Telemedical Interventional Management in Heart Failure (II) to Improve Outcomes: Extended 12-Month Follow-up after stopping Remote Patient Management (RPM)

Prof. Friedrich Koehler, MD, FESC

On behalf of the TIM-HF2 study group: Kerstin Koehler, Sandra Prescher, Oliver Deckwart, Bridget -Anne Kirwan, Karl Wegscheider, Eik Vettorazzi, Susanne Lezius, Sebastian Winkler, Volker Moeller, Gunnar Fiss, Judith Schleder, Magdalena Koehler, Karl Stangl, Stefan D. Anker

Clinicaltrials.gov identifier: NCT01878630

Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Abbott (Honoraria for advisory board activities))
- Research contracts (Research Grant of the German Federal Ministry Education and Research: TIM-HF2)
- Others (Cochlear AG; Boston Scientific (both Honoraria for lectures))

Background

- Remote Patient Management (RPM) consists of a combination of the following: (a) telemonitoring, (b) patient education, and (c) cooperation between a Telemedical Centre (TMC), patients and GPs/ local cardiologists.
- RPM should enable an early detection of HF decompensation, better adherence to lifestyle changes, medication, and interventions to prevent HF-hospital admissions.
- Most RPM intervention trials have followed patients for ≤ 12 months.
- There is very limited mortality / morbidity data available for patients included in RCTs after the RPM intervention was stopped.
- Such data could be pivotal in defining the optimal duration of a RPM intervention when implementing RPM in a real-life setting.

TIM-HF2: Study Design

Study type/patient characteristics: multicentre RCT in Germany, 1538 heart failure (HF) patients, hospitalised for HF maximally 12 months previously, with no major depression (PHQ-9<10) and with a LVEF ≤45% or if >45%, diuretics mandatory; 12-months follow-up under intervention

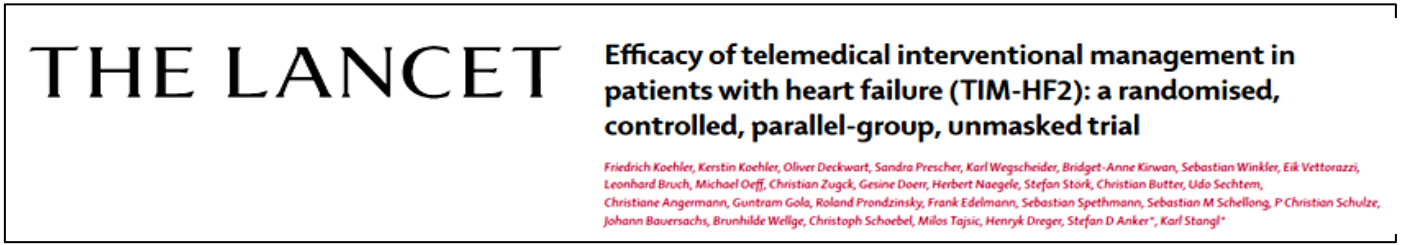
Primary Endpoint: % days lost due to unplanned CVhospital admissions and all-cause death

Secondary Endpoints: all-cause death, cardiovascular death, recurrent HF/CV-hospital admissions, health economics, biomarkers, quality of life

Intervention: Remote Patient Management (RPM) vs Usual Care (UC)

Koehler F et al. Eur J Heart Fail. 2018;20:1485-93

TIM-HF2: Summary of Results


THE LANCET

Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial

Friedrich Koehler, Kerstin Koehler, Oliver Deckwart, Sandra Prescher, Karl Wegscheider, Bridget-Anne Kirwan, Sebastian Winkler, Eik Vettorazzi, Leonhard Bruch, Michael Oeff, Christian Zugck, Gesine Doerr, Herbert Naegele, Stefan Störk, Christian Butter, Udo Sechtem, Christiane Angermann, Guntram Gola, Roland Prondzinsky, Frank Edelmann, Sebastian Spethmann, Sebastian M Schellong, P Christian Schulze, Johann Bauersachs, Brunhilde Wellge, Christoph Schoebel, Milos Tajsic, Henryk Dreger, Stefan D Anker*, Karl Stangl*

Primary outcome (% days lost due to unplanned CV hospital admissions & all-cause death)

- 20% reduction in favor of RPM (ratio 0.80, 95%, CI 0.65–1.00; p=0.046).
- 17.8 days/year vs 24.2 days/year lost for RPM and UC, respectively

All-cause death:

- 30% reduction in favor of RPM (hazard ratio [HR] 0.70, 95%, CI 0.50–0.96; p=0.028).

Koehler F et al. Lancet. 2018;392:1047-57

TIM-HF2 extended follow-up period: Rational

- The extended follow-up period was pre-specified in the TIM-HF2 trial protocol.
- **Objective:** To investigate if the benefits seen on morbidity and mortality for the RPM group during the 12-month follow-up in the main TIM-HF2 trial would be sustained over the subsequent 12 months after stopping the RPM intervention.

TIM-HF2 extended follow-up period: Methods

- Upon completion of the TIM-HF2 final study visit, the RPM intervention was stopped and all patients were followed for morbidity and mortality for an additional 12 months (‘extended follow-up period’) in a real-world setting.
- Information concerning hospital admissions and deaths was obtained via the patients’ health insurance records.
- The robustness of this method was validated over the course of the main TIM-HF2 trial by comparing the health insurance records with the events observed at the TMC for RPM group.
- The Clinical Endpoint Committee (CEC) adjudicated all events occurring during the extended follow-up period using the same criteria as that for the main TIM-HF2 trial.

TIM-HF2 extended follow-up period: Pre-defined outcomes

Primary Outcome

% days lost due to unplanned cardiovascular (CV) hospital admissions and all-cause death

Main Secondary Outcomes

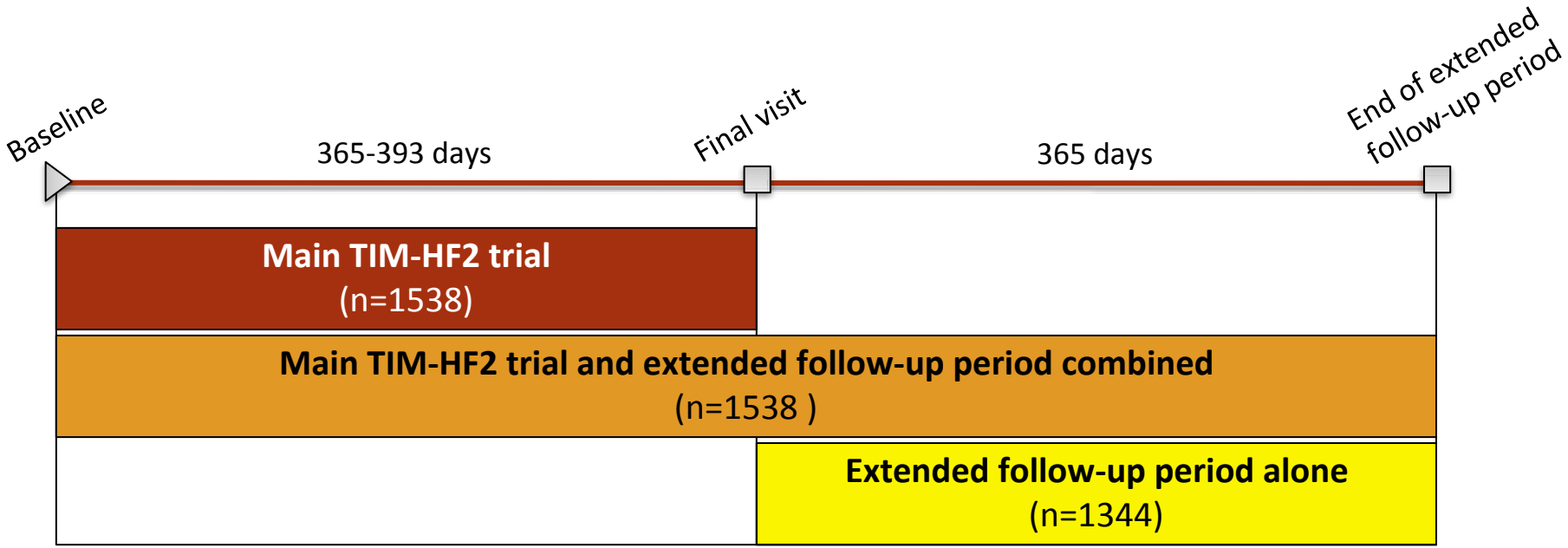
a. All-cause death
b. CV death
c. Recurrent unplanned HF hospital admissions and all-cause death
d. Recurrent unplanned HF hospital admissions and CV-death

Patient characteristics at the start of extended follow-up period

	RPM (n=671)	UC (n=673)	p
Age (years)	71 (11)	71 (11)	0.60
Men	468 (70%)	468 (70%)	0.93
NYHA class			0.17
I	97 (15%)	76 (12%)	
II	347 (52%)	329 (50%)	
III	214 (32%)	239 (37%)	
IV	5 (1%)	8 (1%)	
Bodyweight (kg)	88 (21)	89 (20)	0.29
Self-Care Behaviour Scale (G9-EHFScBS-questionnaire)	14 (5)	16 (6)	<0.0001
No HF hospital admissions during the main TIM-HF2 trial	571 (85%)	539 (80%)	0.10
Estimated GFR (mL/min per 1.73m² of body surface area, Cockroft-Gault)	57 (41-83)	60 (42-85)	0.53
NT-proBNP (pg/mL)	1057 (390-2180)	1071 (396-2699)	0.27
MR-proADM (nmol/L)	1 (1-1)	1 (1-1)	0.64

Data are mean (SD) or patients (%)

Definition of the follow-up periods



Primary Outcome (I)

Main TIM-HF2 trial and extended follow-up period combined

	RPM (n=765)		UC (n=773)			
	No. of patients with event (%)	Weighted average of percentages (95% CI)	No. of patients with event (%)	Weighted average of percentages (95% CI)	Ratio RPM vs. UC (95% CI)	p
% days lost due to unplanned CV hosp. and all-cause death	382 (50%)	9.28% (7.76–10.81)	398 (51%)	11.78% (10.08–13.49)	0.79 (0.62–1.00)	**0.0486**
Days lost		67.7 days (56.6–78.9)		86.0 days (73.6–98.5)		

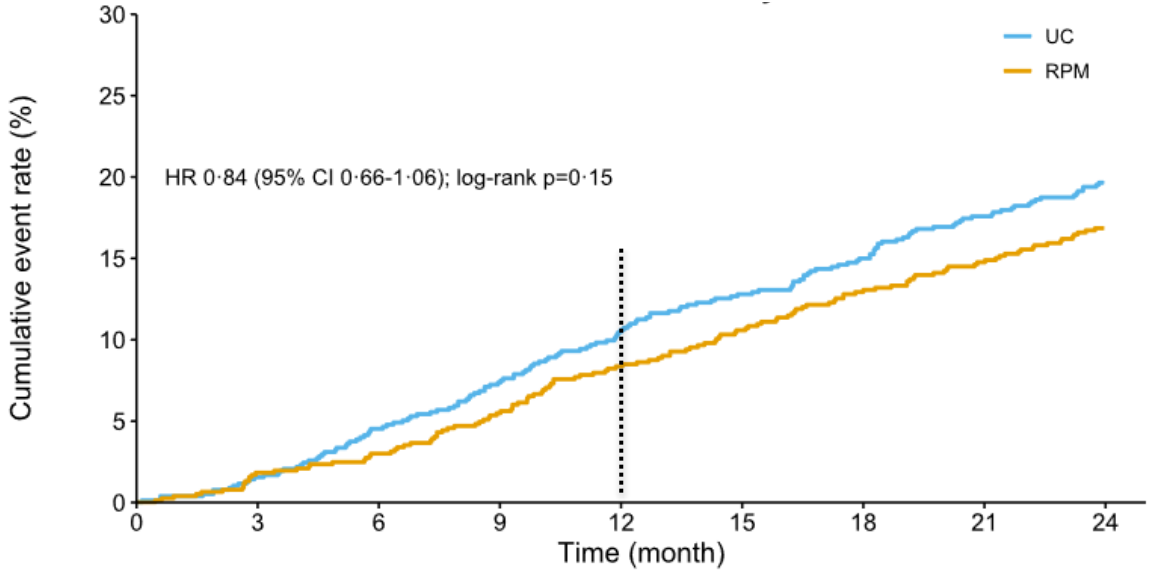
Primary outcome (II)

Extended follow-up period alone

	RPM (n=671)		UC (n=673)			
	No. of patients with event (%)	Weighted average of percentages (95% CI)	No. of patients with event (%)	Weighted average of percentages (95% CI)	Ratio RPM vs. UC (95% CI)	p
% days lost due to unplanned CV hosp. and all-cause death	198 (30%)	5.95% (4.59–7.31)	194 (29%)	6.64% (5.19–8.08)	0.97 (0.78–1.21)	**0.82**
Days lost (days/year)		21.7 days (16.7–26.7)		24.2 days (19.0–29.5)		

All-cause death

Main TIM-HF2 trial and extended follow-up period combined

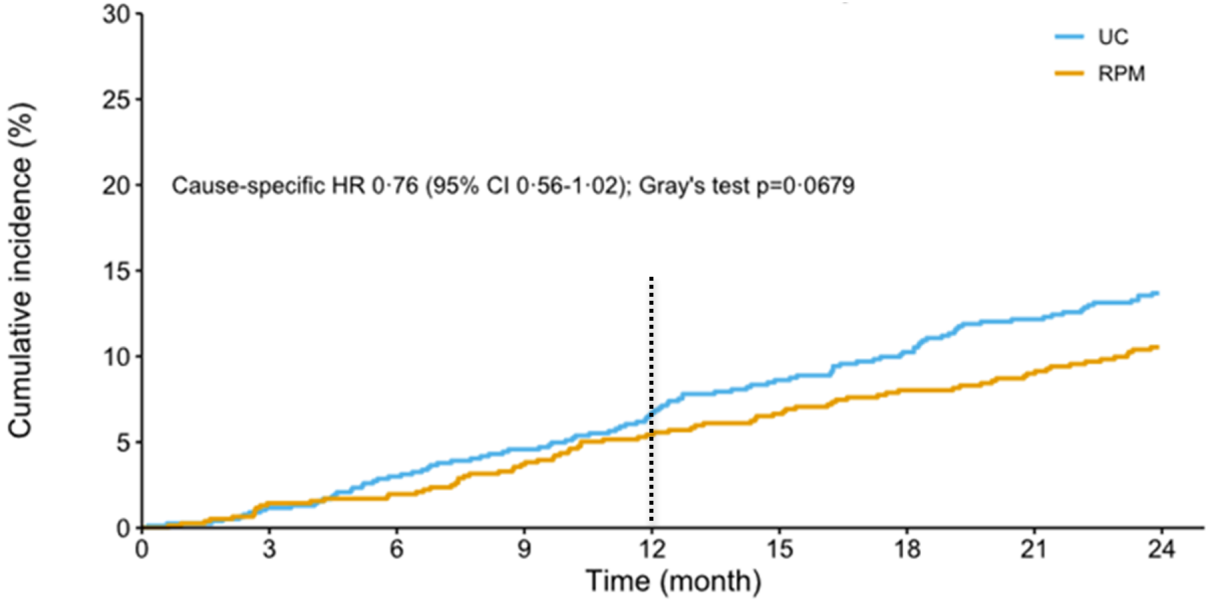


Number at risk

UC	773	761	738	716	692	674	657	637	621
RPM	765	751	742	723	701	684	666	652	636

Cardiovascular death

Main TIM-HF2 trial and extended follow-up period combined



Number at risk

UC	773	761	738	716	692	674	657	637	621
RPM	765	751	742	723	701	684	666	652	636

Aalen-Johansen cumulative incidence

Recurrent HF hospital admissions (I)

Main TIM-HF2 trial

	RPM (n=765, 739.6 patient years)			UC (n=773, 754.4 patient years)				
	No. of patients with HF hosp. (%)	No. of HF hosp.	Incidence (95% CI)	No. of patients with HF hosp. (%)	No. of HF hosp.	Incidence (95% CI)	Ratio RPM vs. UC (95% CI)	p
HF hospital admissions and all-cause death	164 (21)	280	0.441 (0.369–0.528)	223 (29)	405	0.653 (0.553–0.771)	**0.676** (0.529–0.862)	**0.0016**
HF hospital admissions and CV death	153 (20)	265	0.414 (0.345–0.498)	210 (27)	379	0.596 (0.502–0.707)	**0.696** (0.541–0.894)	**0.0047**

IRR=Incidence rate ratio; incidence = events/100 patient years of follow-up; CV=cardiovascular; HF=heart failure; hosp.=hospital admissions

Recurrent HF hospital admissions (II)

Main TIM-HF2 trial and extended follow-up period combined

	RPM (n=765, 1409.3 patient years)			UC (n=773, 1407.4 patient years)				
	No. of patients with HF hosp. (%)	No. of HF hosp.	Incidence (95% CI)	No. of patients with HF hosp. (%)	No. of HF hosp.	Incidence (95% CI)	Ratio RPM vs. UC (95% CI)	p
HF hospital admissions and all-cause death	274 (36)	539	0.503 (0.434–0.585)	312 (40)	656	0.661 (0.572–0.764)	**0.762** (0.619–0.938)	**0.0103**
HF hospital admissions and CV death	247 (32)	489	0.441 (0.377–0.516)	288 (37)	606	0.589 (0.507–0.685)	**0.749** (0.603–0.930)	**0.0089**

IRR=Incidence rate ratio; incidence = events/100 patient years of follow-up; CV=cardiovascular; HF=heart failure; hosp.=hospital admissions

Recurrent HF hospital admissions (III)

Extended follow-up period alone

	RPM (n=671, 639.9 patient years)			UC (n=673, 639.8 patient years)				
	No. of patients with HF hosp. (%)	No. of HF hosp.	Incidence (95% CI)	No. of patients with HF hosp. (%)	No. of HF hosp.	Incidence (95% CI)	Ratio RPM vs. UC (95% CI)	p
HF hospital admissions and all-cause death	148 (22)	229	0.447 (0.363–0.552)	140 (21)	249	0.521 (0.425–0.640)	**0.858** (0.640–1.150)	**0.31**
HF hospital admissions and CV death	131 (20)	204	0.373 (0.299–0.464)	129 (19)	231	0.471 (0.381–0.582)	**0.791** (0.583–1.074)	**0.13**

IRR=Incidence rate ratio; incidence = events/100 patient years of follow-up; CV=cardiovascular; HF=heart failure; hosp.=hospital admissions

Conclusions

- The positive impact of RPM on morbidity persisted up to one year after stopping the RPM intervention, but in an attenuated manner.
- RPM resulted in a significant reduction in recurrent HF-related hospital admissions over the course of the main TIM-HF2 trial and in the two time periods combined.
- All-cause (& CV) mortality were similar between groups after stopping RPM.
- Patients initially assigned to RPM had a better self-management behaviour score at the start of the extended follow-up period – this was not associated with a sustained impact on any of the outcomes during the follow-up period alone.
- **In summary, the results suggest that the RPM intervention is only effective, if the RPM intervention is 'turned on'.**

Acknowledgements

- All study patients of the TIM-HF2 trial
- German Federal Ministry Education and Research (Research grant number 13KQ0904B)
- Health insurance companies for providing data regarding clinical events
- PD Dr. Christoph Melzer for endpoint adjudication (CEC)
- Ann-Kathrin Ozga for supporting the statistical analysis (Medical Center Hamburg-Eppendorf (UKE), Institute of Medical Biometry and Epidemiology)

Supplement

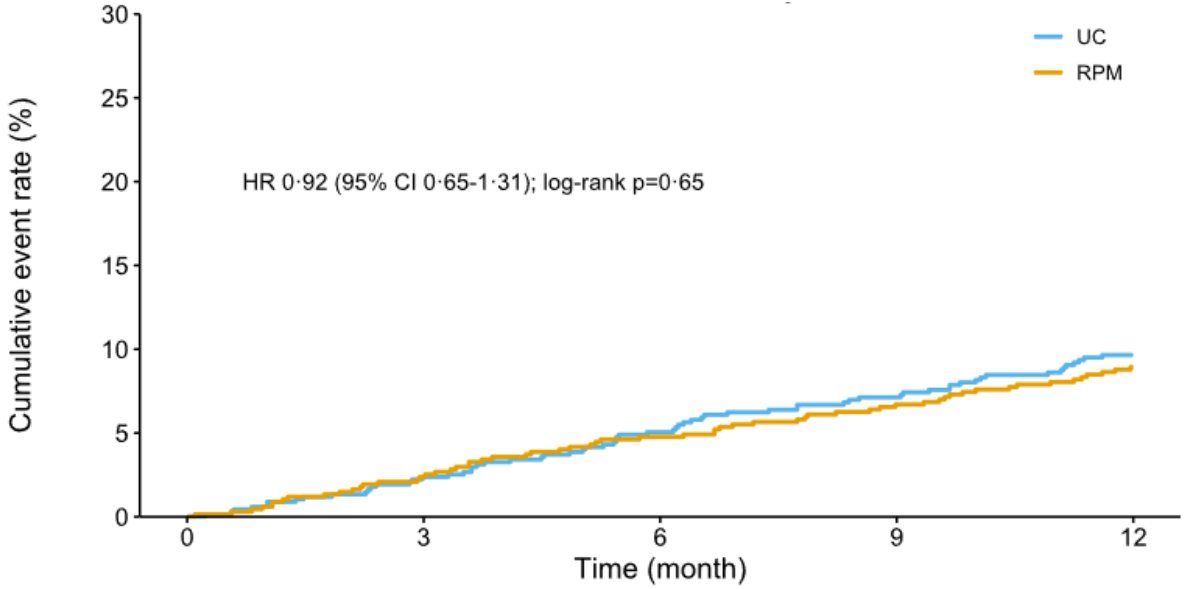
Medication at the start of extended follow-up period

	RPM (n=671)	UC (n=673)	p
ACE inhibitor or ARB	523 (79%)	493 (79%)	0.83
ARN inhibitor	66 (10%)	55 (9%)	0.46
Beta-blocker	600 (91%)	561 (90%)	0.43
Aldosterone antagonist	337 (51%)	315 (50%)	0.79
Loop diuretics	612 (93%)	568 (91%)	0.19
Thiazides	140 (21%)	139 (22%)	0.67
Vitamin K antagonists	169 (26%)	153 (24%)	0.63
NOACs	166 (25%)	156 (25%)	0.92
Digitalis glycosides	100 (15%)	104 (17%)	0.47
Antiarrhythmic drugs	81 (12%)	73 (12%)	0.74

Data are patients (%)

All-cause death (II)

Extended follow-up period alone



Number at risk

UC	673	657	639	625	608
RPM	671	655	639	627	612