebrovascular disease at baseline are well-known cardiovascular risk factors.

Besides the reported strengths, the major limitation of the reported findings is the retrospective design of this analysis. Although a prior stroke was not defined as exclusion criterion, we have to consider that patients might have been excluded from the study owing to stroke-related disability. Furthermore, there was no information available concerning the individual prescreening before enrolment. In addition, the comparably low stroke rate during follow-up may have influenced our findings. There was no continuous ECG or blood pressure monitoring in the intervention arm of both studies; therefore, some parameters that may be relevant regarding occurrence of a stroke/TIA like AF burden, heart rate variability, or the presence of nocturnal dip of blood pressure are missing in this analysis. Patients with higher atherosclerotic burden (older age and history of PAOD) had a higher incidence of cerebrovascular disease at baseline and/or stroke/TIA in 12 months after randomization in this analysis. Because there are no data regarding aortic calcification, supra-aortic vessel status, or aortic pressure control, we are not able to analyse this in detail.

Conclusions

The overall stroke rate during the follow-up of the TIM-HF studies was rather low. NITC to reduce mortality and hospitalization of CHF patients had no impact on the stroke/TIA rate. CHF patients with higher levels of NT-proBNP and a history of PAOD at baseline were under a higher risk to suffer ischaemic stroke/TIA during follow-up. Whether a biomarker-guided (e.g. NT-proBNP) management may influence the stroke/TIA rate in CHF patients had to be investigated in a randomized prospective trial. In a substantial number of CHF patients, echocardiography was not included in the diagnostic workup after acute ischaemic stroke/TIA. From our point of view, a transesophageal echocardiography is indicated in those patients to rule out cardiac thrombi or valve vegetation.

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No other persons have made substantial contributions to this manuscript.

Conflict of interest

K. G. H. reports study grants by Bayer and Sanofi-Aventis, lecture fees/advisory board fees from Bayer, Sanofi-Aventis, Pfizer, Bristol-Myers-Squibb, Boehringer Ingelheim, Daiichi Sankyo, W.L. Gore & Associates, Biotronik, and Medtronic. S. T. reports lecture fees by Boehringer Ingelheim. O. D. has received personal fees and speakers' honoraria from Novartis Pharma GmbH. M. H. and K. K. have nothing to declare.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariate comparison of baseline variables of patients with or without remote non-invasive telemedical-care.
Table S2. Univariate comparison of baseline variables of patients with ischemic stroke or TIA during study follow-up with or without remote non-Invasive telemedical-care.

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