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Caracterització i identificació dels factors de risc i pronòstics en pacients amb malaltia renal crònica establerta i insuficiència cardíaca

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TESI DOCTORAL

Caracterització i identificació dels factors de risc i pronòstics en pacients amb malaltia renal crònica establerta i insuficiència cardíaca.

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LLISTAT D'ABREVIATURES

- **ACR**: Relació albúmina/creatinina
- **ARA-II**: Bloquejadors dels receptors de l'angiotensina II
- **ARNI**: Inhibidors combinats dels receptors de l'angiotensina II i de la neprilisina
- **BNP**: Pèptid natriurètic cerebral
- **CA-125**: Antigen carbohidrat 125
- **eGFR**: Filtrat glomerular estimat
- **FE**: Fracció d'ejecció
- **HFmrEF**: Insuficiència cardíaca amb fracció d'ejecció lleugerament reduïda
- **HFpEF**: Insuficiència cardíaca amb fracció d'ejecció preservada
- **HFrEF**: Insuficiència cardíaca amb fracció d'ejecció reduïda
- **IC**: Insuficiència cardíaca
- **IECAs**: Inhibidors de l'enzim convertidor de l'angiotensina
- **iSGLT2**: Inhibidors del cotransportador sodi-glucosa tipus 2
- **MRA**: Antagonistes dels receptors de l'aldosterona
- **MRC**: Malaltia renal crònica
- **NT-proBNP**: Fracció aminoterminal del pèptid natriurètic cerebral
- **SRAA**: Sistema renina-angiotensina-aldosterona
- **SRAAi**: Inhibidors del sistema renina-angiotensina-aldosterona
- **VEXUS**: Venous Excess UltraSound.

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RESUM

La motivació per escriure aquesta tesi doctoral ha sorgit de la necessitat d'aprofundir en l'estudi d'un perfil molt concret de pacients històricament poc representats dins de la recerca clínica, que és la població amb malaltia renal crònica (MRC), i en la seva interacció amb la insuficiència cardíaca (IC). El fet que coexisteixin ambdues patologies és freqüent i s'associa a un pitjor pronòstic. Malgrat això, encara hi ha una manca de coneixement sobre com interactuen, especialment en els pacients amb estadis més avançats de MRC.

Aquesta tesi doctoral ha estat redactada en format de compendi d'articles. Es presenten dos estudis que han estat publicats en dues revistes científiques. El primer té com a objectiu analitzar la prevalença i incidència de IC en pacients amb MRC avançada (estadis 4 i 5) no sotmesos a teràpia renal substitutiva, així com identificar els factors de risc associats al seu desenvolupament i l'impacte pronòstic. El segon estudi es centra en el perfil de pacients amb descompensació aguda d'IC amb fracció d'ejecció reduïda, amb l'objectiu de determinar la prevalença de MRC en aquest context i avaluar com el deterior agut de la funció renal pot influir en el pronòstic i en la prescripció del tractament mèdic dirigit per guies durant l'ingrés hospitalari.

Les hipòtesis plantejades són que la insuficiència cardíaca és una comorbiditat freqüent en pacients amb MRC avançada i que la seva presència s'associa de manera independent a un pitjor pronòstic clínic, així com que la implementació precoç i intensiva del tractament mèdic dirigit per guies en pacients amb IC amb fracció d'ejecció reduïda i MRC és una estratègia factible i segura en el context d'una descompensació aguda de IC.

En definitiva, aquesta tesi vol aportar més informació sobre la interacció cardiorenal, millorant l'estratificació del risc d'aquests pacients i aportar més dades que puguin ajudar a millorar el seu maneig terapèutic.

ABSTRACT

The motivation for writing this doctoral thesis arose from the need to deepen the study of a very specific patient profile that has historically been underrepresented in clinical research: the population with chronic kidney disease (CKD), and its interaction with heart failure (HF). The coexistence of both conditions is common and is associated with a worse prognosis. Nevertheless, there is still limited knowledge regarding the mechanisms of their interaction, particularly in patients with more advanced stages of CKD.

This doctoral thesis is presented in the format of a compendium of articles and includes two studies that have been published in two scientific journals. The first study aims to analyze the prevalence and incidence of HF in patients with advanced CKD (stages 4 and 5) not receiving renal replacement therapy, as well as to identify the risk factors associated with its development and its prognostic impact. The second study focuses on patients admitted with acute decompensated HF with reduced ejection fraction, with the objective of determining the prevalence of CKD in this setting and evaluating how acute deterioration of renal function may influence prognosis and the prescription of guideline-directed medical therapy during hospitalization.

The hypotheses of this thesis are that heart failure is a frequent comorbidity in patients with advanced CKD and that its presence is independently associated with a worse clinical prognosis, and that the early and intensive implementation of guideline-directed medical therapy in patients with HF with reduced ejection fraction and CKD is a feasible and safe strategy in the context of acute HF decompensation.

In summary, this thesis aims to provide further insight into the cardiorenal interaction, improve risk stratification in this patient population, and contribute data that may help optimize their therapeutic management.

1. Introducció

1.1 La insuficiència cardíaca.

La insuficiència cardíaca (IC) és una síndrome clínica complexa i creixent, amb una elevada prevalença, morbiditat i mortalitat a nivell mundial. El seu impacte sanitari i social continua augmentant, especialment en poblacions envellides i amb múltiples comorbiditats.

Es defineix, segons les guies de pràctica clínica internacionals, com un síndrome clínic caracteritzat per símptomes i/o signes causats per una anomalia estructural i/o funcional cardíaca, corroborada per nivells elevats de pèptids natriurètics i/o evidència objectiva de congestió pulmonar o sistèmica(1). L'actual classificació distingeix IC amb fracció d'ejecció reduïda (HFrEF) amb fracció d'ejecció ≤40%, lleugerament reduïda (HFmrEF) amb fracció d'ejecció entre el 41-49%, preservada (HFpEF) amb fracció d'ejecció ≥50%.

La IC afecta més de 64 milions de persones a tot el mon (1-2% de la població adulta), amb una prevalença en augment degut a l'envelliment poblacional i la millor supervivència després d'esdeveniments cardiovasculars aguts, podent arribar a >10% en persones d'edat superior a 70 anys(1). Els principals factors de risc clàssics per desenvolupar IC són la hipertensió arterial, la diabetis, la malaltia coronaria, el tabaquisme i l'obesitat(2–4).

El pronòstic dels pacients amb IC continua sent desfavorable, amb una mortalitat intra-hospitalària estimada del 2-17%(5). En el registre europeu de IC (ESC-HF-LT)(6) la taxa de mortalitat per qualsevol causa a l'any va variar entre el 22% i el 37% en IC aguda i entre el 7% i el 16% en la IC crònica en el conjunt dels 21 països europeus i/o mediterranis.

La IC constitueix la via final comuna en la història natural de moltes patologies cardiovasculars. La gran majoria de pacients amb IC presenten diverses comorbiditats, tant cardiovasculars com no cardiovasculars, que contribueixen significativament a l'augment de risc de mortalitat, hospitalitzacions i pèrdua d'esperança de vida(7).

1.2 La malaltia renal crònica com a factor de risc per desenvolupar IC.

Múltiples estudis de cohort i anàlisis epidemiològiques han evidenciat que la malaltia renal crònica (MRC) és un factor de risc independent pel desenvolupament d'IC(8), fins i tot després de l'ajust per factors de risc cardiovascular tradicionals.

La MRC es defineix com la presencia d'anomalies en l'estructura o la funció renal durant al menys 3 mesos, amb implicacions per la salut del pacient(9). La seva prevalença és molt elevada, sent un dels principals problemes de salut pública del mon, i es calcula que podria afectar al 10-15% de la població espanyola.

La classificació reconeguda de la MRC, proposada per la Kidney Disease Outcomes Quality Initiative (KDOQI) i la Kidney Disease: Improving Global Outcomes (KDIGO)(10), es fonamenta en dos paràmetres clau: el filtrat glomerular estimat (eGFR) i la presència d'albúmina a l'orina (relació albúmina/creatinina, ACR). Aquesta classificació defineix cinc etapes de la MRC segons el eGFR: estadi 1 (eGFR ≥90 ml/min/1,73m²) definida com funció renal normal, estadi 2 (eGFR entre 60-89 ml/min/1,73m²) lleument disminuïda, estadi 3a (eGFR=45-59 ml/min/1,73m²) i 3b (eGFR=30-44 ml/min/1,73m²) moderadament disminuïda, estadi 4 (eGFR=15-29 ml/min/1,73m²) severament disminuïda i finalment estadi 5 (eGFR <15 ml/min/1,73m²) com malaltia renal terminal.

Es subclassifiquen en funció de l'ACR en A1 (<30mg/g: normal), A2 (30-300 mg/g: moderadament augmentada) i A3 (>300 mg/g: severament augmentada).

Entre els principals factors de risc per desenvolupar MRC s'inclouen l'edat avançada, la predisposició genètica i les comorbiditats pre-existents, sent les més freqüents la diabetis mellitus, l'obesitat i la hipertensió arterial.

Per tant, la MRC i la IC comparteixen nombrosos factors de risc, tant tradicionals com específics, que expliquen la seva relació bidireccional i l'elevada prevalença conjunta. Els factors de risc tradicionals compartits són el tabac, l'edat avançada, la hipertensió arterial, la diabetis i l'obesitat. Ara bé, comparteixen tota una sèrie d'altres factors de risc, més específics, tal com l'anèmia, la inflamació crònica, l'albuminúria, l'acumulació de toxines urèmiques, la resistència a la insulina, la disminució del metabolisme mineral (hiperfosfatèmia, hiperparatiroïdisme) i l'activació del sistema neurohormonal.

Un registre recent mostra una prevalença de MRC (estadi 3 o superior) en pacients amb IC de gairebé 60%(11). Estudis multicèntrics reporten prevalences entre el 32% i el 59% per MRC i al voltant del 8-11% per MRC avançada (estadi 4 o 5). La presencia de MRC en pacients amb IC augmenta significativament el risc de mortalitat, hospitalitzacions per IC i progressió de la malaltia cardíaca com de la malaltia renal. El pronòstic global és desfavorable: s'ha descrit una supervivència a dos anys del 76% en pacients amb MRC i IC, en comparació amb el 93% en aquells sense cap de les dues patologies(12). Un metanàlisis que incloïa 1.076.104 pacients amb IC, després d'un seguiment mitjà de 681 ± 704 dies, va reportar taxes de mortalitat bruta del 16% en pacients amb MRC i de l'11% en aquells sense MRC (odds ratio combinat no ajustat: 2.34; interval de confiança 95%: 2.2-2.50; p=0,001)(13).

En els estudis realitzats específicament en pacients amb MRC de base, la proporció de casos amb MRC avançada ha estat reduïda. Així, a l'estudi ARIC(14), que va incloure 14.857 pacients sense IC prèvia, només es van reclutar 403 participants amb eGFR < 60 ml/min. Aquests pacients presentaven un risc tres vegades superior de desenvolupar IC en comparació amb aquells amb eGFR > 90 ml/min/1,73m².

1.3 La síndrome cardiorenal.

Sota el terme de síndrome cardiorenal s'agrupen aquelles condicions clíniques en què hi ha una interacció bidireccional entre cor i ronyó, de manera que la disfunció aguda o crònica d'un dels òrgans pot induir la disfunció aguda o crònica de l'altre(15). Clàssicament s'ha classificat en 5 categories, basant-se en quin òrgan es creu que és el principal causant del deterior de la funció dels dos òrgans i de si es tracta d'un dany agut o crònic.

En la insuficiència cardíaca aguda pot aparèixer un dany renal relacionat amb la congestió sistèmica, l'ús de diürètics i el procés de descongestió del pacient(16). S'han postulat diversos mecanismes fisiopatològics, com ara l'alteració hemodinàmica pròpia de la IC aguda, el baix cabal cardíac, la congestió venosa, l'activació neurohormonal, la inflamació i l'alliberament de citoquines, tots ells implicats en el desenvolupament d'aquest dany renal agut. Aquesta alteració de la funció renal, al seu torn, augmenta el risc d'empitjorament de la IC, així com el de desenvolupar arrítmies o cardiopatia isquèmica. En la insuficiència cardíaca crònica, diversos mediadors i mecanismes contribueixen a la progressió del dany cardiovascular i al deteriorament de la funció renal, tals com l'activació del sistema renina-angiotensina-aldosterona, la disfunció endotelial i la inflamació subclínica.

La MRC, al seu torn, genera un estat proinflamatori sistèmic i crònic que afavoreix els processos de remodelatge vascular i miocàrdic, incloent lesions ateroscleròtiques, calcificació vascular, calcificació valvular i fibrosis miocàrdica. La calcificació vascular i valvular accelera la rigidesa arterial, la postcàrrega cardíaca i l'hipertròfia ventricular esquerra, que junt amb la fibrosis contribueixen a la disfunció cardíaca i a un pitjor pronòstic cardiovascular. A més, alteracions electrolítiques com la hipomagnesèmia poden potenciar la calcificació vascular, i la inflamació crònica amplifica el risc de progressió de la MRC i d'aparició de complicacions cardiorenals.(17)

1.4 El diagnòstic de IC en el pacient amb MRC.

El diagnòstic d'IC en aquest grup de pacients és especialment complex, ja que sovint resulta difícil diferenciar entre una insuficiència cardíaca real i una sobrecàrrega de volum, una situació habitual en pacients amb MRC(18).

Els símptomes i signes clínics de la IC poden ser atípics o solapar-se amb manifestacions pròpies de la MRC, dificultant el diagnòstic diferencial. Els biomarcadors clàssics, com el BNP i el NT-proBNP, solen estar elevats en pacients amb MRC, fins i tot en absència d'IC, degut a la menor eliminació renal, cosa que disminueix la seva especifitat diagnòstica. Per aquest motiu, els llindars convencionals utilitzats per al diagnòstic d'IC no són vàlids en pacients amb MRC i cal ajustar-los en funció del filtrat glomerular(19). El CA-125 és un biomarcador de congestió que no es modifica pel grau de malaltia renal i que té valor pronòstic en la IC aguda(20).

Pel que fa a les tècniques d'imatge, fins a un 80% dels pacients amb MRC avançada poden presentar alteracions ecocardiogràfiques(21) i les tècniques més recents, com el VEXUS (Venous Excess UltraSound) per avaluar congestió, tampoc permeten diferenciar si aquesta és secundaria a elevacions de pressions intracavitària o a una sobrecàrrega de volum pura.

1.5 El tractament de la IC en el pacient amb MRC.

La majoria d'assaigs clínics han exclòs tradicionalment els pacients amb MRC avançada, fet que ha limitat de manera significativa l'evidència disponible sobre el benefici i la seguretat dels fàrmacs amb impacte pronòstic en aquest context clínic. No obstant això, en els darrers anys, els criteris d'inclusió en relació al eGFR s'han anat flexibilitzant progressivament, fet que ha permès obtenir dades més representatives d'aquesta població.

Actualment, es disposa de cinc famílies de fàrmacs amb benefici pronòstic en el tractament de la IC amb fracció d'ejecció reduïda:

- Betablocadors.
- Inhibidors del sistema renina-angiotensina-aldosterona (SRAAi) que inclouen:
    - Els inhibidors de l'enzim convertidor de l'angiotensina (IECAs).
    - Els bloquejadors dels receptors de l'angiotensina-2 (ARA-II).
    - Els inhibidors combinats dels receptors de l'angiotensina-II i la Neprilisina (ARNI): sacubitril/valsartà.
- Inhibidors del cotransportador de sodi-glucosa tipus 2 (iSGLT2).
- Antagonistes dels receptors de l'aldosterona (MRA).
- Estimuladors de la guanilat ciclasa soluble (vericiguat).

Pel que fa als tractaments amb efecte pronòstic en la insuficiència cardíaca amb fracció d'ejecció reduïda, l'evidència disponible avala l'ús de betablocadors i ARNI en pacients amb un eGFR≥30 ml/min/1.73m^2, iSGLT2 en aquells amb eGFR≥20 ml/min/1.73m^2, i de vericiguat en pacients amb eGFR≥15 ml/min/1.73m^2 (22).

En un estudi que va incloure pacients participants dels assaigs clínics pivotals amb ARNI en IC amb fracció d'ejecció reduïda (PARADIGM-HF) i preservada (PARAGON-HF), que durant el seguiment van presentar un eGFR<30 ml/min/1.73m^2, es va concloure que el tractament amb sacubitril/valsartà mantenia un perfil de seguretat renal adequat sense perdre el benefici cardiovascular associat al fàrmac(23). Pel que fa als IECAS/ARA-II en pacients amb MRC avançada (eGFR <30 ml/min/1.73 m2), la discontinuació d'aquests fàrmacs no s'ha associat a canvis clínicament rellevants en el eGFR ni en la progressió del deterior de la funció renal(24). Així mateix, les resultats favorables observats en els assaigs pivotals amb iSGLT2 i vericiguat en pacients HFrEF es mantenen també en el subgrup de pacients amb MRC avançada (eGFR <30 ml/min/1.73m^2), reforçant la seguretat i eficàcia d'aquests tractaments en aquest perfil de pacients de risc elevat(25–27). Finalment, un registre que incloïa 33942 pacients amb IC amb FE reduïda va mostrar que la prescripció de MRA disminueix a mesura que empitjora la funció renal; tanmateix, el seu perfil de seguretat es manté consistent al llarg tot l'espectre de valors de eGFR(28).

Pel que fa als tractaments amb efecte pronòstic en la insuficiència cardíaca amb fracció d'ejecció superior al 40% (HFmrEF i HFpEF), només els iSGLT2 i un MRA no esteroidal, la finerenona, han demostrat benefici pronòstic. A l'estudi FINEARTS-HF(29), que va avaluar la finerenona en pacients amb IC amb fracció d'ejecció superior al 40% i va incloure participants amb un eGFR≥25 ml/min/1.73m2, es va observar una reducció significativa de l'endpoint combinat d'empitjorament de la IC i mort cardiovascular.

Tot i que és freqüent observar un descens inicial de la taxa de eGFR després de l'inici de tractaments amb efecte pronòstic, la funció renal tendeix a estabilitzar-se amb el temps, tot mantenint-se la seva eficàcia clínica(30). En el cas dels fàrmacs inhibidors del SRAAi , s'accepta un increment de la creatinina de fins al 30–50% respecte als valors basals o un augment del potassi fins a ≤5,5 mmol/L(31). De manera similar, la lleu disminució inicial de l'eGFR observada durant els primers dies després de l'inici d'un SGLT2i no hauria de comportar la suspensió del tractament, atès que aquesta reducció reversible del eGFR s'associa amb un benefici renal a llarg termini.

Pel que fa al maneig de la IC aguda en pacients amb malaltia renal, la evidència disponible continua sent limitada, centrant-se principalment en estratègies de descongestió i no tant en la implementació de la teràpia recomanada per les guies clíniques. En un dels principals estudis dedicats a la titulació de fàrmacs amb evidència pronòstica en IC aguda, el STRONG-HF(32), tot i que la MRC no constituïa un criteri d'exclusió per se, la mitjana d'eGFR en el grup sotmès a tractament d'alta intensitat era de 61,9 ml/min/1.73m2. Cal destacar que un eGFR inferior a 30 ml/min constituïa un límit per a la titulació dels RAASi.

En conclusió, els pacients amb MRC establerta constitueixen una població insuficientment representada en els assaigs clínics, amb un risc elevat d'esdeveniments cardiovasculars i amb una morbimortalitat significativa.

2. Hipòtesis

Aquesta tesi doctoral està motivada per la necessitat d'aprofundir en el coneixement d'una població històricament menys estudiada, que és la població amb MRC. Per aquest motiu ens vàrem plantejar dos estudis per tal de conèixer els factors de risc d'aquesta població que desenvolupen IC i valorar, durant la fase aguda de descompensació d'IC, com la malaltia renal pot afectar al pronòstic i al tractament.

Hipòtesis

- Els pacients amb MRC avançada (estadis 4 i 5) la insuficiència cardíaca és una comorbiditat freqüent i la seva presència s'associa de manera independent a un pitjor pronòstic clínic.
- En pacients hospitalitzats per descompensació d'insuficiència cardíaca amb fracció d'ejecció reduïda i malaltia renal crònica, la implementació precoç i intensiva del tractament mèdic dirigit per guies en una descompensació aguda de IC és segur i factible.

3. Objectius de la tesis

3.1 Objectiu principal

- Avaluar la interrelació entre la malaltia renal crònica avançada i la insuficiència cardíaca, analitzant els factors associats al desenvolupament d'insuficiència cardíaca en pacients amb malaltia renal crònica avançada, així com l'impacte de la coexistència d'ambdues patologies en el pronòstic clínic i el maneig terapèutic dels pacients.

3.2 Objectius secundaris

- Determinar els factors de risc per al desenvolupament d'IC en pacients amb MRC avançada.
- Comparar el pronòstic clínic dels pacients amb MRC avançada segons la presència o absència d'insuficiència cardíaca.
- Determinar en pacients amb descompensació aguda de IC la prevalença de MRC i valorar com aquesta afecta al pronòstic i tractament de la IC.

4. Compendi de publicacions

4.1 Article 1

CHARACTERISTICS OF PATIENTS WITH HEART FAILURE AND ADVANCED CHRONIC KIDNEY DISEASE (STAGES 4-5) NOT UNDERGOING RENAL REPLACEMENT THERAPY (ERCA-IC STUDY).

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Article

Characteristics of Patients with Heart Failure and Advanced Chronic Kidney Disease (Stages 4–5) Not Undergoing Renal Replacement Therapy (ERCA-IC Study)

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Abstract: Background: Despite the frequent coexistence of heart failure (HF) in patients with advanced chronic kidney disease (CKD), it has been understudied, and little is known about its prevalence and prognostic relevance. Methods: **A** retrospective study of 217 patients with advanced CKD (stages 4 and 5) who did not undergo renal replacement therapy (RRT). The patients were followed up for two years. The primary outcome was all-cause death or the need for RRT. Results: Forty percent of patients had a history of HF. The mean age was 78.2 ± 8.8 years and the mean eGFR was 18.4 ± 5.5 mL/min/1.73 m^2. The presence of previous HF identified a subgroup of high-risk patients with a high prevalence of cardiovascular comorbidities and was significantly associated with the composite endpoint of all-cause hospitalization or need for RRT (66.7% vs. 53.1%, HR 95% CI 1.62 (1.04–2.52), $p = 0.034$). No differences were found in the need for RRT (27.6% vs. 32.2%, $p = 0.46$). Nineteen patients without HF at baseline developed HF during the follow-up and all-cause death was numerically higher (36.8 vs. 19.8%, $p = 0.1$). Conclusions: Patients with advanced CKD have a high prevalence of HF. The presence of previous HF identified a high-risk population with a worse prognosis that required close follow-up.

Keywords: advanced chronic kidney disease; cardiorenal; heart failure; kidney dysfunction; prognosis; mortality

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1. Introduction

Chronic kidney disease (CKD) and heart failure (HF) are prevalent diseases with high morbidity and mortality rates [1]. Both entities share a common burden of traditional cardiovascular risk factors, such as hypertension and diabetes, which are known to cause or worsen CKD and HF [2]. Moreover, the presence of one of the two may precipitate or exacerbate the other [3,4]. This has led to the concept of the cardio-renal syndrome [5]. The cardio-renal syndrome is a term used to describe a condition in which there is an intricate interplay between the heart and the kidneys, resulting in one or both organs being affected. It is classified into five types of cardio-renal syndrome, depending on which organ causes the initial damage: Type 1 and Type 2 in heart disease; Type 3 and 4 in kidney disease; and Type 5, where both coexist, especially in patients with diabetes mellitus. However, this distinction between the different types of cardio-renal syndrome can be challenging and, frequently, clinically irrelevant [6,7]. The high burden of shared cardiovascular disease and the clear worsening of the patient's prognosis when both organs are affected make joining efforts in a multidisciplinary approach for cardiorenal patients mandatory.

Extensive evidence shows that CKD is frequent in HF and associated with a worse prognosis in both acute and chronic HF [8,9]. However, most studies have focused on patients with CKD in stages 1–3. Hence, information about advanced CKD (stages 4–5) in HF is scarce. Conversely, studies on CKD looking at HF also focus on the less severe CKD stages (mean estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) [3] or in advanced CKD already in renal replacement therapies [10]. Therefore, little is known about the interaction between HF and advanced CKD in patients not receiving renal replacement therapies. Although the percentage of patients with both HF and advanced CKD is low, the absolute number of patients is not irrelevant. Moreover, this group of patients poses a clinical challenge because most of the medications studied and approved for the treatment of HF are limited to patients with CKD in stages 1 to 3b (i.e., eGFR $\geq$ 30 mL/min/1.73 m^2) [11].

Therefore, this study aimed to analyze the prevalence of HF in patients with advanced renal disease (stages 4 and 5) and to assess whether the presence of HF conferred a worse prognosis than in patients without HF.

2. Materials and Methods

This was a retrospective analysis of adult patients with advanced CKD (stages 4 and 5) who were followed up at the Nephrology outpatient clinic. We included all patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 CKD-EPI formula.

Patients were included from the Nephology outpatient clinic on 1 January 2020 and were followed up until 31 December 2021, or they died. We excluded patients on RRT programs or who had undergone a kidney transplant. Follow-up and treatment were performed according to local protocols and the treating physician's criteria. The chronic kidney was classified as stage 4 Severe CKD (GFR = 15–29 mL/min/1.73 m^2) and stage 5 End Stage CKD (GFR < 15 mL/min/1.73 m^2) [12]. Heart failure diagnosis was made according to the European Society of Cardiology HF guidelines [11]. HF with preserved ejection fraction (EF) (HfpEF) was defined as an EF greater than or equal to 50%, HF with reduced EF (HfrEF) as an EF less than or equal to 40%, and HF with mildly reduced EF (HFmrEF) as an EF between 41% and 49%.

At the inclusion date, we analyzed baseline characteristics, including cardiovascular risk factors, comorbidities, cardiac and renal history, baseline laboratory tests, and medical treatment. If available, we collected the presence of previous heart failure (HF) and ejection fraction data from the most recent echocardiogram.

The primary endpoint was to analyze the clinical differences and outcomes between patients with advanced CKD with and without a history of HF. The primary outcome was all-cause mortality or the need for renal replacement therapy. Our secondary endpoints were to characterize the patients with HF history and to analyze the baseline characteristics and outcomes of patients without HF at baseline but who developed HF during the follow-up.

Due to its retrospective nature, the local Ethics Committee (CEIm number 2021/10008) approved the study and waived the need for written informed consent.

Statistical Analysis

Continuous variables are described as the mean and standard deviation and, when they do not follow a normal distribution, as the median and the 25–75 percentile, and categorical variables as frequency and percentage. Clinical differences were analyzed using the X^2 test and Fisher's exact test when appropriate for qualitative variables. Continuous variables were analyzed using the unpaired *t*-student test or Mann–Whitney U test, as appropriate. A Cox proportional hazard model was developed, adjusting for age, sex, diabetes, previous myocardial infarction, atrial fibrillation, valve disease, history of HF, eGFR, use of loop diuretic, beta-blockers and RAS inhibitor (ACEi, ARB2, INRA). A simultaneous adjustment was chosen for all variables included in the model through the Enter procedure. These variables were selected either because they presented statistically significant differences in the bivariate analysis or because they had been identified as potential confounding factors according to the literature. NT-proBNP levels were not included because of the

higher number of missing data. Kaplan–Meier curves were constructed to compare the results between patients who presented decompensated HF and those who did not. The results were expressed in the hazard ratio (HR) with a confidence interval of 95%. Statistical significance was set at $p < 0.05$. Statistical analysis was performed with SPSS version 22.0 software (SPSS, IBM, Chicago, IL, USA).

3. Results

3.1. Baseline Characteristics

A total of 217 patients with advanced renal disease (stages 4 and 5) were included. Eighty-seven patients (40%) had a previous diagnosis of HF (Table 1). These patients were older, more frequently female, and diabetic. There was a high prevalence of cardiovascular risk factors in both groups. The mean eGFR was 18.0 ± 5.5 mL/min/1.73 m^2, and 73.3% of patients were on stage 4, without difference between groups. Non-cardiac comorbidities were not different between groups, but cardiac comorbidities were significantly more frequent in patients with a history of HF.

Table 1. Baseline characteristics between patients with and without heart failure at inclusion.

	No Heart Failure ***n*** **= 130 (60%)**	**Heart Failure** ***n*** **= 87 (40%)**	***p*-Value**
Baseline Characteristics			
Age (years)	72.1 ± 13.1	78.2 ± 8.8	<0.001
Women	47 (36.2)	46 (52.9)	0.015
Hypertension	128 (98.5)	85 (97.7)	0.683
Diabetes mellitus	58 (44.6)	61 (70.1)	<0.001
Dyslipidemia	109 (83.8)	79 (90.8)	0.14
BMI	28.0 ± 5.1	29.6 ± 5.7	0.016
Never smoker	84 (64.6)	57 (65.5)	
Active smoker	25 (19.2)	22 (25.3)	0.25
Previous smoker	21 (16.2)	8 (9.2)	
Stroke/TIA	16 (12.3)	13 (14.9)	0.58
Sleep apnea	15 (11.5)	17 (19.5)	0.10
COPD/Asthma	19 (14.6)	19 (21.8)	0.17
Peripheral vascular disease	31 (23.8)	24 (27.6)	0.54
Cancer	37 (28.5)	19 (21.8)	0.28
Myocardial infarction	13 (10.0)	26 (29.9)	<0.001
Percutaneous coronary intervention	7 (5.5)	23 (26.4)	<0.001
Moderate-severe valve disease	3 (2.3)	15 (17.2)	<0.001
Atrial fibrillation/flutter	14 (10.8)	48 (55.2)	<0.001
Baseline Treatment			
ACEi/ARB2/ARNI	40 (30.8)	18 (20.7)	0.1
Beta blockers	52 (40.0)	56 (64.4)	<0.001
MRA	4 (3.1)	2 (2.3)	0.74
iSLGT2	1 (0.8)	3 (3.4)	0.15
Insulin	27 (20.8)	40 (46.0)	<0.001
Other oral anti-diabetic drugs	24 (18.5)	23 (26.4)	0.16
Antiplatelet therapy	43 (33.1)	36 (41.1)	0.21
Statins	98 (75.4)	68 (78.2)	0.64
Loop diuretic	66 (50.8)	78 (89.6)	<0.001
HCTZ/higrotone	7 (5.4)	14 (16.1)	0.009
Anti-vitamin K	12 (9.2)	21 (24.1)	0.003
Direct-acting anticoagulants	1 (0.8)	14 (16.1)	<0.001
Intravenous iron	21 (16.2)	20 (23.0)	0.21
Oral iron	75 (57.7)	56 (64.4)	0.32
Erythropoietin	52 (40.0)	46 (52.9)	0.062

Table 1. *Cont.*

	No Heart Failure n = 130 (60%)	Heart Failure n = 87 (40%)	p-Value
	Laboratory results		
Creatinine (mg/dl)	3.5 ± 2.2	3.0 ± 1.0	0.005
eGFR (mL/min/1.73 m^2)	17.7 ± 5.5	18.4 ± 5.5	0.18
Potassium (mmol/L)	4.8 ± 0.5	4.6 ± 0.6	<0.001
Creatinine/protein ratio (mg/g)	1008.1 (362.0 − 2184.0)	663.0 (286.1–1859.0)	0.45
HbA1c (%)	6.4 ± 1.3	6.6 ± 1.4	0.15
Hemoglobin (g/dl)	12.1 ± 1.6	12.3 ± 1.9	0.16
Transferrin saturation index (%)	26.4 ± 10.4	24.7 ± 8.7	0.11
LDL cholesterol (mg/dl)	87.3 ± 27.1	78.7 ± 31.7	0.02
NT-proBNP (n = 88) (ng/dl)	1344 (393−3721)	4480 (1417−7755)	<0.001
HS-Troponin T (n = 63) (ng/L)	47.0 (34.3−57.3)	52.0 (31.7−73.8)	0.61

Data are presented as numbers and percentages, mean and standard deviation, or median and interquartile ranges, as appropriate. Abbreviations: BMI: body mass index. TIA: transient ischemic attack. COPD: chronic obstructive pulmonary disease. ACEi: Angiotensin-converting-enzyme inhibitors. ARB2: Angiotensin II receptor blockers. ARNI: angiotensin receptor-neprilysin inhibitor. MRA: mineralocorticoid receptor antagonists. iSLGT2: sodium-glucose cotransporter type 2 inhibitors. HCTZ: hydrochlorothiazide. EGFR: estimated glomerular filtration rate. LDL: low-density lipoprotein. NT-proBNP: N-terminal-pro hormone blood natriuretic peptide. HS troponin T: high-sensitivity troponin T.

The median time from diagnosis of heart failure to inclusion in the study was four years (IQR 2–7.75).

One-fourth of the patients received an ACEI/ARB2/ARNI treatment. Beta-blockers were given to 49.8% of patients and were more frequently used in patients with HF ($p < 0.001$). Mineral receptor antagonists (MRA) and SGLT2 inhibitors were used in a few patients (2.3% and 1.8%, respectively). Loop diuretic use was frequent.

NT-proBNP and US-troponin T levels were measured in 88 and 63 of 217 patients, respectively. NT-proBNP levels were higher in the HF group (median 4480 vs. 1344 pg/mL, $p < 0.001$), while US-Troponin T levels were similar.

In patients with a history of HF, 41.4% had an HF hospitalization the previous year, and 39.1% had required ambulatory intravenous loop diuretic treatment. The mean left ventricular ejection fraction was 56.2 ± 10.8%. Most of the patients (66 patients, 76.7%) had HFpEF, while ten patients (11.6%) had HFrEF and ten patients (11.6%) had HFmrEF. The mean ejection fraction was 61 ± 5%, 45 ± 2%, and 33 ± 5%, respectively. Among patients with HFrEF, 90% were treated with beta-blockers and 30% with ACEI/ARB2 or ARNI. None of the patients received MRA or iSGLT2.

3.2. Outcomes

Hospitalization for HF and the need for ambulatory intravenous diuretics were frequent, especially in patients with HF (Table 2). There were no differences in the hospitalization rate due to impaired renal function or in the need for RRT, which was needed in 30.4% of the population. However, in patients with previous HF, hemodialysis was the primary RRT used (79,2%), whereas in patients without HF, peritoneal dialysis or kidney transplantation were more frequently used ($p = 0.008$).

Table 2. Outcomes of patients with heart failure at inclusion compared to those without HF.

	No Heart Failure (n = 130, 60%)	Heart Failure (n = 87, 40%)	p-Value
Heart failure hospitalization, n (%)	15 (11.5)	35 (40.2)	<0.001
Ambulatory intravenous diuretic, n (%)	11 (8.5)	39 (44.8)	<0.001
Hospitalization due to renal cause, n (%)	35 (26.9)	20 (23.0)	0.51

Table 2. *Cont.*

	No Heart Failure (n = 130, 60%)	Heart Failure (n = 87, 40%)	p-Value
Renal replacement therapies, n (%)	42 (32.2)	24 (27.6)	0.46
Hemodialysis, n (%)	18 (42.9)	19 (79.2)	0.008
Peritoneal dialysis, n (%)	16 (38.1)	5 (20.8)	
Kidney transplant, n (%)	8 (19.0)	0 (0)	
All-cause death, n (%)	29 (22.3)	35 (40.2)	0.005
All-cause death or renal replacement therapy, n (%)	69 (53.1)	58 (66.7)	0.046

The composite of all-cause death or need for RRT (Figure 1A) was more frequent in patients with previous HF. Patients with previous HF had almost twice the mortality compared to those patients with no HF history (40.2% vs. 22.3%; p = 0.005) (Figure 1B). A history of HF was independently associated with the composite endpoint (Table 3).

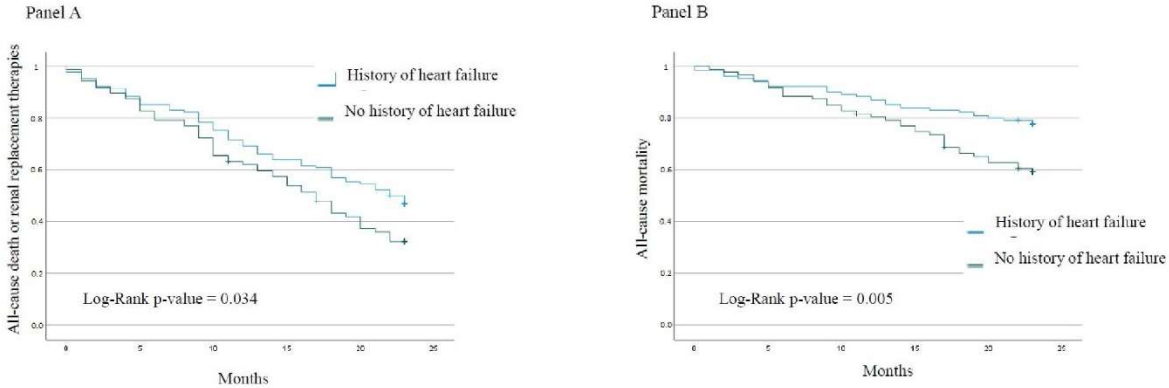


Figure 1. Kaplan–Meier curves for long-term outcome divided by a history of HF. (**Panel A**): All-cause death or renal replacement therapies. (**Panel B**): All-cause mortality.

Table 3. Multivariate Cox proportional model for the hazard ratio of 2-year all-cause mortality or need for renal replacement therapies.

	Adjusted HF (97%CI for HR)	p-Value
Female	0.82 (0.56–1.21)	0.32
Age, per year	1.003 (0.99–1.022)	0.74
Previous HF	1.62 (1.04–2.52)	0.034
Diabetes mellitus	0.72 (0.49–1.05)	0.09
Myocardial infarction	1.72 (1.08–2.73)	0.022
Moderate-to-severe valve disease	0.98 (0.51–1.88)	0.95
Atrial fibrillation	1.03 (0.66–1.62)	0.90
eGFR, per mL/min/1.73 m^2	0.87 (0.84–0.90)	<0.001
RAAS inhibitors	1.19 (0.76–1.87)	0.44
Beta-blockers	0.89 (0.61–1.31)	0.55
Loop diuretics	1.21 (0.78–1.86)	0.40

Abbreviations: HF: heart failure. eGFR: estimated glomerular filtration rate. RAAS inhibitors: Renin angiotensin aldosterone system inhibitors.

Patients without HF History

Of the 130 patients with advanced CKD and no history of previous HF, only 19 (14.6%) developed HF during the 2-year follow-up period. Patients who developed HF were older

(77.2 ± 7.4 vs. 71.2 ± 13.6; $p = 0.007$), and there were no differences in sex and cardiovascular risk factors except for a higher prevalence of diabetes mellitus (68.4% vs. 40.5%; $p = 0.024$). There were no differences in extracardiac and cardiac comorbidities. Medical treatment was similar, except for a higher use of insulin and anti-vitamin K anticoagulants in patients with HF onset (16.2 vs. 47.4%, $p = 0.002$, and 6.3 vs. 26.3%, $p = 0.016$, respectively). Of the patients who developed HF, 15 (78.9%) required hospitalization due to HF, and 11 (57.9%) required ambulatory intravenous diuretic treatment (Table 2). NT-proBNP levels were reported in 30 patients. It was significantly higher in patients who developed HF (3070 [1130–5888] vs. 658 [336–1760] pg/mL; $p = 0.035$). No differences in Troponin T levels ($n = 20$) were observed. The all-cause death rate was numerically higher (36.8 vs. 19.8%, $p = 0.1$). The composite of death or renal replacement therapy (53.1% of patients), hospitalization due to renal cause (26.9%), and the need for renal replacement therapy (32.3%) were similar between groups.

4. Discussion

In this cohort of patients with advanced renal disease (stages 4 and 5), 40% had a history of HF. The presence of previous HF identified a subgroup of high-risk patients, which was significantly and independently associated with the composite endpoint of all-cause hospitalization or the need for renal replacement therapy (HR 95% CI 1.62 (1.04–2.52), $p = 0.034$). Nineteen patients without HF at baseline developed HF during the 2-year follow-up. These patients were older and more frequently had diabetes; all-cause death was numerically higher (36.8 vs. 19.8%, $p = 0.1$).

The prevalence of HF in patients with end-stage kidney disease has been estimated to be between 35.8% [10] and 44% [13], similar to our study. It is worth noting that very few studies have analyzed this group of patients since studies have focused on patients on renal replacement therapies [14] or in less advanced CKD stages [3].

Patients with a history of HF were older and, more frequently, female. The prevalence of traditional cardiovascular risk factors was extremely high in our cohort, with 98.1% of patients having hypertension and 86.6% having dyslipidemia. More than half of the patients had diabetes mellitus, which was significantly higher in patients with HF (70.1%). Although the prevalence we observed is higher than in other series [15], a similar rate of cardiovascular risk factors has been described in patients with advanced chronic kidney disease, particularly those requiring renal replacement therapy or those with diabetic kidney disease [16,17]. Older age and high prevalence of cardiovascular risk factors, particularly diabetes mellitus, might explain the higher prevalence of cardiovascular diseases in patients with previous HF. Non-cardiac comorbidities did not differ between the groups. Although patients with previous HF had a higher prevalence of coronary artery disease and diabetes mellitus, 76.7% had HF with preserved ejection fraction. This high proportion of patients with HFpEF is consistent with previous studies, which have also reported a high prevalence of HF with preserved ejection fraction [18]. However, our findings contrast with other studies, in which HF with preserved ejection fraction accounted for only approximately 38% of HF patients. It is worth noting, though, that the ejection fraction was not measured in almost 20% of HF patients [10].

RAS inhibitor use was low in our series, with only 26.7% of patients receiving it. In contrast to our data, a Swedish registry with 24,283 patients with HFrEF, nearly 10% of whom had advanced CKD (stages 4 and 5), showed that 66% used RAS antagonists [9]. Although RAS inhibitors have a class I indication in the latest HF guidelines [11], the same document advises using ACE inhibitors, angiotensin II receptor blockers, sacubitril/valsartan, and mineralocorticoid receptor antagonists are contraindicated or should be used with caution or seek specialist advice. However, in a recent review, Beldhuis et al. conclude that in patients with HFrEF and CKD stage 4, there is evidence of the safety and efficacy of SGLT2 inhibitors, and with less evidence, ACE inhibitors, vericiguat, digoxin, and omecamtiv mecarbil. There is a lack of data on efficacy and safety for any HFrEF therapies in CKD stage 5 (eGFR < 15 mL/min/1.73 m^2 or dialysis) [19]. Finally, a recent study in patients

with advanced and progressive CKD showed that discontinuing RAS inhibitors was not associated with significant between-group differences in the long-term rate of decrease in eGFR [20]. Thus, a more aggressive approach to using RAS inhibitors should be adopted, especially in patients with HF and reduced ejection fraction, where they have a class I level of evidence A [11].

Overall, patients with HF were a high-risk group, with frequent HF hospitalization and the need for ambulatory intravenous diuretics. This group had nearly four times more risk of having a new HF hospitalization or ambulatory endovenous diuretic treatment than patients without baseline heart failure. Little information is available on patients with advanced CKD. In the ARIC study 3, which included more than 14,000 patients with CKD, the relative risk of developing HF was 1.94 in patients with eGFR < 60 mL/min/1.73 m^2 compared to patients with FG > 90 mL/min/1.73 m^2. However, only 2.7% (n = 403) had an eGFR < 60 mL/min/1.73 m^2. In an analysis of three community-based cohort studies [21], the adjusted risk difference (95% CI) for HF was 4.6 (2.4, 6.7); $p < 0.001$. However, again, only 2.8% of patients had eGFR < 45 mL/min/1.73 m^2. Kottgen et al. reported that the incidence of de novo HF was between 17 to 21%, similar to the 15% of patients without HF at baseline that developed HF in our study. The only differences between patients who developed HF and those who did not were older age and diabetes mellitus. Therefore, patients with diabetes and older patients should be identified as extremely high-risk. All-cause death was numerically higher (36.8 vs. 19.8%, $p = 0.1$). However, this data should be interpreted cautiously as only 19 patients developed HF during follow-up.

The composite endpoint of all-cause death and the need for renal replacement therapies was 66.7% in the previous HF group compared with 53.1%, $p = 0.046$. The presence of previous HF was independently associated with the composite endpoint in multivariable analysis (HR 95CI 1.62 (1.04–2.52), p= 0.034). Studies on mortality in patients with advanced CKD have focused on patients undergoing dialysis or requiring a kidney transplant. The two-year survival rate reported in Medicare patients with HF and end-stage renal disease that received dialysis or had a functioning kidney transplant was 60.8% and 81.1%, respectively. This survival rate was lower than in patients without HF (76.9% and 92%, respectively) [10]. The mortality rate was also high in patients not undergoing renal replacement treatment. In the Swedish Register of patients with HF, the one-year mortality rate in patients with eFGR < 60 mL/min/1.73 m^2 was about 23%, reaching 67% in HFpEF patients at the 5-year follow-up [9]. In our study, the two-year survival rate in patients with and without previous HF was 59.8% and 79.8%, which is higher than in patients without advanced CKD but lower than in patients already on renal replacement therapy.

Although the use of any renal replacement therapy was similar between groups, the type of therapy used differed. Notably, in patients with previous HF in whom renal replacement was indicated, only 20.8% were started on peritoneal dialysis. However, this method should be considered a first-line treatment in patients with HF [22]. Overall, this excess of risk highlights the need for specialized cardiorenal units, where cardiologists and nephrologists work together to improve the management and treatment of these patients [23,24].

Finally, previous studies showed that elevated NT pro-BNP and hs-TnT levels were significantly associated with cardiovascular events and higher HF risk [25,26]. Consistent with these studies, we found that NT-proBNP levels in patients with previous HF were significantly higher than those without HF. Moreover, patients who developed HF during follow-up also had significantly higher NT-proBNP levels. Nonetheless, only 40% and 30% of patients in our study had available NT-proBNP and US-troponin T levels, respectively.

Limitations

The main limitation of our study is that it was a retrospective study, which means that we relied on data collected for clinical purposes rather than for research purposes. This meant that some important data, such as cardiac biomarkers and echocardiography, were unavailable for some patients, which may have limited our ability to characterize the study

population fully. Additionally, as a hospital-based registry, there is a risk of selection bias, as patients who were not considered candidates for renal replacement therapies due to age, frailty, or comorbidities may not have been included in our study.

It is important to note that at the time of our study, the use of SLGT2 inhibitors for treating heart failure or chronic kidney disease was not yet approved. As a result, the number of patients in our study taking these medications was extremely low.

Despite these limitations, we believe that our study provides valuable insights into the prevalence and clinical characteristics of heart failure in patients with chronic kidney disease and adds to the growing body of literature on this crucial topic.

5. Conclusions

Patients with advanced CKD who are not on renal replacement therapy have a high prevalence (40%) and incidence (15%) of HF. Patients with a history of HF have a remarkably high prevalence of cardiovascular risk factors and cardiovascular comorbidities such as myocardial infarction or atrial fibrillation. The prognosis was poor, with a significantly higher composite of all-cause death or need for renal replacement therapy in patients with previous HF (66.7%, vs. 53.1 %, HR (95% CI) 1.62 (1.04–2.52), $p = 0.034$). For this reason, multidisciplinary management involving cardiologists and nephrologists is critical for improving these patients' prognoses.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Hospital del Mar (CEIm number 2021/10008).

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study at the time of the SARS-CoV2 pandemic situation. In that context, we considered that calling patients to the hospital for obtaining informed consent was not ethically acceptable due to putting patients at unnecessary risk.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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4.2 Article 2

TITLE: “INITIATION AND TITRATION OF GUIDELINE-DIRECTED MEDICAL THERAPY DURING HOSPITALIZATION FOR ACUTE DECOMPENSATION OF HEART FAILURE WITH REDUCED EJECTION FRACTION"

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Original article

Initiation and titration of guideline-directed medical therapy during hospitalization for acute decompensation of heart failure with reduced ejection fraction

Inicio y titulación de fármacos indicados por guías durante el ingreso por descompensación aguda de insuficiencia cardiaca con fracción de eyección reducida

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ABSTRACT

Background and objectives: Heart failure with reduced ejection fraction (HFrEF) is a leading cause of morbidity and mortality worldwide. Initiating or maintaining guideline-directed medical therapy (GDMT) during hospitalization is crucial, as early intervention can significantly influence the prognosis. GDMT includes renin–angiotensin–aldosterone system inhibitors (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blocker (ARB), angiotensin receptor-neprilysin inhibitor (ARNI) and mineralocorticoid receptor antagonist (MRA)), beta-blockers and sodium-glucose cotransporter-2 inhibitors (SGLT2i). Our objective was to evaluate the percentage of patients achieving quadruple therapy during hospitalization, document reasons for non-achievement, and describe outcomes in special subgroups (chronic kidney disease (CKD) or advanced age).
Methods: We conducted a prospective single-center study from September 2021 to February 2024, including patients hospitalized for acute decompensated HFrEF with ejection fraction ≤40% treated by the heart failure unit (HFU) of our hospital.
Results: One hundred ninety-six patients were included, with a mean age of 69.2 years. Common comorbidities included hypertension (70.4%), diabetes (41.8%) and CKD (35.2%). The median hospital stay was 8 days. At discharge, ACEI/ARB/ARNI were prescribed in 92.9% of patients, beta-blockers in 88.8%, MRA in 68.9%, and SGLT2i in 91.8%. A remarkable 58.2% of patients received quadruple therapy.
Conclusions: Our study highlights the tolerability and safety of GDMT initiation and titration in hospitalized patients with HFrEF. A substantial proportion of patients were successfully managed with quadruple therapy at discharge, including those with chronic kidney disease (CKD) or advanced age. The main limiting factors were hypotension, renal function deterioration, and electrolyte imbalances.

Abbreviations: HFrEF, heart failure with reduced ejection fraction; RAASi, renin–angiotensin–aldosterone system inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GDMT, guideline-directed medical therapy.

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Palabras clave:
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Fracción de eyección deprimida
Terapia farmacológica dirigida por guías
Cuádruple terapia
Titulación farmacológica

RESUMEN

Antecedentes y objetivos: La insuficiencia cardiaca con fracción de eyección reducida (ICFEr) es una de las principales causas de morbimortalidad a nivel mundial. Iniciar o mantener la terapia farmacológica dirigida por guías (GDMT) durante la hospitalización es crucial, ya que la intervención temprana puede mejorar significativamente el pronóstico. La GMDT incluye inhibidores del sistema renina-angiotensina-aldosterona, betabloqueadores e inhibidores del cotransportador sodio-glucosa 2 (iSGLT2). Nuestro objetivo fue evaluar el porcentaje de pacientes que alcanzaron la terapia cuádruple durante la hospitalización, documentar las razones para no alcanzarla, y describir los resultados en subgrupos especiales (enfermedad renal crónica [ERC] o edad avanzada).

Métodos: Estudio prospectivo unicéntrico realizado entre septiembre de 2021 y febrero de 2024, que incluyó pacientes hospitalizados por descompensación aguda de ICFEr con fracción de eyección ≤40%, tratados en la unidad de insuficiencia cardíaca (UIC) de nuestro hospital.

Resultados: Se incluyeron 196 pacientes, con una edad media de 69,2 años. Las comorbilidades más comunes fueron hipertensión (70,4%), diabetes (41,8%) y ERC (35,2%). Estancia hospitalaria media: 8 días. Al alta, el 92,9% recibió IECAS/ARA II/ARNI, el 88,8% betabloqueadores, el 68,9% antialdosterónicos y el 91,8% iSGLT2, con un 58,2% de cuádruple terapia al alta.

Conclusiones: Nuestro estudio muestra que iniciar y/o aumentar la dosis de GMDT intraingreso es seguro y bien tolerado en los pacientes hospitalizados con ICFEr. Una proporción importante recibió la terapia cuádruple al alta, incluyendo pacientes con ERC o edad avanzada, siendo la hipotensión, el deterioro de la función renal y las diselectrolitemias los principales factores limitantes.

Introduction

Heart failure with reduced ejection fraction (HFrEF) presents a significant burden on healthcare systems globally, characterized by high morbidity, mortality, and frequent hospitalizations.[1] Optimizing therapeutic strategies during hospitalization is paramount to improving patient outcomes and reducing healthcare costs associated with unplanned acute decompensations.[2–4] Guideline-directed medical therapy (GDMT), comprising renin–angiotensin–aldosterone system inhibitors (RAASi) (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blocker (ARB), angiotensin receptor-neprilysin inhibitor (ARNI) and mineralocorticoid receptor antagonist (MRA)), beta-blockers, and sodium-glucose cotransporter-2 inhibitors (SGLT2i), forms the cornerstone of management for HFrEF.[5] Early initiation and aggressive titration of these medications have demonstrated efficacy in improving survival and reducing hospital readmissions in numerous studies.[6–9]

Despite the proven benefits of complete GDMT,[10] achieving optimal therapy during hospitalization remains a challenge. Issues such as hypotension, renal dysfunction, and electrolyte disturbances often complicate medication titration and limit the attainment of target doses. Understanding the factors influencing the successful implementation of quadruple therapy and their impact on in-hospital outcomes is essential for improving clinical practices and patient care.

Patients with chronic kidney disease (CKD) pose a particularly significant challenge in pharmacological titration during hospital admission, due to their increased renal function lability, which complicates the treatment implementation.[11] These patients often present with a higher degree of renal dysfunction and a greater risk of dyslectrolytemia, hindering the management of their condition during hospitalization. Elderly patients also pose a challenge, as they are often underrepresented in clinical trials and have a high percentage of comorbidities and frailty that complicate their in-hospital management.

This prospective single-center study aimed to evaluate the feasibility of implementing quadruple therapy in patients hospitalized for acute decompensated HFrEF, with a specific focus on those with CKD and older patients. By analysing patient demographics, baseline characteristics, medication utilization, and in-hospital complications, we sought to elucidate the barriers and facilitators to achieving optimal therapeutic targets during acute care.

Methods

Observational prospective single-center study, including all patients discharged after an admission for acute decompensated heart failure (HF) with documented ejection fraction (EF) ≤40% between September 1, 2021, and February 28, 2024, in Hospital del Mar, Barcelona, Spain. Our hospital serves a reference population of approximately 300,000–350,000 inhabitants.

Our heart failure unit (HFU) handles the hospitalization of all patients with decompensated heart failure in our hospital, regardless of their ventricular function, unless the patient has severe dementia, complex geriatric profiles with severe frailty or HF is a minor complication during the admission. The in-patient HFU has a dedicated specialized HF cardiologist and nurse exclusively assigned to this cohort of patients.

Patients with chronic kidney disease with glomerular filtration rates (GFR) below 20 mL/min/1.73 m^2, as calculated by the CKD-EPI formula, were excluded.

We analysed baseline characteristics, including cardiovascular risk factors, comorbidities, cardiac history, and medical treatment and dose at the inclusion date. We collected the presence of previous HF and ejection fraction data from the most recent echocardiogram, if available.

The treatment administered was determined by the patient's treating medical team according to clinical guidelines. Hypotension was defined as blood pressure <95 mmHg based on the study cutoff point of the PARADIGM trial.[12] Bradycardia was defined as heart rate <50 beats per minute. Renal function deterioration was defined as an increase in creatinine levels greater than 0.3 mg/dL from baseline and/or a decrease in GFR greater than 25%. Hyperkalemia was defined as a potassium level equal or greater to 5 mmol/L and hypokalemia as potassium levels below 3.5 mmol/L.

GDMT therapy was initiated once the patient exhibited hemodynamic stability and improvement in congestion symptoms, if present. RAAS inhibitors were titrated every 24–48 h depending on clinical/hemodynamic tolerance. If hyperkalemia or renal function deterioration was documented, depending on the severity, titration was halted, doses were reduced or the medication was discontinued at the discretion of the HFU treating physician. New potassium binders were not used due to economic restrictions within our healthcare system. Beta-blockers were up-titrated every 48–72 h, also based on the patient's congestion status. SGLT2i were started early, usually within 48–72 h of the patient's arrival in the emergency department.

The primary objective of our study was to determine the percentage of patients in whom GDMT was successfully implemented at discharge and to report the doses administered at that time. Secondary objectives included documenting reasons for unsuccessful implementations and identifying limiting factors (such as worsening renal function, hyperkalaemia, or need for renal replacement therapy).

The local Ethics Committee (CEIm number 2020/9638) approved the study and all patients signed a written informed consent.

Statistical analysis

Continuous variables are described as the mean and standard deviation, and when they do not follow a normal distribution, as the median and the 25–75 percentile, and categorical variables as frequency and percentage. Analysis of clinical differences was performed using the χ^2 test and Fisher's exact test when appropriate for qualitative variables. Continuous variables were analysed using the unpaired Student's *t*-test or Mann–Whitney *U* test, as appropriate. Multivariable regression models were avoided due to the relatively small sample size.

We conducted a sub-analysis restricted to patient with an eGFR 20–30 mL/min/1.73 m^2, since drug titration in this group of patients is challenging, and another one in patients over 75 years of age.

Statistical significance was set at $p < 0.05$. Statistical analysis was performed the SPSS version 22.0 software (SPSS, IBM, Chicago, IL, USA).

Results

We included a total of 196 patients, of whom 79.1% were male with a mean age of 69.2 (13.7) years. There was a high prevalence of cardiovascular risk factors (Table 1). CKD (defined as GFR <60 mL/min/1.73 m^2) was found in 35.2% of patients. A total of 76 patients (38.8%) had a prior diagnosis of heart failure (HF) (Fig. 1). Regarding baseline treatment, nearly 60% of patients were on ACEI/ARB/ARNI, and over 40% were receiving beta-blockers. Although the percentage of previous heart failure was significant and the proportion of diabetes exceeded 40%, the percentage of patients on SGLT2 inhibitors was low.

The need for inotropic support and coronary care unit admission were low (Table 2). Renal function deterioration during hospitalization was documented in 59.7% of patients. Hypokalaemia was the most frequent electrolyte disturbance (36.2%).

Focusing on treatment at discharge, we achieved a high prescription rate: 92.9% for ACEI/ARB/ARNI, 91.8% for SGLT2i, 88.8% beta-blockers and 68.9% for MRA (Table 3). Patients were discharged on intermediate doses of GDMT. 58.2% of them being discharged on the quadruple therapy. Patients discharged on the quadruple therapy had a lower prevalence of chronic kidney disease and prior HF (Table 1), and creatinine, potassium and NT-proBNP were also lower on admission. There were no differences documented in systolic blood pressure or heart rate at admission between the two groups (Table 2). They also experienced less deterioration in renal function during hospitalization (48.2% vs. 75.6%; $p < 0.001$) and less hyperkalaemia (15.8% vs. 40.2%; $p < 0.001$), with a shorter hospital stay as well (7 days [6–9]; $p < 0.001$). In patients where quadruple therapy was not achieved at discharge, 81.7% had documented reason for that. They main reasons were renal dysfunction or potassium abnormalities (42.7% of patients), hypotension (28%), and cost, patient refusal or bradycardia in 11% of the patients. In those patients in whom quadruple therapy was achieved, a higher proportion of treatment with ARNI compared to ACEI/ARB was attained. Final doses of the four drugs were similar between groups (Table 3).

The subgroup of patients with eGFR less than 30 mL/min/1.73 m^2 at discharge represented 15.8% of the total (Table 4). These patients presented a higher percentage of cardiovascular risk factors, chronic kidney disease defined, and atrial fibrillation (AF). There were no significant differences in prior treatment with beta-blockers, RAAS inhibitors, or aldosterone antagonists, but the use of SGLT2 inhibitors and loop diuretics was higher (Table 4). At admission, they had worse eGFR (29.7 (12.1) vs. 63.97 (22.1) mL/min/1.73 m^2; $p < 0.001$) and higher NT-proBNP. No differences were found in systolic blood pressure at admission or in the percentage requiring admission to the coronary care unit or inotropic support. Almost all these patients (94.7%) had worsening renal function during hospitalisation. Potassium levels at discharge did not differ significantly between groups.

At discharge, quadruple therapy was achieved in only 10.5% of these patients. However, the treatment rates achieved for the individual therapeutic groups were high (84.2% for beta-blockers; 78.9% for SGLT2i; 68.4% for ACEI/ARB/ARNI). Expectedly, the proportion of MRAs at discharge was very low.

Patients 75 years of age or older had a markedly higher prevalence of dependency for daily living activities, chronic kidney disease (55.7% vs. 23.8%; $p < 0.001$) and a greater burden of comorbidities, including chronic obstructive pulmonary disease (COPD), AF, and a history of HF. During hospitalization, these patients experience further deterioration in renal function and a higher incidence of hypokalemia (Table 5).

The proportion of de novo heart failure was notably high in our study. Interestingly, a relatively high proportion of these patients were being treated with ACEI/ARB/ARNI (49.2%) and beta-blockers (30%), mainly due to hypertension, AF, and previous myocardial infarction. In both de novo and chronic heart failure, the proportion of patients discharged on the four pillars of treatment was significantly higher (all $p < 0.05$). However, the only difference between the two groups at discharge was a lower rate of MRA in patients with chronic heart failure (see Supplementary Table 1).

Discussion

In a cohort of patients hospitalised in a HFU due to a heart failure decompensation, an intensive medication titration strategy resulted in high prescription rates for quadruple therapy and individual drug classes: over 90% for ACEI/ARB/ARNI and SGLT2i, nearly 90% for beta-blockers, and close to 70% for MRAs. A total of 58.2% of patients were discharged on quadruple therapy. In the subgroup of patients with eGFR 20–30 mL, the rates of beta-blockers and SGLT2 inhibitors were around 80%, with nearly 70% for ACEI/ARB/ARNI.

In the group of patients over 75 years old, we did not find statistically significant differences in the achievement of quadruple therapy at discharge, nor in the rates of renin-angiotensin system inhibitors (RASi), beta-blockers, or mineralocorticoid receptor antagonists (MRA) when compared to patients under 75 years old. Notably, there was a higher proportion of SGLT2 inhibitors prescribed at discharge (97.1% vs. 88.9%; *p* 0.043).

The initiation and titration of GDMT in the treatment of HFrEF is of utmost importance, considering that prior randomized trials have shown that treatment with these drugs at target doses reduces morbidity and mortality.[5,13] The concept of stepwise and slow titration has changed in recent years, advocating for a titration model with a faster initiation of the four key drugs and a more aggressive dose escalation.[6] The STRONG-HF study[7] in patients hospitalized for acute heart failure showed that all-cause mortality and heart failure readmissions after 180 days were reduced through an aggressive treatment approach involving rapid up-titration of GDMT and meticulous follow-up compared to standard care. Expert consensus recommends initiating GDMT during AHF hospitalization after initial stabilization.[14] However, most of the evidence focuses on titrating patients in stable phase, once discharged from acute decompensation if they required hospital admission. The acute decompensation phase is a vulnerable and complex stage where pharmacological titration is usually relegated to a secondary role, as the priority is depletion and clinical stabilization. Nevertheless, it presents a crucial opportunity to initiate and optimize GDMT, and there is

Table 1
Baseline characteristics of patients with and without quadruple therapy (4T) at discharge.

	Total (n = 196)	No 4T (n = 82)	4T (n = 114)	p-Value
Baseline characteristics				
Female	41 (20.9)	21 (25.6)	20 (17.5)	0.171
Age (years (SD))	69.2 (13.7)	71.1 (14.0)	67.8 (13.3)	0.097
Age >75 years	70 (35.7)	33 (40.2)	37 (32.5)	0.262
Hypertension	138 (70.4)	57 (69.5)	81 (71.1)	0.816
Dyslipidaemia	111 (56.6)	42 (51.2)	69 (60.5)	0.195
Diabetes mellitus	82 (41.8)	34 (41.5)	48 (42.1)	0.928
Barthel score 100	124 (64.2)	46 (56.8)	78 (69.6)	0.066
Stroke	31 (15.8)	15 (18.3)	16 (14.0)	0.420
KD	69 (35.2)	43 (52.4)	26 (22.8)	**<0.001**
Sleep apnoea	17 (8.7)	8 (9.8)	9 (7.9)	0.648
Peripheral vascular disease	38 (19.4)	19 (23.2)	19 (16.7)	0.256
COPD	51 (26.0)	21 (25.6)	30 (26.3)	0.912
Cancer	39 (19.9)	18 (22.0)	21 (18.4)	0.541
Previous MI	40 (63.5)	20 (69.0)	20 (58.8)	0.405
Atrial fibrillation	72 (36.7)	31 (37.8)	41 (36.0)	0.792
Chronic HF	75 (38.3)	39 (47.6)	36 (31.6)	**0.023**
HF hospitalization in the previous year	19 (25.3%)	8 (20.5%)	11 (30.6%)	0.318
NYHA class				0.102
I	54 (27.6)	16 (19.5)	38 (33.3)	
II	131 (66.8)	70 (61.4)	70 (61.4)	
III	11 (5.6)	5 (6.1)	6 (5.3)	
Treatment before admission				
ACEI/ARB	83 (42.3)	30 (36.6)	53 (46.5)	0.166
ARNI	33 (16.8)	15 (18.3)	18 (15.8)	0.644
Beta-blocker	92 (46.9)	38 (46.3)	54 (47.4)	0.887
MRA	33 (16.8)	7 (8.5)	26 (22.8)	**0.008**
SGLT2 inhibitor	40 (20.4)	18 (22.0)	22 (19.3)	0.649
Diuretic	77 (39.3)	39 (47.6)	38 (33.3)	**0.044**

CKD: chronic kidney disease; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; HF: heart failure; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; RAAS: renin–angiotensin–aldosterone system; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose co-transporter 2 inhibitor.

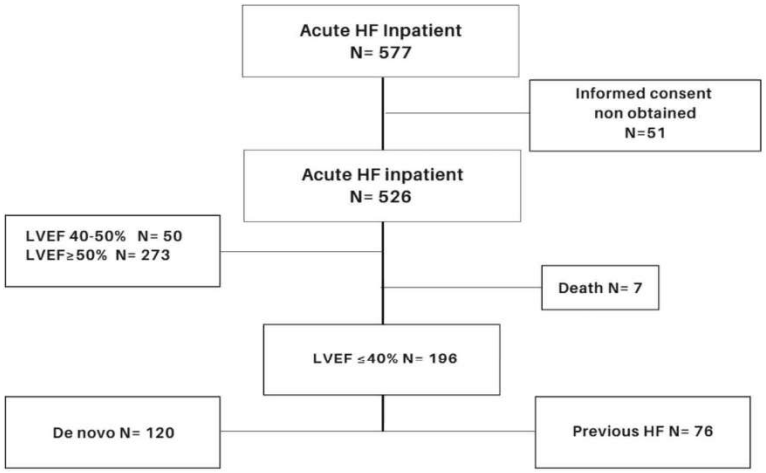


Fig. 1. Flow chart. HF: heart failure; LVEF: left ventricular ejection fraction.

increasing evidence that patients should be discharged on quadruple therapy.[15] This setting permits frequent hemodynamic and laboratory monitoring, symptom evaluation, and reinforcement of patient education.[16] The reduction or withdrawal of GDMT during hospital admission is a often observed and is known to worsen patient prognosis.[4] A Canadian registry evaluated drug eligibility according to guidelines and pivotal studies from January 2017 to April 2020.[17] Based on these criteria, the estimated proportion of patients eligible for treatment to improve prognosis at discharge was 94.9% for beta-blocker, 84.4% for MRA, 80.7% for ACEI/ARB, 73.6% for ARNI, and 88.6% for SGLT2

Table 2
Hospitalization and discharge parameters of patients with and without quadruple therapy (4T).

	Total (n = 196)	No 4T (n = 82)	4T (n = 114)	p-Value
Hospitalization				
Cr at admission*	1.35 (0.72)	1.66 (0.95)	1.12 (0.32)	**<0.001**
eGFR at admission	60.6 (23.6)	49.6 (23.7)	68.6 (20.2)	**<0.001**
K at admission	4.46 (0.60)	4.66 (0.65)	4.31 (0.52)	**<0.001**
NT-proBNP†	7398 (3643–15357)	10018 (4372–21898)	6486 (2890–11991)	**0.007**
SBP at admission	138.0 (28.5)	136.8 (30.2)	138.9 (27.3)	0.611
DBP at admission	84.8 (20.0)	80.0 (18.1)	88.3 (20.6)	**0.004**
HR at admission	98.1 (26.5)	96.6 (23.7)	99.2 (28.4)	0.511
LVEF, %	29.2 (7.2)	30.7 (7.1)	28.1 (7.2)	**0.015**
Acute kidney injury (n (%))	117 (59.7)	62 (75.6)	55 (48.2)	**<0.001**
Hyperkalaemia	51 (26.0)	33 (40.2)	18 (15.8)	**<0.001**
Hypokalaemia	71 (36.2)	31 (37.8)	40 (35.1)	0.696
CCU admission	34 (17.3)	18 (22.0)	16 (14.0)	0.149
Ionotropic support	19 (9.7)	11 (13.4)	8 (7.0)	0.135
Length of hospitalization†	8 (6-12)	10 (7-15)	7 (6-9)	**<0.001**
Cr at discharge*	1.34 (0.62)	1.63 (0.79)	1.14 (0.33)	**<0.001**
eGFR at discharge	59.39 (23.22)	48.3 (22.9)	67.3 (20.1)	**<0.001**
eGFR <30 mL/min/1.73 m^2 at discharge	19 (9.7)	17 (20.7)	2 (1.8)	**<0.001**
Potassium at discharge	4.23 (0.47)	4.25 (0.52)	4.22 (0.43)	0.561
K >5 mmol/L at discharge	8 (4.1)	3 (3.7)	5 (4.4)	0.552
SBP at discharge	109.5 (16.3)	111.6 (18.0)	108.0 (14.9)	0.138
DBP at discharge	64.1 (12.6)	61.9 (12.4)	65.7 (12.6)	**0.036**
SBP <95 mmHg	31 (15.8)	14 (17.1)	17 (14.9)	0.683
HR at discharge	73.4 (12.8)	73.5 (13.7)	73.3 (12.1)	0.931

Cr: creatinine; K: potassium; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LVEF: left ventricular ejection fraction; CCU: coronary care unit.

* Cr values are presented in mg/dL and potassium values in mmol/L.

† NT-proBNP values are presented as median (interquartile range); length of hospitalization is presented as median (interquartile range).

Table 3
Discharge treatment of patients with and without quadruple therapy (4T).

	Total (n = 196)	No 4T (n = 82)	4T (n = 114)	p-Value
Treatment at discharge				
ACEI/ARB	77 (39.3)	36 (43.9)	41 (36.0)	0.262
Enalapril	15 (19.5)	9 (25)	6 (14.6)	0.549
Valsartan	59 (76.6)	26 (72.2)	33 (80.5)	
Enalapril, mean dose	9.83 (9.52)	6.67 (3.31)	14.58 (13.82)	0.223
Valsartan, mean dose	94.24 (46.25)	83.08 (37.39)	103.03 (51.02)	0.089
ARNI	105 (53.6)	32 (39)	73 (64.0)	**<0.001**
ARNI, mean dose	75.71 (40.94)	72.66 (40.34)	77.05 (41.20)	0.614
ACEI/ARB/ARNI	182 (92.9)	68 (82.9)	114 (100)	**<0.001**
Beta-blocker	174 (88.8)	60 (73.2)	114 (100)	**<0.001**
Bisoprolol	152 (87.4)	52 (86.7)	100 (87.7)	0.843
Carvedilol	22 (12.6)	8 (13.3)	14 (12.3)	
Bisoprolol, mean dose	4.54 (2.61)	4.40 (2.61)	4.61 (2.61)	0.635
Carvedilol, mean dose	20.68 (17.24)	17.03 (14.61)	22.77 (18.77)	0.466
MRA	135 (68.9)	21 (25.6)	114 (100)	**<0.001**
MRA, mean dose	25.65 (10.87)	26.19 (20.11)	25.44 (8.30)	0.868
SGLT2 inhibitor	180 (91.8)	66 (80.5)	114 (100)	**<0.001**
Diuretic	182 (92.9)	77 (93.9)	105 (92.1)	0.630
Diuretic, mean dose of furosemide	60.55 (44.40)	64.21 (54.34)	58.48 (35.38)	0.391

Medication doses are presented in mg/day.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; 4T, quadruple therapy.
Values are expressed as n (%) for categorical variables and mean (SD) for continuous variables.

Table 4
Baseline characteristics, hospitalization parameters and discharge treatment in patients stratified by renal function (eGFR) at discharge.

	eGFR <30 mL/min/1.73 m^2 (n = 19)	eGFR ≥30 mL/min/1.73 m2 (n = 177)	p-Value
Female	3 (15.8)	38 (21.5)	0.407
Age (years)	70.0 (20.0)	69.1 (12.9)	0.849
Age >75 years	9 (47.4)	61 (34.5)	0.265
Hypertension	18 (94.7)	120 (67.8)	**0.009**
Dyslipidaemia	15 (78.9)	96 (54.2)	**0.031**
Diabetes mellitus	15 (78.9)	67 (37.9)	**<0.001**
Barthel score 100	9 (47.4)	60 (34.5)	0.266
Stroke	4 (21.1)	27 (15.3)	0.351
CKD	17 (89.5)	52 (29.4)	**<0.001**
Sleep apnoea	2 (10.5)	15 (8.5)	0.509
Peripheral vascular disease	5 (26.3)	33 (18.6)	0.296
COPD	2 (10.5)	49 (27.7)	0.083
Cancer	6 (31.6)	33 (18.6)	0.180
Previous MI	6 (75.0)	34 (61.8)	0.381
Atrial fibrillation	12 (63.2)	60 (33.9)	**0.012**
Chronic HF	11 (57.9)	64 (36.2)	0.064
HF hospitalization in the previous year	4 (36.4)	15 (23.4)	0.286
NYHA class			0.205
I	2 (10.5)	52 (29.4)	
II	16 (84.2)	115 (65.0)	
III	1 (5.3)	10 (5.6)	
Treatment before admission			
ACEI/ARB	10 (52.6)	73 (41.2)	0.340
ARNI	4 (21.1)	29 (16.4)	0.401
Beta-blocker	12 (63.2)	80 (45.2)	0.136
MRA	2 (10.5)	31 (17.5)	0.345
SGLT2 inhibitor	9 (47.4)	31 (17.5)	**0.002**
Diuretic	12 (63.2)	65 (36.7)	**0.025**
Hospitalization parameters			
Cr at admission*	2.31 (0.85)	1.24 (0.62)	**<0.001**
eGFR at admission	29.68 (12.11)	63.97 (22.09)	**<0.001**
K at admission‡	4.67 (0.62)	4.44 (0.60)	0.109
NT-proBNP†	21898 (10048-35000)	6376 (3487-14164)	**<0.001**
SBP at admission	146.5 (32.3)	137.1 (28.1)	0.173
DBP at admission	81.8 (19.0)	85.1 (20.1)	0.491
HR at admission	86.8 (17.4)	99.3 (27.1)	**0.05**
LVEF, %	30.7 (5.6)	29.0 (7.4)	0.247
AKI	18 (94.7)	99 (55.9)	**<0.001**
Hyperkalaemia	8 (42.1)	43 (24.3)	0.093
Hypokalaemia	7 (36.8)	64 (36.2)	0.953
CCU admission	3 (15.8)	31 (17.5)	0.850
Ionotropic support	2 (10.5)	17 (9.6)	0.574
Length of hospitalization†	11 (8-15)	8 (6-11)	**0.011**
Cr at discharge*	2.72 (0.81)	1.20 (0.36)	**<0.001**
eGFR at discharge	22.3 (5.3)	63.4 (20.7)	**<0.001**
Potassium at discharge‡	4.37 (0.56)	4.22 (0.46)	0.187
K >5 mmol/L at discharge	3 (15.8)	5 (2.8)	**0.032**
SBP at discharge	114.3 (17.3)	109.0 (16.2)	0.182
DBP at discharge	63.5 (13.8)	64.2 (12.5)	0.811
SBP <95 mmHg	16 (84.2)	149 (84.2)	0.649
HR at discharge	74.0 (16.0)	73.3 (12.4)	0.833
Treatment at discharge			
4T	2 (10.5)	112 (63.3)	**<0.001**
ACEI/ARB	3 (15.8)	74 (41.8)	**0.021**
ARNI	10 (52.6)	95 (53.7)	0.931
ACEI/ARB/ARNI	13 (68.4)	169 (95.5)	**<0.001**
Beta-blocker	16 (84.2)	158 (89.3)	0.361
MRA	2 (10.5)	133 (75.1)	**<0.001**
SGLT2i	15 (78.9)	165 (93.2)	0.054
Diuretic	19 (100)	163 (92.1)	0.228

CKD: chronic kidney disease; MI: myocardial Infarction; COPD: chronic obstructive pulmonary disease; HF: heart failure; NYHA: New York Heart Association; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; RAAS: renin–angiotensin–aldosterone system; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose co-transporter 2 inhibitor. Cr: creatinine; K: potassium; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; AKI: acute kidney injury; LVEF: left ventricular ejection fraction; CCU: coronary care unit; 4T: quadruple therapy; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor.

* Cr values are presented in mg/dL.

‡ Potassium values are presented in mmol/L

† NT-proBNP values are presented as median (interquartile range); length of hospitalization is presented as median (interquartile range).

Table 5
Baseline characteristics, hospitalization parameters and discharge treatment in patients stratified by age.

	Age <75 years (n = 126, 64.3%)	Age ≥75 years (n = 70, 35.7%)	p-Value
Female	18 (14.3)	23 (32.9)	**0.002**
Age (years)	62.3 (12.0)	81.3 (4.6)	**<0.001**
Hypertension	84 (66.7)	54 (77.1)	0.124
Dyslipidaemia	65 (51.6)	46 (65.7)	0.056
Diabetes mellitus	50 (39.7)	32 (45.7)	0.412
Barthel score 100	94 (75.2)	30 (44.1)	**<0.001**
Stroke	16 (12.7)	15 (21.4)	0.109
CKD	30 (23.8)	39 (55.7)	**<0.001**
Sleep apnoea	11 (8.7)	6 (8.6)	0.97
Peripheral vascular disease	21 (16.7)	17 (24.3)	0.196
COPD	25 (19.8)	26 (37.1)	**0.008**
Cancer	23 (18.3)	16 (22.9)	0.439
Previous MI	22 (66.7)	18 (60.0)	0.583
Atrial fibrillation	36 (28.6)	36 (51.4)	**0.001**
Chronic HF	40 (31)	36 (51.4)	**0.007**
NYHA class			**<0.001**
I	46 (36.5)	8 (11.4)	
II	75 (59.5)	56 (80.0)	
III	5 (4.0)	6 (8.6)	
Treatment before admission			
ACEI/ARB	53 (42.1)	30 (42.9)	0.914
ARNI	17 (13.5)	16 (22.9)	0.093
ACEI/ARB/ARNI	70 (55.6)	46 (65.7)	0.166
Beta-blocker	53 (42.1)	39 (55.7)	0.067
MRA	21 (16.7)	12 (17.1)	0.932
SGLT2 inhibitor	20 (15.9)	20 (28.6)	**0.035**
Diuretic	37 (29.4)	40 (57.1)	**<0.001**
Hospitalization parameters			
Cr at admission*	1.33 (0.75)	1.38 (0.63)	0.621
eGFR at admission	65.7 (24.0)	51.5 (20.1)	**<0.001**
K at admission‡	4.5 (0.6)	4.4 (0.6)	0.245
NT-proBNP†	6069.5 (3108.0–14418.0)	10041.5 (5153.0–19769.0)	**0.010**
SBP at admission	141.0 (28.9)	132.7 (27.2)	**0.048**
DBP at admission	88.2 (20.4)	78.6 (17.8)	**<0.001**
HR at admission	102.5 (26.7)	90.2 (24.4)	**0.001**
LVEF, %	28.8 (7.7)	29.9 (6.3)	0.249
AKI	68 (54.0)	49 (70.0)	**0.028**
Hyperkalaemia	32 (25.4)	19 (27.1)	0.790
Hypokalaemia	35 (27.8)	36 (51.4)	**<0.001**
CCU admission	22 (17.5)	12 (17.1)	0.955
Ionotropic support	12 (9.5)	7 (10.0)	0.914
Length of hospitalization†	8 (6–10)	9 (6–13)	0.112
Cr at discharge*	1.32 (0.64)	1.38 (0.57)	0.545
eGFR at discharge	64.5 (23.3)	50.1 (20.0)	**<0.001**
Potassium at discharge‡	4.3 (0.45)	4.2 (0.50)	0.462
K >5 mmol/L at discharge	3 (2.4)	7 (10.0)	**0.026**
SBP at discharge	110.3 (16.9)	108.1 (15.3)	0.382
DBP at discharge	67.4 (12.1)	58.3 (11.4)	**<0.001**
SBP <95 mmHg	19 (15.1)	12 (17.1)	0.704
HR at discharge	73.9 (12.0)	72.4 (14.1)	0.450
Treatment at discharge			
4T	77 (61.1)	37 (52.9)	0.262
ACEI/ARB	51 (40.5)	26 (37.1)	0.647
ARNI	68 (54.0)	37 (52.9)	0.881
ACEI/ARB/ARNI	119 (94.4)	63 (90.0)	0.247
Beta-blocker	115 (91.3)	59 (84.3)	0.138
MRA	91 (72.2)	44 (62.9)	0.175
SGLT2i	112 (88.9)	68 (97.1)	**0.043**
Diuretic	118 (93.7)	64 (91.4)	0.563

CKD: chronic kidney disease; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; HF: heart failure; NYHA: New York Heart Association; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; RAAS: renin–angiotensin–aldosterone system; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose co-transporter 2 inhibitor. Cr: creatinine; K: potassium; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; AKI: acute kidney injury; LVEF: left ventricular ejection fraction; CCU: coronary care unit; 4T: quadruple therapy.

* Cr values are presented in mg/dL.

‡ Potassium values are presented in mmol/L.

† NT-proBNP values are presented as median (interquartile range); length of hospitalization is presented as median (interquartile range).

inhibitor. Despite that, several studies have shown that the number of patients discharged on GDMT is low. The use of ACEI/ARB/ARNIs at discharged ranged from 44.1% to 77%, the use of beta-blockers from 34% to 82.5%, MRA from 21% to 94%. Whereas the use of SGLT2i was considerably low (15.4%),[7,17,18] likely reflecting the fact that several of the studies were conducted before SGLT2i were recommended as GDMT. A recent study of 33,036 patients hospitalized for newly diagnosed HFrEF found that more than 4 out of 5 patients were projected to be eligible for quadruple therapy at discharge; however, fewer than 1 in 6 were actually prescribed.[19] Comparing these data with our study, we achieved an ACEI/ARB/ARNI prescription rate of 92.9% (with a higher proportion of ARNIs compared to ACEI/ARBs (53.6% vs. 39.3%)), 88.8% beta-blockers, and 68.9% MRA and 91.8% SGLT2 inhibitors. These results may reflect the specific organizational model implemented at our institution. Patients requiring admission due to acute decompensated heart failure are admitted to beds managed by the HF Unit, where a single medical team is responsible for the patients from the very moment they leave the emergency room until they are discharged home. This team includes a specialist HF nurse who plays a central role in educational aspects of the disease, the socio-family dimension, and the transition to discharge, coordinating the appropriated follow up (Telemedicine programme or Day Care Unit) in our specialized HF Unit.[20] Multiple studies have demonstrated the benefits of managing HF patients in specialized units, showing improvements in therapeutic adherence, reductions in hospital readmissions, and enhanced survival rates.[21–23] The IMPLEMENT-HF study[24] showed that patients who underwent treatment optimization guided by a virtual specialized team achieved higher percentage of GDMT at discharge, with 93.4% receiving beta-blockers, 47.2% ACEIs/ARBs, 24.5% ARNIs, 49.1% MRAs, and 32.1% on SGLT2 inhibitors. Furthermore, most patients were discharged with doses between 1 and 49% of the target. Similarly, in our study, most patients were discharged on intermediate doses of GDMT. Notably, 58.2% were discharged on quadruple therapy, a markedly higher proportion than that reported in a recent study of patients with HFrEF managed in a cardiology department, where only 32.5% received quadruple therapy at discharge.[25] This finding supports the hypothesis that management within a dedicated, specialized in-hospital heart failure team may be associated with improved implementation of GDMT in HFrEF.

In IMPLEMENT-HF study, most patients were discharged with doses between 1 and 49% of the target dose, achieving higher proportion of target dose in beta-blockers and MRAs. In our study, most patients achieved intermediate doses of prognostic drugs GDMT at discharge.

According to guidelines and previous studies, it was estimated that 82% of patients admitted for HFrEF were eligible for quadruple therapy and 93% for triple therapy.[19,24] However, only 15.3% received quadruple therapy and 41.5% received triple therapy. In the CHAMP-HF registry[18] of stable US outpatients with HFrEF, among patients eligible for all 3 therapies, only 22% of patients were prescribed triple therapy with ACEI/ARB/ARNI, beta-blocker, and MRA, and only 1% were simultaneously prescribed triple therapy at target dosages.

With regards to patients discharged on quadruple therapy, we observed that they tend to exhibit more favourable clinical profiles, including lower serum creatinine and potassium levels, and reduced incidence of renal function deterioration and hyperkalaemia compared to those not achieving complete therapy. Additionally, we identified a lower prevalence of chronic kidney disease and prior heart failure among these patients, underscoring the impact of baseline comorbidities on treatment. Surprisingly, among patients aged over 75 years, we found no relevant differences in the achievement of quadruple therapy at discharge, nor in the prescription rates of ACEI/ARB/ARNI, beta-blockers, or MRAs compared to patients under 75 years. Notably, the use of SGLT2i was slightly higher in the older group (97.1% vs. 88.9%; $p = 0.043$).

The main limitations encountered during in-hospital titration were hypotension, renal function and potassium levels disturbances, similar to those described in other titration studies. The prevalence of CKD in our study was similar to the Canadian Register (35.2% vs. 31.4%).[17] In patients with established CKD, most drug classes are safe and effective up to stage 3B CKD (eGFR >30 mL/min/1.73 m^2). For more advanced CKD (stage 4), there is evidence of safety and efficacy of SGLT2i (eGFR >20 mL/min/1.73 m^2 for empagliflozin), and initiation during hospitalization has been shown to be safe.[26,27] The evidence for ACEI, vericiguat, digoxin and omecamtiv mecarbil is restricted to improvement of cardiovascular death/heart failure hospitalization.[28] In the subgroup with chronic kidney disease and filtration rates below 30 mL/min/1.73 m^2 at discharge, we achieved 68.4% RAASi, 84.2% beta-blockers, 10.5% MRA, and 78.9% SGLT2 inhibitors. The percentage of beta-blocker and SGLT2i at discharge was similar irrespective of the eGFR. As expected, the number of patients on RAASi was lower in the subgroup of patients with eGFR less than 30 mL/min/1.73 m^2 at discharge. Nevertheless, our RAASi rate was still substantially higher than the ones reported in other studies, where only 22.0% of patients with eGFR <30 mL/min/1.73 m^2 were prescribed a RAASi.[29] When deciding to initiate or maintain GDMT, we took into account the baseline treatment with MRA and RAASi, and the typical fluctuations in renal function that occur during acute heart failure decompensations, knowing that as long as they are related to the persistence of congestive status, they do not worsen patient prognosis.[30]

Limitations

Our study has several limitations that warrant consideration. Firstly, it is a single-center observational prospective study, therefore the generalizability of our findings to broader populations may be restricted. Additionally, while we included a substantial number of patients, a larger sample size could provide more robust insights, particularly in analyzing specific subgroups such as those with advanced chronic kidney disease. The absence of a rigid titration protocol may have influenced treatment practices and clinical outcomes despite adherence to clinical guidelines. Furthermore, our study primarily focused discharge status; longer-term follow-up would be necessary to assess sustained treatment efficacy and patient outcomes.

As this is a prospective observational study, no causal relationships can be established and the associations observed should be interpreted cautiously and considered hypothesis-generating. These considerations underscore the need for cautious interpretation and further multicenter studies to validate our findings across diverse patient populations.

Conclusions

Despite encountering common barriers such as hypotension, renal dysfunction, and electrolyte imbalances, we successfully initiated and titrated GDMT in a significant proportion of patients during hospitalization. We achieved a RAASi prescription rate of 92.9% (with a higher proportion of ARNIs compared to ACE inhibitors/ARBs (53.6% vs. 39.3%), 88.8% beta-blockers, MRA antagonists (68.9%), and SGLT2 inhibitors (91.8%). Overall, 58.2% of patients were discharged with complete quadruple therapy, highlighting the feasibility of aggressive in-hospital medication titration within a heart failure unit. In patients with eGFR <30 mL/min, the use of beta-blockers and SGLT2i was not different to those with eGFR >30 mL/min, and the use of RAASi was 68.4%.

In the group of patients over 75 years old, with a higher frailty and comorbidities, there was a high rate of guideline-directed medical therapy at discharge with no differences compared to patients under 75 years old, with the exception of the SGLT2i which were prescribed at a higher rate.

Our findings support the implementation of aggressive therapeutic strategies for HFrEF during acute decompensation, despite inherent challenges, to improve the number of patients on GDMT, and, potentially, outcomes and quality of life.

CRediT authorship contribution statement

Conceptualization and methodology: SVM, NF and SRB. Software: NB, NRF. Validation: SVM, NF and SRB. Statistical analysis: NF. Data collection and informed consent: PRR, AMLA, JJOS and FMM. Investigation and data curation: MVE, JVM, ROMM. Writing – original draft preparation: SVM. Writing – review and editing: SVM, SRB and LCBT. Visualization: SVM, BVM. Supervision: SVM, NF, SRB. Project administration: SVM.

All authors have read and agreed to the published version of the manuscript.

Ethical considerations

The local Ethics Committee (CEIm number 2020/9638) approved the study and all patients signed a written informed consent.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author Valdivielso More, S. used ChatGPT in order to improve readability and language of the manuscript. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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Conflict of interest

SVM has received travel support and congress inscriptions fees from Novartis, Bayer, Rovi, Servier and Bristol. NF has received speaker fees from Novartis and Astra Zeneca, and travel support from Novartis, and Novo Nordisk. SRB has received speaker fees from Novartis, Rovi, Bayer, and Astra Zeneca, and travel support from Novartis, Bayer, Sanofi, and Pfizer. MV has received travel support form Bayer. RMM has received speaker fees from Esteve and travel support from Bayer, Novartis and Boehringer Ingelheim. JVJ has received speaker fees from Novo Nordisk and Ferrer, and travel support from Novo Nordisk, Rovi and Daiichi Sankyo. PRR has received travel support from Novartis. AMLA has received travel support from Boehringer Ingelheim. FMM has received travel support from Boehringer Ingelheim. BVM has received speaker fees from Boston Scientific, consultant fees from Medtronic and Shockwave Medical and proctor fees from Lifetech Scientific. LCBT has received travel support and congress inscriptions fees from Bayer. The other authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.medcli.2025.107247.

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5. Resum global dels resultats

L'objectiu del nostre primer treball de la tesi doctoral va ser descriure les característiques basals de la població amb MRC avançada per poder identificar els factors de risc associats al desenvolupament d'IC i poder avaluar-ne el seu impacte pronòstic.

Vam incloure 217 pacients amb MRC avançada (eGFR≤30ml/min/1.73m2) no sotmesos a teràpia renal substitutiva ni a transplantament renal. El 40% dels pacients presentaven el diagnòstic d'IC prèvia. Aquests presentaven edat més avançada, més proporció de sexe femení, diabetis mellitus (70.1%) i malaltia cardiovascular prèvia (infart de miocardi previ, fibril·lació auricular i malaltia valvular moderada o severa). No trobarem diferències en quant a les comorbilitats no cardiovasculars. A destacar que la funció renal basal era similar entre els pacients amb i sense IC, indicant que les diferències pronòstiques observades no es podien només atribuir al grau de deteriorament de la funció renal.

Un 76.7% dels pacients amb IC tenien una IC amb fracció d'ejecció preservada. Les formes amb fracció d'ejecció reduïda o lleument reduïda eren menys comunes. La taxa de prescripció d'inhibidors del sistema renina-angiotensina-aldosterona, d'antagonistes del receptor mineralocorticoid i dels inhibidors dels SGLT2 va ser baixa.

Durant el seguiment a dos anys, els pacients amb historia d'IC prèvia varen presentar una incidència més elevada d'hospitalitzacions per IC i una major necessitat de tractament diürètic endovenós ambulatori. No es documentaren diferencies en la taxa d'hospitalització per causa renal o en la necessitat d'iniciar teràpia renal substitutiva. La mortalitat per totes les causes va ser pràcticament el doble en el grup amb IC (22.3% vs 40.2%; p=0.005) i l'endpoint combinat de mortalitat per totes les causes o necessitat d'iniciar teràpia renal substitutiva va ser més freqüent en els pacients amb IC prèvia (53.1% vs 66.7%; p= 0.046). En l'anàlisi multivariant, ajustat per edat, sexe, comorbiditats cardiovasculars, funció renal i tractament farmacològic, la presència d'IC prèvia es va associar de manera independent amb un major risc de l'endpoint combinat de mortalitat o d'inici de teràpia renal substitutiva. Això confirma el seu paper com marcador pronòstic advers en pacients amb MRC avançada.

Dels pacients sense antecedents d'IC a l'inici de l'estudi, un 15% varen desenvolupar IC durant el seguiment. Aquests eren d'edat més avançada i amb una major prevalença de diabetis mellitus. No vàrem trobar diferències en altres factors de risc cardiovasculars o en comorbilitats no cardiovasculars. Tot i que el nombre d'events va ser limitat, la mortalitat va ser numèricament superior en aquest subgrup, refermant la importància clínica del desenvolupament d'IC com a factor de mal pronòstic en la MRC avançada.

En resum, aquest primer estudi demostra que la IC és una comorbiditat molt comuna en pacients amb MRC avançada. Els pacients amb IC tenen un perfil clínic diferent i la seva presència condiciona un pronòstic global clarament desfavorable.

Aquest primer estudi ens va mostrar una taxa baixa d'utilització de fàrmacs amb potencial efecte pronòstic, probablement pel baix percentatge de pacients amb FE deprimida i en ser una població de risc elevat de complicacions per la seva pròpia complexitat clínica. Aquest fet ens va fer preguntar-nos si la implementació del tractament indicat per guies en pacients amb IC amb FE deprimida, durant una hospitalització per descompensació aguda, era factible i segura en pacients amb malaltia renal crònica.

Per tant, el segon estudi de la tesi té com a objectiu avaluar la implementació del tractament mèdic dirigit segons les guies de pràctica clínica en pacients amb descompensació aguda d'IC amb fracció d'ejecció reduïda i MRC. També vol analitzar

l'impacte de la MRC en el maneig terapèutic durant l'ingrés hospitalari d'aquests pacients.

Es van incloure un total de 196 pacients hospitalitzats per una descompensació aguda d'IC amb FE reduïda. L'edat mitjana era de 69.2 (13.7) anys amb predomini de sexe masculí (79.1%). La MRC es va definir per nivells de eGFR <60 mL/min/1.73 m². Aquesta estava present en el 35.2% dels pacients. La taxa de factors de risc cardiovascular era elevada i el 38.8% tenien el diagnòstic d'IC prèvia.

El va documentar deteriorament de la funció renal durant l'ingrés hospitalari en el 59.7% dels pacients, amb un elevat percentatge d'alteracions hidroelectrolítiques, sent la hipopotasèmia la més freqüent (63.2%). La necessitat de tractament amb fàrmacs inotrops o d'ingrés a una unitat de crítics coronaris va ser baixa, sense documentar diferències significatives segons la funció renal.

En el moment de l'alta hospitalària, la taxa de prescripció de tractaments indicats per guies va ser molt elevada: 92.9% d'inhibidors del sistema renina-angiotensina (IECA/ARA-II/ARNI), 91.8% d'inhibidors de SGLT2, 88.8% de betabloquejadors i 68.9% d'antagonistes del receptor de l'aldosterona (MRA). El 58,2% dels pacients varen rebre quàdruple teràpia. Aquests últims presentaven una menor prevalença de MRC i d'insuficiència cardíaca prèvia. També tenien valors menors de creatinina, potassi i NT-proBNP a l'ingrés. Van presentar menor deteriorament de la funció renal, menys hiperpotassèmia i menor estància hospitalària. El 81,7% dels pacients en que no es va assolir la quàdruple teràpia es documenta una justificació clínica, sent l'alteració de la funció renal, dels nivells de potassi i la hipotensió simptomàtica les causes més freqüents.

El 15.8% de pacients tenien un eGFR <30 mL/min/1,73 m² a l'alta. Aquests pacients tenien més proporció de factors de risc cardiovascular clàssics, de MRC i de fibril·lació auricular. No es presentaren diferències en quant als valors de pressió arterial sistòlica a l'ingrés, ni en la necessitat de suport de tractament amb inotrops o d'ingrés a la unitat de crítics coronaris. El 94.7% dels pacients d'aquest subgrup presentaren deteriorament de la funció renal i en el moment de l'alta, només el 10,5% va rebre quàdruple teràpia. Ara bé, les taxes de prescripció de cada fàrmac de forma individual varen ser altes, especialment pels betabloquejadors (84.2%), els inhibidors de SGLT2 (78.9%) i els IECA/ARA-II/ARNI (68.4%). Els MRA varen ser els fàrmacs amb menor percentatge de prescripció a l'alta (10.5%).

En el subgrup de pacients majors de 75 anys, la prevalença de MRC era més alta (55.7%), sent pacients amb una major dependència funcional i amb un percentatge més alt de comorbiditats, incloent-hi la fibril·lació auricular, la malaltia pulmonar obstructiva crònica i la presència d'insuficiència cardíaca prèvia. Es va documentar també major grau de deteriorament de la funció renal intraingrés i major incidència de diselectrolitèmies, especialment d'hipopotassèmia. No obstant, no es va trobar una menor prescripció de fàrmacs amb indicació per guies en el moment de l'alta.

6. Resum global de la discussió

Aquesta tesi doctoral aborda la interacció complexa que existeix entre la IC i la MRC, dues patologies amb elevada prevalença i que s'associen a un pronòstic desfavorable. A través dels nostres dos estudis s'ha analitzat, per una part, quin impacte clínic i pronòstic té la IC en pacients amb MRC avançada i, per l'altra, el maneig terapèutic dels pacients amb descompensació aguda d'IC amb FE reduïda segons el grau de deterior de la funció renal.

El primer estudi confirma que la IC és una patologia freqüent en els pacients amb MRC avançada, amb una elevada prevalença que arriba a ser del 40% i amb una incidència del 15% durant el seguiment. Els pacients amb el diagnòstic previ d'IC tenen un risc més elevat de presentar events durant el seguiment, tenint un impacte pronòstic independent. Si ens centrem en els pacients que desenvolupen IC durant el seguiment, la incidència és similar a la descrita en les cohorts poblacionals, sent pacients amb edat més avançada i amb una elevada prevalença de diabetis mellitus. Els nostres resultats reforcen la idea de que la IC no és només una comorbiditat freqüent en la MRC avançada, sinó un element clau en la progressió clínica i pronòstica d'aquests pacients.

El segon article es centre en un aspecte molt important, com és el maneig farmacològic de la IC aguda durant una hospitalització, una etapa crítica dins la història de la malaltia pel seu impacte pronòstic, però també una opció per a l'optimització terapèutica d'una forma intensiva i precoç. Tot i que més d'un terç dels pacients tenien el diagnòstic de malaltia renal crònica i que la incidència de deteriorament de la funció renal durant l'ingrés va ser molt elevada, l'estratègia d'iniciar i optimitzar el tractament farmacològic indicat per guies durant l'ingrés en una unitat especialitzada d'insuficiència cardíaca va permetre assolir taxes molt elevades de prescripció d'aquests fàrmacs a l'alta. Aquest fet mostra que la malaltia renal prèvia o el deterior agut intraingrés no ha de suposar una contraindicació sistemàtica per a la iniciació o titulació del tractament modificador del pronòstic en pacients amb IC i fracció d'ejecció reduïda. Els resultats també mostren que en subgrup de pacients amb un deterior de la funció renal més avançat hi ha menor percentatge d'assoliment de la quàdruple teràpia, a expenses d'una menor prescripció d'antagonistes del receptor de l'aldosterona pel major risc d'hiperpotassèmia i de deteriorament renal.

Els dos estudis aporten dades rellevants dins de l'espectre de la síndrome cardiorenal: des del pacient amb MRC avançada, on s'ha valorat l'impacte de la IC en el seu pronòstic, fins al pacient amb descompensació aguda d'IC, que pot presentar un risc elevat de deteriorament de la funció renal. Aquest fet, que a priori podria constituir una limitació per a l'ajust terapèutic, en realitat representa una oportunitat per a la seva optimització. Aquestes dades mostren que aquest perfil de pacient, d'elevada complexitat i alt risc d'events, requereixen d'un abordatge coordinat i multidisciplinar entre cardiologia i nefrologia, amb un seguiment estret en unitats cardiorenals per tal de poder millorar el maneig terapèutic i el pronòstic global.

7. Conclusions

1. La insuficiència cardíaca és una comorbiditat molt prevalent en pacients amb malaltia renal crònica avançada (estadis 4 i 5), amb una incidència rellevant durant el seguiment, sent l'edat avançada i la presència de diabetis mellitus els principals factors associats a la seva aparició.

2. Els pacients amb malaltia renal crònica avançada i antecedent d'insuficiència cardíaca constitueixen un subgrup d'alt risc, caracteritzat per una elevada càrrega de factors de risc cardiovascular i un pitjor pronòstic.

3. La malaltia renal crònica és altament prevalent en pacients hospitalitzats per descompensació aguda d'insuficiència cardíaca amb fracció d'ejecció reduïda, i el deteriorament de la funció renal durant l'ingrés és un fenomen freqüent.

4. La implementació precoç i intensiva del tractament mèdic dirigit per guies durant l'ingrés hospitalari és factible i segura quan es realitza en unitats especialitzades d'insuficiència cardíaca sota una monitorització clínica i analítica estreta. Tan mateix, en els pacients amb malaltia renal més avançada persisteixen limitacions en l'assoliment complet de la quàdruple teràpia.

8. Línies de futur

Els resultats d'aquesta tesi doctoral remarquen la importància de la relació entre la IC i la MRC, però és cert que continuen havent-hi encara aspectes sobre la interacció entre ambdues patologies on l'evidència continua sent escassa. Cal destacar que recentment s'ha publicat un registre multicèntric nacional de pacients amb MRC[10] , amb el descriptiu de les característiques basals de 1107 pacients amb MRC però encara sense disposar dades en quant al seguiment a llarg termini. Actualment tenim en marxa un registre prospectiu de pacients que ingressen per descompensació de IC amb pràcticament mil pacients inclosos on analitzarem el pronòstic a llarg termini en funció del grau de deterior de la funció renal.

En quant al tractament modificador del pronòstic en la IC, és fonamental avaluar la seva efectivitat i seguretat en pacients amb MRC avançada, amb la realització d'estudis específicament dissenyats per a aquest subgrup de pacients, tant a curt com a llarg termini. També és important l'impacte que pot tenir la implementació precoç d'aquest tractament sobre els esdeveniments a llarg termini. Així mateix, s'han d'avaluar també estratègies de titulació de fàrmacs de forma estructurada que facilitin l'assoliment i el manteniment de la teràpia quàdruple en pacients malaltia renal crònica avançada, incloent els sotmesos a teràpia renal substitutiva o a transplantament renal. Actualment estem en fase de revisió de les dades sobre titulació de fàrmacs pronòstics en pacients amb malaltia renal que han completat el seguiment pel nostre programa de Telemedicina.

Finalment, és imprescindible desenvolupar estratègies específiques de seguiment i reforçar els models d'atenció multidisciplinària cardiorenals per tal de poder millorar el pronòstic i la qualitat de vida dels pacients amb IC i MRC avançada. En aquest context, durant el període d'elaboració de la present tesi doctoral s'ha treballat activament per la creació de la unitat cardiorenal del nostre centre, que ha obtingut l'acreditació conjunta de la Societat Espanyola de Cardiologia i la Societat Espanyola de Nefrologia al febrer de 2026. Disposem de l'aprovació del Comitè d'Ètica d'Investigació (CEIC) per la recollida de dades de la unitat en el marc d'un projecte orientat a continuar l'estudi d'aquesta població.

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