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Telemedicine in heart failure: Pre-specified and exploratory subgroup analyses from the TIM-HF trial☆,☆☆

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ABSTRACT

Background: Meta-analyses have suggested that remote telemedical management (RTM) positively affects clinical outcomes in chronic HF patients. The results of two recent randomised RTM trials do not corroborate these results. We aim to report prospectively defined and exploratory subgroup analyses for the TIM-HF trial and to identify a patient profile that could potentially benefit from RTM for further investigation in randomised clinical trials.

Methods: In TIM-HF, 710 stable chronic HF patients, in NYHA class II or III with a history of HF decompensation within 2 years previously or a LVEF ≤ 25% were randomly assigned (1:1) to RTM or usual care. The primary outcome was total death and secondary outcomes included days lost due to death or HF hospitalisation and a composite of cardiovascular death and HF hospitalisation. Twelve subgroups were prospectively defined and patient profiling was investigated for the subgroup with a prior history of HF decompensation, an LVEF ≥ 25% and a PHQ-9 score < 10.

Results: The subgroup treatment effects were significant for total mortality for the PHQ-9 subgroup only (p for interaction < 0.027). For the outcome 'number of days lost due to hospitalisation for HF or death', the subgroup treatment effects were significant (p for interaction < 0.05) for patients with a prior HF decompensation or an ICD implant or a PHQ score of < 10 and for the patient-profiling subgroup.

Conclusions: Telemedicine management may not be appropriate for all HF patients. Future research needs to investigate which HF population may benefit from this intervention.

1. Introduction

The number of patients with chronic heart failure (HF) continues to increase worldwide, and this syndrome exerts a substantial burden on society and on healthcare systems in terms of morbidity, mortality and high consumption of resources primarily caused by repeated and in some instances, lengthy hospital stays [1,2]. Chronic HF is a multifaceted condition and the evolution of its medical management over the past two decades, from the 90's in particular, reflects the understanding of the underlying patho-physiology of this diagnosis and the results of randomised clinical trials have shown that selective poly-therapy for patients with mild-to-moderate heart failure reduces its progression and mortality risk [3].

In recent years, the focus for the management of chronic HF has shifted as developments in modern telecommunication technologies

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have created new options to deliver telemedical care as an adjunct to the medical management of HF patients [4]. It has been suggested that well structured out-patient care may prevent the need for hospitalisation, facilitate early intervention thus preventing 'crisis' management, prevent complications or the progression to a more severe disease status [5]. Recent meta-analyses [6–8] have shown that telemedical monitoring in chronic HF can reduce total mortality during a follow-up of 6 to 12 months in addition to reducing the number and duration of hospitalisations for worsening HF. Since the publication of these meta-analyses, two recently reported prospectively conducted randomised multi-centre clinical trials do not corroborate these findings [9,10].

These contrasting results pose a challenge to the medical profession as the answers to the following issues need to be re-addressed: Does remote telemedical management (RTM) have a role in the management of HF patients? If yes, which HF population is most likely to benefit from this intervention, which type of telemedical support is warranted and which clinically meaningful outcome can be positively affected by this intervention? In this report, we address two of these challenges, namely how the potential HF population which could benefit from RTM could be identified and which outcome could be the most meaningful to use for this intervention from a clinical perspective. To this end, we present the results of the prospectively defined subgroup analyses and two additional post hoc analyses from the Telemedical Interventional Monitoring in Heart Failure (TIM-HF trial) [10,11].

2. Materials and methods

2.1. Trial design

A description of the TIM-HF study design in addition to the main results has been published elsewhere [11]. Briefly, between January 2008 and June 2009, 710 eligible patients with chronic HF were enrolled in 165 cardiology, internal medicine or general medicine practices in Germany. Patients were randomly allocated (1:1) to either RTM or to usual care and were followed for a minimum of 12 months with out-patient visits at 3, 6, 9 and 12 months during the first year and at 18 and 24 months in the second year. Clinical evaluation and blood testing were carried out during the follow-up visits and documented on paper case report forms. Two self-administered questionnaires — the depression model of the Patient Health Questionnaire (PHQ-9) [12] and the 36-item Short Form health survey of the Medical Outcome Study (SF-36) questionnaires [13] were completed by patients at baseline and at each follow-up visit. The protocol was approved by the institutional review board at each participating centre and conducted in accordance with the principles of the Declaration of Helsinki (1996), International Conference on Harmonization Good Clinical Practice, and local and national regulations. All patients provided written informed consent. The trial was designed, implemented, and overseen by a steering committee. SOCAR Research, Nyon, Switzerland, was responsible for data analysis. The clinical endpoint committee (CEC), blinded to study group assignment, classified all deaths and hospitalisations using the prospectively defined criteria detailed in the CEC charter. The authors had access to the study data and vouch for the accuracy and completeness of the reported analyses.

2.2. Study intervention

The RTM system used is described previously [14,15]. Briefly, the system is based on a wireless Bluetooth device together with a personal digital assistant (PDA) as the central structural element (Fig. 1). Data transfer was performed using cell phone technologies. A 3-lead-electrocardiogram, a blood pressure device and a weighing scale with 50 g precision were all part of the integrated sensor-network: The patient performed a daily self-assessment using these devices and the data was transferred to the telemedical centre which provided physician-led medical support 24 h a day, 7 days a week for the entire study period. Patients were contacted by the telemedical centre physician in accordance with the standard operating procedures or when requested by the patient to verify measurements, to give consultation or to initiate or change concomitant treatments. The telemedical centre contacted the patient's local physician at least every 3 months. Data privacy was ensured using dynamic encryption. The general responsibility for the patients' care remained with local physician.

Other than RTM support, patients assigned to the usual care group were followed and treated in the same manner as patients assigned to RTM. At the study start, the treating physicians were instructed to treat patients in accordance with the current guidelines for the management of HF, irrespective of group assignment.

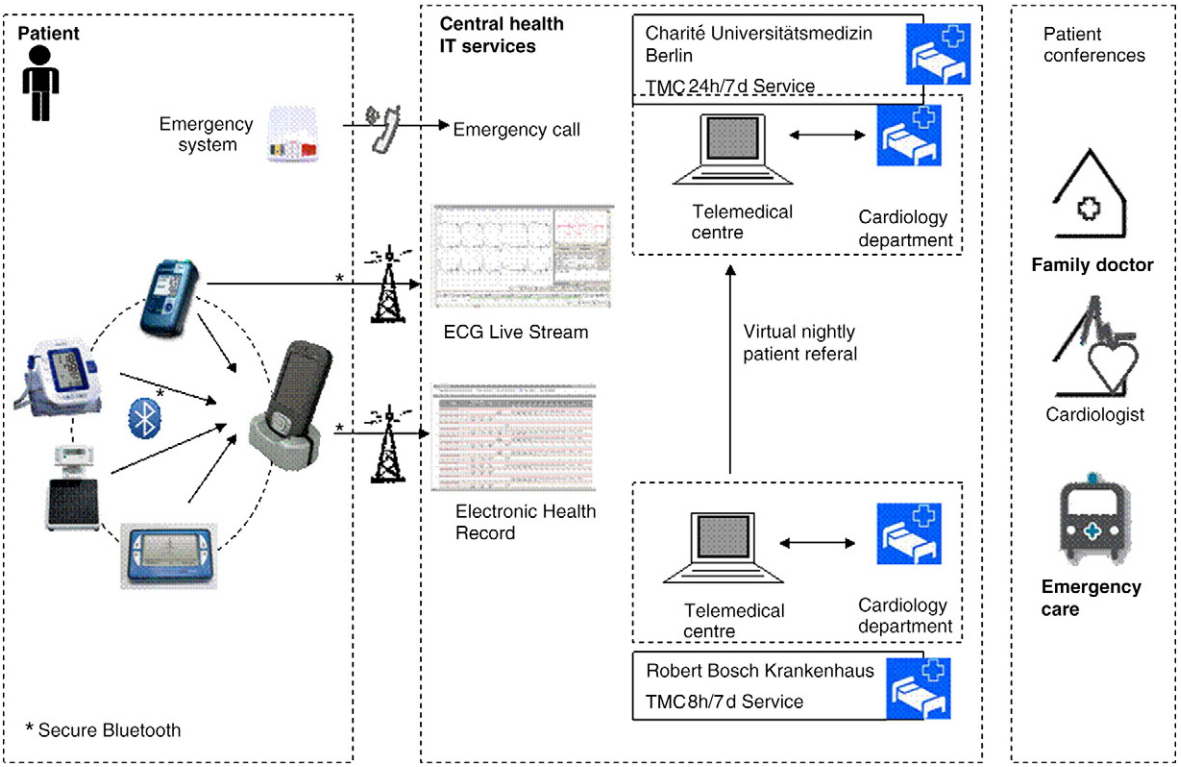

Fig. 1. Overview of RTM system and service structure. Devices for electrocardiogram, blood pressure and body weight measurements are connected via Bluetooth at the patient's home. A Personal digital assistant transmits the data via its integrated cell phone module to the central servers. In TIM-HF, there were two telemedical centres — one located in Berlin and the second one in Stuttgart that communicate via electronic patient records. A home emergency call system enabled the patient to have direct contact the cardiologist located at the telemedical centre.

2.3. Study outcomes

The primary outcome in the TIM-HF trial was total mortality. The first secondary outcome was a composite of cardiovascular mortality and hospitalisation for HF and other secondary outcomes included days lost due to hospitalisation for worsening HF and total mortality, cardiovascular mortality, all-cause hospitalisation, cardiovascular hospitalisation and hospitalisation for worsening HF.

2.4. Subgroups

In total, 12 subgroups (see Fig. 2), based on baseline demographic and clinical characteristics were defined prospectively and detailed in the statistical analysis plan (SAP). The SAP also detailed that the subgroup analyses would be performed for the primary outcome (i.e. total mortality) and for the secondary outcome — composite of cardiovascular mortality and hospitalisation for worsening HF. We performed an additional subgroup analysis (using the pre-defined subgroups) for the secondary outcome 'number of days lost due to HF hospitalisation and mortality' (all cause).

The availability of subgroup analysis results for prospective RTM trials is limited. Because of this, the selection of the subgroup in our exploratory subgroup analyses was based on clinical judgement, where we looked at patient characteristics which could potentially impact on outcome (i.e. event rates and/or responsiveness to therapy). The subgroup concerned consisted of patients with a previous episode of HF decompensation, who had a baseline Left ventricular ejection fraction (LVEF) ≥ 25 % and who presented with a baseline PHQ-9 score < 10, indicating a low burden of depressive symptoms. With this combination of clinical characteristics, we combined (a) a characteristic defining a population at increased risk to have repeated hospitalisations (hence the criterion of prior hospitalisation), with (b) a criterion defining patients with preserved ejection fraction (hence the criterion of a baseline LVEF ≥ 25 %), and (c) an additional characteristic defining patients most likely to be compliant with the requirements of the study protocol and to respond to recommendations by the telemedical staff members (hence the criterion PHQ-9 score < 10).

2.5. Statistical analysis

The subgroup analyses were defined prospectively for both the primary outcome (total mortality) and for the secondary composite outcome — cardiovascular death and hospitalisation for worsening HF and were detailed in a formal SAP. An additional ad-hoc subgroup analysis was performed for the same subgroups for the secondary endpoint — 'days lost due to HF hospitalisation and death (all cause)'.

Event rates were expressed as the number of events per 100 patient years of follow-up at risk. Cox-proportional hazards regression models [16] were used to estimate hazard ratios and their 95% confidence intervals. The treatment-by-subgroup interaction was evaluated by means of a Cox proportional-hazards model with covariate for treatment, subgroup, and their interaction using the SAS® proc phreg procedure.

For the analysis 'days lost due to HF hospitalisation and death (all cause)', the fraction of follow-up time lost due to death or HF hospitalisation was defined as the number of days lost divided by the intended follow-up. For patients who died, the number of days lost between the date of death and the date of intended follow-up plus the number of days spent in hospital for HF was counted. For patients who completed the study as planned or who withdrew prematurely from follow-up, the fraction of follow-up time was defined as number of days lost (due to HF hospitalisation) divided by the follow-up time realised (i.e. up to the censoring date). The model adjusted means were obtained and compared using a mixed model including terms for treatment, subgroup and their interaction treatment-by-subgroup.

For the subgroup which combined patients who had a history of HF decompensation prior to randomisation, a baseline LVEF ≥ 25% and a baseline PHQ score < 10 points,

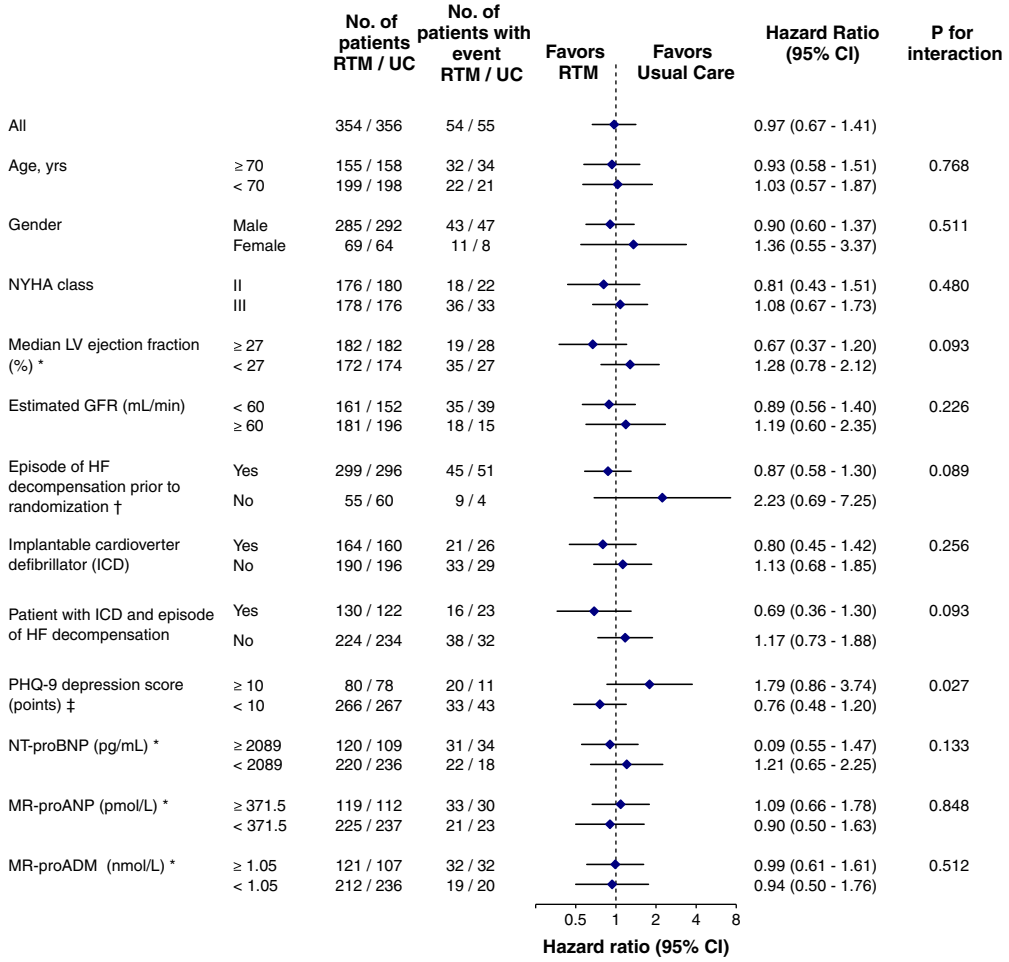

Fig. 2. Effect of RTM on total mortality in predefined subgroups. For each subgroup, the number of patients for whom data was available is shown. The horizontal lines indicate 95% confidence interval. Estimated GFR, estimated glomerular filtration rate; NYHA, New York Heart Association functional class; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; MR-proADM, Mid-regional pro-adrenomedullin; MR-proANP, Mid-regional pro-atrial natriuretic peptide; LV, left ventricular; ICD, implantable defibrillator; PHQ-9, The depression model of the Patient Health Questionnaire; CI, confidence interval; RTM, remote telemedical management. * The baseline tertile values were used as cut-off points for the biomarker subgroups and the median baseline left ventricular ejection fraction for the ejection fraction subgroup. † HF decompensation was defined as any hospitalisation for worsening heart failure within 24 months prior to inclusion in the study and /or treatment with IV diuretics within 24 months prior to inclusion in the trial. ‡ Patients with a PHQ-9 score between 0 and 9 were considered as having 'no depression' and patients with a score ≥ 10 points were considered as being 'depressed'.

baseline characteristics were compared for the two groups who presented with and who did not present with these characteristics using a two-sample *t*-test for normally distributed continuous variables and a Wilcoxon test for the non-normal distributions. Continuous variables were summarised as means with standard deviation, and categorical variables as frequencies and percentages. Categorical baseline characteristics were compared using the Chi-squared test.

The primary outcome, first secondary outcome and the outcome 'days lost due to HF hospitalisation and death (all cause)' were analysed in the same manner as the prospectively defined subgroups. Statistical significance was attached to p values <0.05. All analyses were conducted with SAS software, version 9.2 (SAS institute).

3. Results

As reported previously [10], a total of 710 patients with chronic HF were enrolled in the TIM-HF study with 354 patients randomly assigned to the RTM group and 356 to the usual care group. The median follow-up was 26 months (mean 21.5 months). Of the 354 patients randomly assigned to receive RTM, 287 (81%) were at least 70% compliant with the daily transfer of data to the telemedicine centres and had no break in information transfer >30 days (except during hospitalisations) [10]. Overall, patient follow-up was 99.7% complete. Baseline clinical and laboratory characteristics in addition to the use of cardiovascular medications were similar between the two groups [10].

3.1. Subgroup analyses for the primary outcome

The results of the pre-defined unadjusted subgroup analysis for the primary outcome (total mortality) are shown in Fig. 2. The subgroup treatment effects were significantly different from each other for the PHQ-9 subgroup (p for interaction = 0.027). There were no other significant interactions between the treatment effects and various baseline characteristics of the patients for total mortality.

3.2. Subgroup analyses for the first secondary outcome

The results of the pre-defined unadjusted subgroup analysis for the first secondary outcome (composite of cardiovascular mortality and hospitalisation for worsening HF) are shown in Fig. 3. There were no significant interactions between the treatment effects and various baseline characteristics of the patients for this secondary outcome.

3.3. Subgroup analyses for the secondary outcome: days lost due to HF hospitalisation and death (all cause)

The results of the unadjusted subgroup analyses for the secondary outcome – days lost due to HF hospitalisation and death (all cause) –

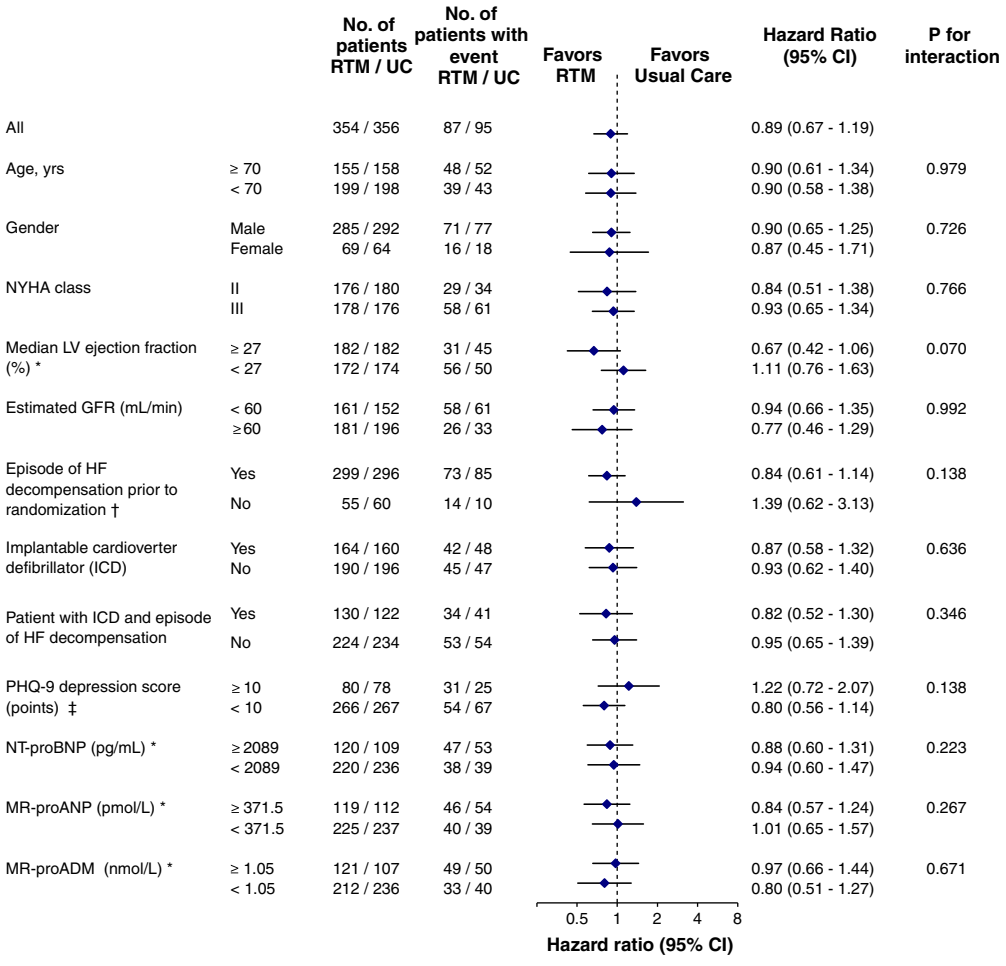

Fig. 3. Effect of RTM on hospitalisation for heart failure or cardiovascular death in predefined subgroups. For each subgroup, the number of patients for whom data was available is shown. The horizontal lines indicate 95% confidence interval. Estimated GFR, estimated glomerular filtration rate; NYHA, New York Heart Association functional class; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; MR-proADM, Mid-regional pro-adrenomedullin; MR-proANP, Mid-regional pro-atrial natriuretic peptide; LV, left ventricular; ICD, implantable defibrillator; PHQ-9, The depression model of the Patient Health Questionnaire; CI, confidence interval; RTM, remote telemedical management. * The baseline tertile values were used as cut-off points for the biomarker subgroups and the median baseline left ventricular ejection fraction for the ejection fraction subgroup. † HF decompensation was defined as any hospitalisation for worsening heart failure within 24 months prior to inclusion in the study and /or treatment with IV diuretics within 24 months prior to inclusion in the trial. ‡ Patients with a PHQ-9 score between 0 and 9 were considered as having 'no depression' and patients with a score ≥10 points were considered as being 'depressed'.

are shown in Table 1. The patient subgroup that had an episode of HF decompensation prior to randomisation assigned to RTM lost fewer days due to death or hospitalisation for worsening HF than patients in the same subgroup assigned to usual care (mean days lost: 30.1 ± 5.2 vs 44.5 ± 5.2, p = 0.049 for patients assigned to RTM and usual care, respectively) whereas for patients who did not have a previous history of HF decompensation prior to randomisation, those assigned to RTM lost more days due to death or hospitalisation for worsening HF than patients in the same subgroup assigned to usual care (mean days lost: 47.5 ± 12.1 vs 11.0 ± 11.6, p = 0.029 for patients assigned to RTM and usual care respectively). The subgroup treatment effects were significantly different from each other (p for interaction = 0.005). For the subgroup — patients with an ICD and an episode of HF decompensation and the PHQ-9 subgroup, the subgroup treatment effects were significantly different from each other (p for interaction < 0.05). For the other prospectively defined subgroups, there were no subgroup treatment effects observed (p for interaction > 0.05).

3.4. Exploratory subgroup analyses (patient profiling)

The subgroup of patients who at baseline had a history of HF decompensation, a LVEF ≥ 25% and a PHQ score < 10 points represented 47% of the TIM-HF population. For information, the baseline characteristics of this patient subgroup compared to those without these characteristics are given in Table 2. Both patient groups were similar for the majority of the baseline characteristics except that patients with a prior history of HF decompensation, LVEF ≥ 25% and baseline PHQ score < 10 points tended to be older, had a higher LVEF and systolic blood pressure measurement but lower biomarker values. They also had fewer ICD and/or CRT implants and they were more frequently classified as being in NYHA class II.

The unadjusted results for the primary and secondary outcomes are shown in Tables 1 and 3. The subgroup treatment effects were significantly different from each other for total mortality (p for interaction = 0.042), for cardiovascular mortality (p for interaction = 0.024) and for days lost due to HF hospitalisation and death (all cause) (p for interaction = 0.033). For the other secondary time to event analyses, the subgroup treatment effects were not significantly different from each other (p for interaction > 0.05) — cf Table 3.

4. Discussion

For the prospectively defined subgroups, the subgroup treatment effects were significant for total mortality for the PHQ-9 subgroup (p for interaction < 0.027) only. For the outcome days lost due to HF hospitalisation and death (all cause), the subgroup treatment effects were significant (p for interaction < 0.05) for patients with a prior history of HF decompensation or an ICD implant or a PHQ score of < 10 and for the patient-profiling subgroup. For this subgroup, subgroup treatment effects (p for interaction < 0.05) were also observed for total mortality and cardiovascular death. We consider the results hypothesis generating and the basis for the planning of future clinical research.

Given the greatly contrasting results between the recently published randomised clinical trials [9,10] and prior meta-analyses [6–8], we are of the opinion that this exploratory analysis is of value to potentially identify a HF patient population that may benefit from RTM, to be further investigated in well conducted and sufficiently powered randomised clinical trials in addition to perhaps, identifying the most clinically and economically meaningful outcome in telemedicine management clinical trials.

4.1. Results from prior studies

The TIM-HF trial was designed to determine whether physician-led RTM compared to usual care would positively impact on total mortality in ambulatory, stable chronic heart failure (CHF) patients. Over a median follow-up of 26 months (mean 21.5 months), compared to usual care, RTM had no significant effect on total mortality (hazard ratio, 0.97; 95% confidence interval [CI], 0.67 to 1.41; P = 0.87) [10]. The Telemonitoring to Improve Heart Failure Outcomes (Tele-HF) [9] study found that, compared to the usual care group, there was no reduction

Table 1
Days lost due to HF hospitalisation and death (all cause).[a]

		Treatment	Number of patients	Estimate of days lost	Tx p value for subgroup	P for interaction*
				Mean ± SE		
Median LV ejection fraction (%)[b]	≥27	RTM	182	21.30 ± 6.64	0.14	0.23
		Usual care	182	35.18 ± 6.64		
	<27	RTM	172	44.90 ± 6.83	0.82	
		Usual care	174	42.70 ± 6.79		
Episode of HF decompensation prior to randomisation[c]	Yes	RTM	299	30.06 ± 5.17	0.05	0.005
		Usual care	296	44.50 ± 5.20		
	No	RTM	55	47.47 ± 12.06	0.029	
		Usual care	60	11.02 ± 11.55		
Patient with ICD and episode of HF decompensation	Yes	RTM	130	29.42 ± 7.86	0.026	0.037
		Usual care	122	54.67 ± 8.11		
	No	RTM	224	34.71 ± 5.99	0.63	
		Usual care	234	30.61 ± 5.86		
PHQ depression score[d]	≥10 points	RTM	80	49.40 ± 10.05	0.16	0.035
		Usual care	78	29.14 ± 10.18		
	<10 points	RTM	266	27.80 ± 5.51	0.07	
		Usual care	267	41.95 ± 5.50		
HF decompensation + LVEF ≥ 25% and PHQ < 10 points	Yes	RTM	164	22.04 ± 7.00	0.029	0.033
		Usual care	169	43.52 ± 6.90		
	No	RTM	190	42.03 ± 6.51	0.42	
		Usual care	187	34.64 ± 6.56		

For each subgroup, the number of patients for whom data was available is shown in addition to the estimated adjusted means and standard error. The treatment effect P value is given for each subgroup category in addition to the overall P value for interaction. SE, standard error; Tx, treatment (i.e. of RTM); Estimated GFR, estimated glomerular filtration rate; LV, left ventricular; ICD, implantable defibrillator; PHQ-9, The depression model of the Patient Health Questionnaire; RTM, remote telemedical management. P values for the interaction between subgroup and treatment.

[a] Effect of RTM on days lost due to HF hospitalisation and death (all cause) in predefined subgroups.

[b] The median baseline left ventricular ejection fraction was used as cut-off for the ejection fraction subgroup.

[c] HF decompensation was defined as any hospitalisation for worsening heart failure within 24 months prior to inclusion in the study and /or treatment with IV diuretics within 24 months prior to inclusion in the trial.

[d] Patients with a PHQ-9 score between 0 and 9 were considered as having 'no depression' and patients with a score ≥ 10 points were considered as being 'depressed'.

Table 2
Baseline characteristics.

	Subgroup HF decompensation prior randomisation + LVEF ≥ 25% + PHQ-9 score < 10 points		
	Yes (n = 333)	No (n = 377)	p value
Demographics and history			
Age, years	67.6(± 11.1)	66.3 ± 10.2	0.05
Male	276(82.9)	301(79.8)	0.300
NYHA functional class			
II	184(55.3)	172(45.6)	0.010
III	149(44.7)	205(54.4)	
Left ventricular ejection fraction, %	30.4(± 3.5)	23.9(± 5.7)	<0.001
Body weight, kg	84.2(± 18.1)	85.1(± 19.0)	0.559
Body mass index, kg/m^2 †	28.2(± 5.2)	28.4(± 5.4)	0.667
Systolic blood pressure, mm Hg	124(± 17)	119(± 16)	<0.001
Diastolic blood pressure, mm Hg	75(± 9)	74(± 11)	0.094
Heart rate, beats/min	70(± 13)	71(± 13)	0.528
Time since HF diagnosis, years	6.5(± 6.6)	7.0(± 6.4)	0.062
Ischemic cardiomyopathy	188(56.5)	208(55.2)	0.731
Living alone	63(18.9)	89(23.6)	0.129
Myocardial infarction	165(49.5)	187(49.6)	0.989
Coronary revascularisation (CABG/PCI)‡	179(53.8)	194(51.5)	0.541
ICD implantation	137(41.1)	187(49.6)	0.024
CRT implantation	41(12.3)	73(19.4)	0.011
Medical comorbidities			
Hypertension	230(69.1)	246(65.3)	0.280
Hyperlipidemia	254(76.3)	274(72.7)	0.273
Diabetes mellitus	123(36.9)	158(41.9)	0.176
Hyperuricemia	115(34.5)	150(39.8)	0.149
Laboratory values at baseline			
Haemoglobin, g/L	138(± 17)	140(± 15)	0.374
Uric acid, μmol/L	444.62 (± 116.56)	445.35 (± 124.71)	0.827
C-reactive protein, mg/L	6.75(± 10.96)	6.80(± 9.41)	0.200
Serum sodium, mmol/L	140(± 3)	139(± 3)	0.106
Potassium, mmol/L	4.62(± 0.60)	4.59(± 0.60)	0.554
Serum creatinine, μmol/L	110(± 33)	115(± 36)	0.167
Estimated glomerular filtration rate, ml/minute/1.73 m^2 §	64.7(± 21.1)	62.0(± 20.9)	0.086
Total cholesterol, mmol/L	4.87(± 1.20)	4.83(± 1.25)	0.551
NT-proBNP, pg/mL	1949(± 3047)	2785(± 3738)	0.002
MR-proADM, nmol/L	0.93(± 0.49)	1.04(± 0.51)	<0.001
MR-proANP, pmol/L	293.4(± 205.1)	356.1(± 250.3)	0.001
Medications at baseline			
Diuretics	309(92.8)	356(94.4)	0.372
ACE inhibitors/ARBs	319(95.8)	358(95.0)	0.598
Digitalis glycoside	97(29.1)	123(32.6)	0.315
Beta-blockers	309(92.8)	348(92.3)	0.806
Aldosterone antagonists	207(62.2)	249(66.0)	0.281
Antiplatelet therapy/anticoagulant therapy	296(88.9)	345(91.5)	0.239
Allopurinol	66(19.8)	94(24.9)	0.104
Lipid-lowering	225(67.6)	243(64.5)	0.383
Vasodilaters‖	58(17.4)	53(14.1)	0.219
Antiarrhythmic	49(14.7)	69(18.3)	0.200
Insulin	47(14.1)	72(19.1)	0.076
Oral hypoglycaemic	52(15.6)	70(18.6)	0.298

Data are presented as means ± SD or n(%). Percentages are based on the number of patients who underwent randomisation. * The body-mass index is the weight in kilogrammes divided by the square of the height in metres. † Coronary revascularisation includes coronary artery by-pass grafting and percutaneous coronary intervention. ‡ Estimated glomerular filtration rate was calculated by using the MDRD formula: 186 × [Serum Creatinine (μmol/L) / 88.4] − 1.154 × Age − 0.203 × [1.21 if black] × [0.742 if female]. To convert the values for creatinine to milligrammes per decilitre, divide by 88.4. § Vasodilators include nitrates and Ca antagonist medications.
NYHA, New York Heart Association; ICD, implantable defibrillator; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; MR-proADM, Mid-regional pro-adrenomedullin; MR-proANP, Mid-regional pro-atrial natriuretic peptide; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; RTM, remote telemedical management.

in the risk of hospital re-admission (for any reason) or total mortality in HF patients assigned to telemonitoring who had been recently hospitalised for worsening HF (HR 1.04, 95% CI, 0.91 to 1.19, P = 0.75). The TELE-HF sub-group analyses did not identify a patient subgroup in which telemonitoring was effective.

The Trans-European Network-Home-Care Management System (TEN-HMS) Study [17] on the other-hand showed that HF patients who were randomised to telemedicine immediately following a hospitalisation for HF, had lower mortality and hospitalisation rates than patients in the usual care group.

The results of TIM-HF and Tele-HF do not corroborate with the results of the TEN-HMS-study and the meta-analyses. One of the reasons for this may be that the meta-analyses combined many small dissimilar RTM studies which investigated HF patients with varying risk profiles who were followed for different durations. In addition, the RTM approaches were not the same in all trials included in the meta-analyses. The meta-analyses have for the most part, collectively considered a telephone monitoring approach (with or without personal intervention) and a technology assisted monitoring approach relying on information communication technology with transfer of physiological data collected remotely, as remote patient monitoring (RPM). We would argue that these two telemedicine interventions are very different and therefore should not be considered as being the same intervention in the meta-analyses.

4.2. Subgroup results

The TIM-HF subgroup analyses show that some patient subgroups may potentially benefit from a RTM intervention while other subgroups may not. This is in contrast to the findings of the subgroup analyses of the TELE-HF trial. This may be explained by differences in (a) the population included in both studies, (b) the follow-up periods as the mean follow-up was 21.6 months in TIM-HF whereas in TELE-HF, each patient was followed for 6 months. Compliance with the transfers of the data may also have had an impact on the subgroup analysis as at the final visit in TELE-HF, only 55% of the patients allocated to the intervention group were still using the system three times a week. In TIM-HF, 81% of patients allocated to the intervention group were at least 70% compliant with the daily transfer of data to the telemedicine centres and had no break in information transfer >30 days (except during hospitalisations).

Previous clinical trials have shown the negative impact which depression has on clinical outcomes in patients with heart failure including an increased risk of poor functional status, hospital readmission, and death. In the present study, the subgroup treatment effects were significantly different from each other for the PHQ-9 subgroup for all cause mortality (p for interaction = 0.027) and for the days lost due to hospitalisation for worsening HF and total mortality. As this has not been assessed in the previous RTM studies, we advocate screening in addition for depression in future RTM studies.

We consider the results of the TIM-HF subgroup analyses hypothesis generating and the basis for the planning of future clinical research. TIM-HF2 is currently planned using the above described triple-subgroup.

4.3. Choice of clinical outcome and duration of follow-up

Telemedical management approaches rely on the principle that a regular observation of selected physiological factors will enable early detection of clinical deterioration and therefore enable a timely intervention to prevent unfavourable outcomes. In our opinion, with this kind of adjunct intervention in the management of HF patients, it is more clinically and economically appropriate to focus on keeping HF patients alive and out of hospital rather than focusing on mortality alone. HF hospitalisations are a major burden to society in addition to negatively impacting on quality of life. We would argue that the outcome days lost due to HF hospitalisation and death (all cause) is an outcome of quality of life adjusted survival and is perhaps a more appropriate study outcome to use to assess the impact of telemedicine management in HF patients.

Table 3
Incidence of events.

Outcomes		RTM (n = 333)		Usual care (n = 377)			p value	P for interaction
		No. events	No. of patients with event (incidence per 100 patient-yr at risk)	No. events	No. of patients with event (incidence per 100 patient-yr at risk)	HR (95% CI)		
Primary outcomes								
Total mortality								
Prior HF decompensation + LVEF ≥ 25% + PHQ-9 < 10 points	Yes	19	19 (6.19)	30	30 (9.91)	0.63 (0.35–1.11)	0.108	0.042
	No	35	35 (10.50)	25	25 (7.56)	1.38 (0.83–2.31)	0.216	
Cardiovascular mortality								
Prior HF decompensation + LVEF ≥ 25% + PHQ-9 < 10 points	Yes	12	12 (3.91)	25	25 (8.26)	0.48 (0.24–0.95)	0.030	0.024
	No	28	28 (8.40)	21	21 (6.35)	1.32 (0.75–2.32)	0.341	
Secondary outcomes								
Hospitalisation for heart failure or cardiovascular death								
Prior HF decompensation + LVEF ≥ 25% + PHQ-9 < 10 points	Yes	47	30 (10.44)	66	43 (15.34)	0.68 (0.43–1.09)	0.108	0.144
	No	106	57 (18.72)	94	52 (17.63)	1.06 (0.73–1.55)	0.750	
All-cause hospitalisation								
Prior HF decompensation + LVEF ≥ 25% + PHQ-9 < 10 points	Yes	169	82 (36.71)	173	82 (37.22)	0.98 (0.72–1.34)	0.917	0.270
	No	317	110 (51.85)	221	97 (41.02)	1.24 (0.94–1.63)	0.126	
Cardiovascular hospitalisation								
Prior HF decompensation + LVEF ≥ 25% + PHQ-9 < 10 points	Yes	90	57 (22.50)	108	60 (24.31)	0.93 (0.65–1.34)	0.693	0.322
	No	200	84 (33.06)	140	72 (27.70)	1.19 (0.87–1.62)	0.287	
Hospitalisation for heart failure								
Prior HF decompensation + LVEF ≥ 25% + PHQ-9 < 10 points	Yes	35	23 (8.00)	41	30 (10.70)	0.75 (0.44–1.29)	0.297	0.583
	No	78	41 (13.47)	73	44 (14.92)	0.91 (0.59–1.39)	0.216	

LVEF, Left ventricular ejection fraction; PHQ-9, The depression model of the Patient Health Questionnaire; CI, confidence interval; RTM, remote telemedical management. Hazard ratio, comparison of RTM with Usual Care.

4.4. Study limitations

The TIM-HF trial did not have adequate power to assess therapeutic efficacy in subgroups and our results should therefore be interpreted with caution. Our analyses were underpowered to detect the modest differences in subgroup effects that one might expect to detect if there was a true subgroup effect and our inability to find significant interactions does not show that the treatment effect seen overall necessarily applies to all patients.

4.5. Clinical and research implications

We believe that the lack of a benefit seen in the TIM-HF and Tele-HF studies does not rule out the potential of telemedical management as an effective adjunct to disease management in a defined group of HF patients. An effective combination of the current medical management strategies for HF patients with today's technological resources should logically impact positively on the overall management of these patients by reducing the need for the frequent hospital readmissions for worsening HF and improve quality of life. Future clinical research in telemedical management of HF patients should focus on the identification of the target population most likely to respond to this intervention. In addition, the selection of the most pertinent outcome to assess its impact on the management of HF patients is crucial. As suggested by our exploratory subgroup analyses, profiling of such patient groups may be possible.

5. Conclusion

Heart failure is a dynamic disease. Improvements in the out-patient management of patients with chronic HF are needed to address the increasing burden of worsening HF requiring re-admission to hospital. Going forward, the role of telemedicine management as an adjunct intervention in HF management needs to be investigated in future, well designed randomised clinical trials. The latter should focus on the target population most likely to benefit from this intervention and use the most clinically appropriate outcome to assess the clinical and economical benefit of this intervention.

Conflict of interest

SDA is consultant for Robert Bosch Healthcare GmbH, Thermo Fisher Scientific Germany and St. Jude Medical GmbH and received honoraria for speaking from Thermo Fisher Scientific Germany and St. Jude Medical GmbH.

No other potential conflict of interest relevant to this article was reported.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [18].

Appendix

The members of the TIM-HF study group are as follows:

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