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Optimized HF therapy in patients with advanced cancer in palliative care: dosing strategies from the EMPATICC trial

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Abstract

Cardiac wasting occurs in patients with end-stage cancer, leading to the development of heart failure (HF)-like symptoms characterized by dyspnea, reduced physical function, and diminished quality of life. EMPATICC (EMPower the heArt of patients with Terminal Cancer using Cardiac medicines) is a randomized controlled trial designed to evaluate the impact of optimized HF therapy in patients with advanced cancer receiving specialized palliative care. Given the susceptibility to adverse drug events in this vulnerable population, the trial employed a protocol-driven approach for the initiation and titration of each medication. EMPATICC is a multi-center, randomized, double-blind, controlled, proof-of-concept trial that enrolled 93 patients with stage IV solid tumors (per Union for International Cancer Control [UICC]), under palliative care, with clinical features indicating cardiovascular risk and functional limitation. Participants were randomized 1:1 to receive optimized HF therapy, including sacubitril/valsartan, empagliflozin, ivabradine, and ferric carboxymaltose (FCM), or 1-4 placebo therapies on top of usual care. All trial medications (or placebo) that was available in tablet form were provided in pre-packed containers to support blinding. Blue placebo tablets were used for empagliflozin, white tablets for sacubitril/valsartan, and pink tablets for ivabradine. Blinded staff members did not have access to individual tablet packaging or knowledge of color allocations. Additionally, the meaning of the color-coded tablets was not disclosed to the blind staff members throughout the trial. Dosing protocols were guided by predefined criteria, including blood pressure, renal function, heart rate, hemoglobin, and body weight, and they were implemented by unblinded staff. Algorithms accounted for prior RAAS inhibitor exposure when initiating sacubitril/valsartan; ensured hemodynamic stability and sinus rhythm for ivabradine; assessed renal reserve when starting empagliflozin to support safe and effective titration; and accounted for body weight and hemoglobin levels when initiating FCM. To ensure consistent implementation across five centers in Germany, visual flowcharts were designed. The EMPATICC trial provides a practical, protocol-driven approach for delivering HF therapy in the palliative oncology setting. Dosing algorithms outlined in this study could serve as a model for structured cardiovascular care in patients with advanced cancer.

Key words: heart failure therapy; end-stage cancer; cardiac wasting; clinical trial.

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Introduction

Patients with advanced cancer experience a significant decline in physical function and an increased dependency for their basic daily activities. In this vulnerable population, preserving functional self-care, which includes personal hygiene and short-distance walking, is crucial for maintaining patient autonomy and overall quality of life. Advanced cancer patients show a high prevalence of cardiovascular compromise, including elevated cardiac biomarkers, left ventricular dysfunction, common valvular heart disease, and pericardial effusions.^{1,2} Clinically, these changes present as heart failure (HF)-like symptoms, such as dyspnea, functional impairment, and diminished quality of life.^{3,4} Cardiovascular complications are also estimated to account for up to 30% of mortality in patients with end-stage cancer.^{5,6} While cardio-oncology trials have primarily focused on mitigating cardiotoxicity from specific anti-cancer therapies, there are no studies addressing cardiac dysfunction and symptomatic burden in end-stage cancer patients using established HF therapies. The EMPATICC (EM-Power the heART of patients with Terminal Cancer using Cardiac medicines) is a randomized clinical trial designed to evaluate the safety and efficacy of an optimized HF therapy regimen -including sacubitril/valsartan, empagliflozin, ivabradine, and ferric carboxymaltose- combined with usual care. The trial investigates whether this optimized regimen can improve self-care ability, physical functioning, and overall quality of life in patients with advanced cancer receiving palliative care. Patients with advanced cancer are susceptible to adverse drug effects due to frailty, polypharmacy, and systemic compromise, warranting careful therapeutic planning. To ensure safety and tolerability in this frail population, the EMPATICC trial employed structured, protocol-driven algorithms for the initiation and titration of each medication. We aim to detail the dosing strategy for each agent, highlighting the rigorous and systematic methodology used to achieve the maximal tolerated and clinically effective dosages.

Methods

Overview of study design and participants

EMPATICC is a multicenter, investigator-initiated, randomized, double-blind, controlled proof-of-concept trial conducted across five centers in Germany. The trial aimed to enrol 72–108 patients. Participants were randomized 1:1 to either op-

timized HF therapy (sacubitril/valsartan, empagliflozin, ivabradine, ferric carboxymaltose, plus usual care) or placebo on top of usual care. To maintain blinding, treatment decisions were performed by unblinded investigators who were not involved in patient care or assessments. The trial includes a 30-day randomized phase followed by a 30-day open-label extension where all patients receive open-label optimized HF therapy, allowing additional safety data collection in this high-risk group. The study follows Good Clinical Practice and the Declaration of Helsinki. Ethics approval was obtained from all participating sites. Universitätsmedizin Essen sponsors the trial with unrestricted support from the BROST Stiftung.

Eligible participants were adults (≥ 18 years) with stage 4 solid cancer under palliative care, an expected survival of 1–6 months, and optimized pain control. Inclusion required ≥ 2 cardiovascular risk markers: resting heart rate > 70 bpm, N-terminal-pro-B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/mL, high-sensitivity troponin > 99 th percentile, left ventricular ejection fraction (LVEF) $< 55\%$, $> 15\%$ reduction in LV mass since cancer diagnosis (via echocardiography), transferring saturation (TSAT) $< 20\%$, or moderate/high likelihood of heart failure with preserved ejection fraction (HFpEF) per HFA-PEFF score. Additionally, ≥ 1 functional/symptomatic criterion was required: time to walk 4 meters ≥ 6.0 seconds or inability to do so, inability to wash oneself ≥ 3 of the last 7 days, or NYHA class IV symptoms. These criteria ensured evidence of HF progression and clinical frailty.

The primary endpoint was a hierarchical composite evaluated using the win ratio approach. It comprised: i) the number of days alive and able to wash oneself, ii) the 4-meter walking ability at days 10, 20, and 30, and iii) the patient-reported global assessment (PGA) of well-being on a 7-point Likert scale. Key secondary endpoints included the individual components of the primary endpoint, the change in global quality of life (i.e., EORTC QLQ-C15-PAL question 15), and the change in NT-proBNP during 30 days of follow-up. Safety endpoints include all-cause mortality and monitoring adverse events such as acute kidney injury, hyperkalemia, and symptomatic hypovolemia and hypotension. Statistical analyses followed the ICH E9 guidelines and were pre-specified in the statistical analysis plan. Win ratio approach (Finkelstein–Schoenfeld) was used for primary analysis, with additional modelling using mixed-effects models and proportional odds regression as appropriate.

The trial enrolled 93 patients and adhered to the principles of Good Clinical Practice and the Declaration of Helsinki. Detailed methodological details, including eligibility, statistical analysis, and sample size calculation, are published separately in dedicated design paper.⁷

Medication and dosing strategy

Specifications of the four investigational medicinal products, including pharmaceutical dosage and administration route, are detailed in Table 1. All trial medications and their corresponding placebos were provided in pre-packed containers to support blinding. Blue placebo tablets were used for empagliflozin, white tablets for sacubitril/valsartan, and pink tablets for ivabradine. Blinded staff members did not have access to individual tablet packaging or knowledge of color allocations. Additionally, the meaning of the color-coded tablets was not disclosed to the blind staff members throughout the trial. All treatment decisions and medication adjustments were made by unblinded staff.

Dosing strategy for sacubitril/valsartan

Sacubitril/valsartan was initiated in patients who met hemodynamic eligibility and had no contraindications to renin-angiotensin receptor blockade. Dosage was determined based on whether patients were on prior renin-angiotensin-aldosterone system (RAAS) inhibitors (Figures 1 and 2). For patients without prior RAAS-inhibitor therapy, sacubitril/valsartan was initiated at 24/26 mg twice daily if systolic blood pressure (RRsys) was ≥ 100 mmHg. If RRsys was < 100 mmHg on day 1, sacubitril/valsartan was withheld, and blood pressure was monitored daily. Once RRsys reached ≥ 100 mmHg on any subsequent day, sacubitril/valsartan was delayed for an additional 7 days to ensure hemodynamic stability. Thereafter, sacubi-

Table 1. Overview of heart failure medications used in the EMPATICC trial.

Medication	Available strengths	Dosage form	Route of administration	Notes
Sacubitril/valsartan	24/26 mg, 49/51 mg, 97/103 mg	Film-coated tablet	Oral	Up-titrated based on hemodynamics and tolerability
Ivabradine	5 mg, 7.5 mg	Tablet	Oral	Initiation and escalation guided by resting heart rate
Empagliflozin	10 mg	Tablet	Oral	Initiated only if RRsys ≥ 95 mmHg and eGFR ≥ 20 mL/min/1.73 m ²
Ferric carboxymaltose	50 mg/mL	Sterile solution (infusion/injection)	Intravenous	Dose individualized based on weight and hemoglobin level

RRsys, resting systolic blood pressure; eGFR, estimated glomerular filtration rate; mg, milligram; mL, milliliter; HF, heart failure.

Sacubitril / Valsartan – for patients without prior RAAS-inhibitor therapy

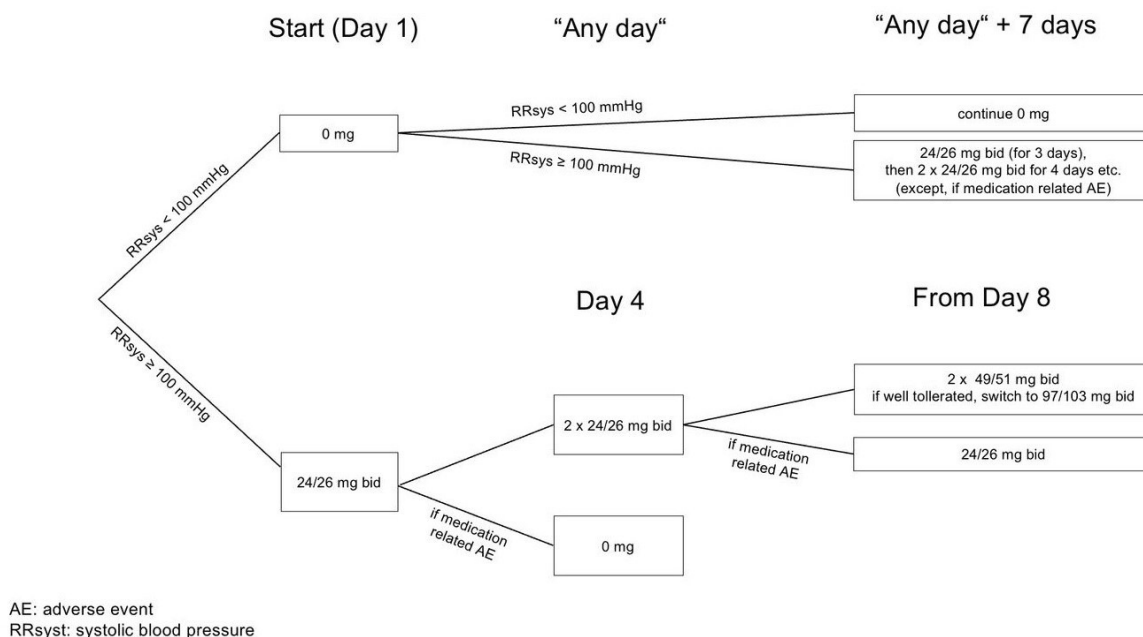


Figure 1. Dose titration scheme of sacubitril/valsartan for patients without prior use of renin-angiotensin aldosterone inhibitor.

Sacubitril / Valsartan – for patients with prior RAAS-inhibitor therapy

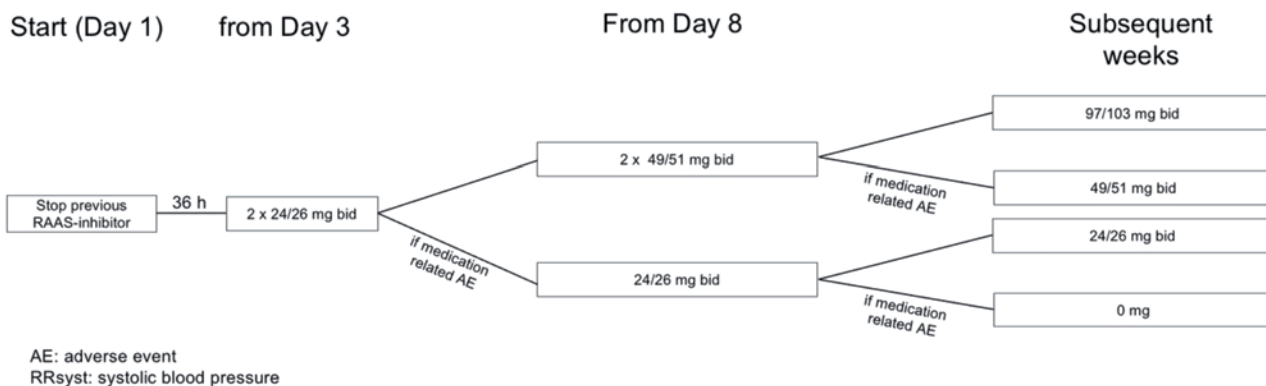


Figure 2. Dose titration scheme of sacubitril/valsartan for patients switching from renin-angiotensin aldosterone inhibitor.

tril/valsartan was initiated at 24/26 mg twice daily for 3 days, followed by an increase to two tablets of 24/26 mg twice daily for 4 additional days from Day 4. If tolerated, the dose was increased to 49/51 mg twice daily from Day 8, and further titrated to 97/103 mg twice daily as tolerated. If medication-related adverse events such as symptomatic hypotension, dizziness, or renal dysfunction occurred at any stage, the dose was then reduced to the previously tolerated level or held. Reinitiation was then considered after clinical stabilization. For patients previously treated with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a

36-hour washout period was observed before initiation. Sacubitril/valsartan was initiated at 24/26 mg twice daily. If tolerated, the dose was escalated to 49/51 mg twice daily beginning on Day 8, and further increased to 97/103 mg twice daily in subsequent weeks. In cases of medication-related adverse events, medication was down-titrated or discontinued.

Dosing strategy for ivabradine

Ivabradine was prescribed in patients with a resting heart rate ≥ 75 bpm and sinus rhythm (Figure 3). Patients with a heart rate

Ivabradine

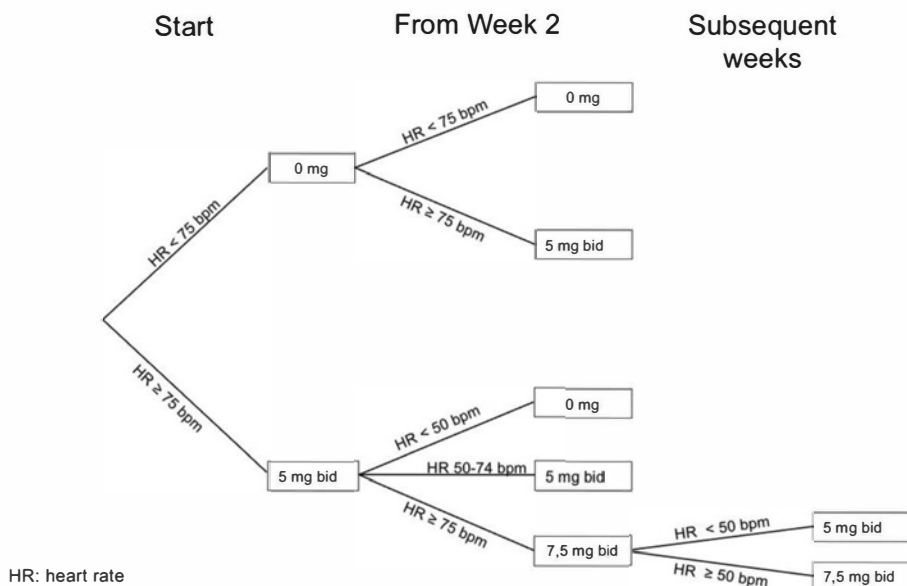


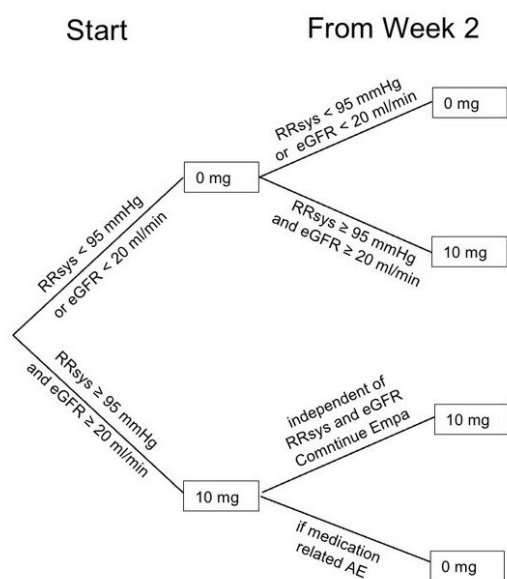
Figure 3. Dose titration scheme of ivabradine.

<75 bpm were not started on ivabradine and were reevaluated after 2 weeks. Ivabradine was initiated at 5 mg twice daily in eligible patients. At week 2 assessment, for eligible patients, if the heart rate remained ≥ 75 bpm and the initial dose was tolerated, up-titration to 7.5 mg twice daily was considered. If the heart rate dropped below 50 bpm or bradycardia-related symptoms developed (fatigue, dizziness), the dose was reduced or discontinued. If heart rate remained 50–74 bpm, dosing was continued at 5 mg twice daily.

Dosing strategy for empagliflozin

Empagliflozin 10 mg once daily was initiated only if systolic blood pressure (RRsys) ≥ 95 mmHg and an estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m² (Figure 4). Patients who did not meet these initiation thresholds at baseline were reassessed at the 2-week visit and started on empagliflozin if

Empagliflozin



AE: adverse event
RRsyst: systolic blood pressure

Figure 4. Dose titration scheme of empagliflozin.

RRsys and eGFR met the same criteria. Once initiated, empagliflozin 10 mg daily was continued regardless of fluctuations in blood pressure or eGFR. In cases of medication-related adverse events such as dehydration, hypotension, and acute kidney injury, dosing was paused and re-evaluated at the next visit.

Dosing strategy for ferric carboxymaltose (FCM)

FCM was administered to patients with transferrin saturation (TSAT) <20%. FCM was administered as a solution for infusion (50 mg/mL) diluted in 0.9% sodium chloride, via intravenous route. Dosing of FCM was based on patient body weight and baseline hemoglobin levels (Table 2). For patients with hemoglobin <10 g/dL (or 6.2 mmol/L), those weighing less than 35 kg received 500 mg, those between 35 kg and <70 kg received 1500 mg, and those weighing ≥ 70 kg received 2,000 mg of intravenous FCM. For patients with hemoglobin between 10 and <14 g/dL (6.2 to <8.7 mmol/L), the respective doses were 500 mg for body weight <35 kg, 1000 mg for those weighing 35 to <70 kg, and 1500 mg for patients weighing ≥ 70 kg. In patients with hemoglobin ≥ 14 g/dL (≥ 8.7 mmol/L), a standard dose of 500 mg was administered, irrespective of the weight. If the total calculated dose exceeded 1000 mg, the remaining amount was delivered as a second infusion at least 7 days later. To ensure blinding, all infusions, including placebo saline, were delivered using black infusion sets wrapped in opaque foil. In case of adverse events, such as hypotension and hypersensitivity, dosing was paused and reassessed at the next study visit.

Discussion

The EMPATICC trial provides a novel, methodologically rigorous approach to the application of HF pharmacotherapy for managing symptomatic burden secondary to cardiovascular compromise in the setting of advanced cancer receiving specialized palliative care. Given the narrow therapeutic window and increased risk of adverse effects in patients with advanced cancer, a structured, protocol-driven dosing approach is essential to ensure safe, consistent, and individualized implementation of HF therapy.

The protocol of the EMPATICC trial targeted multidimensional contributors to symptomatic burden in patients with advanced cancer. The inclusion of sacubitril/valsartan was guided by prior evidence demonstrating its beneficial effects in enhancing cardiac function and supporting reverse remodeling in HF,

Table 2. Recommended ferric carboxymaltose (FCM) dose based on body weight and hemoglobin level.

Body weight	Hemoglobin <10 g/dL <6.2 mmol/L	Hemoglobin 10–<14 g/dL 6.2–<8.7 mmol/L	Hemoglobin ≥ 14 g/dL ≥ 8.7 mmol/L
<35 kg	500 mg	500 mg	500 mg
35 to <70 kg	1,500 mg	1,000 mg	500 mg
≥ 70 kg	2,000 mg	1,500 mg	500 mg

Hgb, Hemoglobin; g/dL, grams per deciliter; mmol/L, millimoles per liter; kg, kilogram; mg, milligram.

and cancer patients, irrespective of their ejection fraction.⁸⁻¹⁰ Empagliflozin was selected due to strong evidence supporting its efficacy across the spectrum of ejection fraction and its favorable impact on cardio-renal-metabolic health.¹¹⁻¹³ Ivabradine was included for its ability to lower resting heart rate without affecting blood pressure.¹⁴ It has also been shown to mitigate anthracycline-related cardiotoxicity and enhance cardiac hemodynamics in patients with advanced cancer.¹⁵ Ferric carboxymaltose addressed functional iron deficiency, which is a common contributor to fatigue and reduced exercise capacity in both cancer and HF populations.^{16,17}

The individual flowcharts for each medication reflect distinct pharmacologic profiles and safety considerations relevant to this frail population. For sacubitril/valsartan, separate pathways were developed based on prior exposure to RAAS inhibitors to account for the risk of hypotension and angioedema during transition.¹⁸ For instance, patients on ACE inhibitors or ARBs had to undergo a 36-hour washout period before initiation. Empagliflozin, due to its diuretic and osmotic effects, has the potential to precipitate intravascular depletion and renal dysfunction, particularly in patients with borderline perfusion.^{19,20} Therefore, in the EMPATICC trial, empagliflozin was initiated only in patients with an eGFR ≥ 20 mL/min/1.73 m² and systolic blood pressure ≥ 95 mmHg. Ivabradine was prescribed for patients in sinus rhythm with a heart rate ≥ 75 bpm and did not require a blood pressure threshold, making it suitable for use even in hypotensive cancer patients. Ferric carboxymaltose dosing was individualized based on hemoglobin level and body weight to avoid both under- and over-replacement, with staged infusions used when cumulative doses exceeded 1,000 mg.

Patients with advanced cancer receiving specialized palliative care represent a population that has a narrow therapeutic window. Factors such as hypotension, anorexia, anemia, renal dysfunction, and advanced frailty significantly limit medication tolerability and increase the risk of adverse events.²¹ As a result, rigid titration protocols may be poorly tolerated in this highly vulnerable population. In the EMPATICC trial, this challenge was addressed by incorporating a methodology that enabled individualized dosing and continuous monitoring throughout the trial. Key clinical thresholds such as systolic blood pressure, heart rate, and renal function were integrated into dosing decisions. This approach allowed adjustment of therapy while the clinical trial was underway, while ensuring continued adherence to a structured, protocol-driven HF treatment approach.

Conclusions

Dosing strategies in the EMPATICC trial were designed to support practical implementation in clinical settings, with visual flowcharts developed to enhance clarity, promote consistency, and enable rapid decision-making. These standardized protocols were implemented across five centers in Germany. The dosing strategies described in this study offer a structured

framework for applying HF therapy in the palliative care context and can inform future cardiovascular care in advanced cancer.

Conflict of interest

See Appendix.

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