Research article

Clin Ter 2018; 169 (6):e287-291. doi: 10.7417/CT.2018.2095

Triple therapy at discharge from internal medicine wards in heart failure patients with reduced ejection fraction: results from an observational study

A. Fortini[1], V. Verdiani[2], G. Panigada[3], C. Angotti[1], L. Masotti[4] for the SMIT Study Group (see appendix)

[1]Internal Medicine, San Giovanni di Dio Hospital, Firenze; [2] Internal Medicine, Misericordia Hospital, Grosseto; [3]Internal Medicine, Santi Cosma e Damiano Hospital, Pescia (Pistoia); [4] Internal Medicine, San Giuseppe Hospital, Empoli (Firenze), Italy

Abstract

Background. Guidelines recommend triple therapy (TT) with ACE inhibitors or ARBs, beta-blockers and mineralcorticoid receptor antagonists in symptomatic heart failure patients with ejection fraction ≤ 35 % (HFrEF). Nevertheless, many patients remain untreated. This study was aimed to evaluate the use of TT in HFrEF patients discharged from internal medicine wards of Tuscany, Italy.

Methods and Results. We analyzed the database of a multicenter observational study which included 770 patients consecutively hospitalized for HF in 32out of 36 Internal Medicine Units of Tuscany, Italy. The value of ejection fraction was available in 490 of the 725 patients discharged alive. Of the 117 patients with HFrEF, only 46 (39.3%) were on TT at discharge while 71 (60.7%) were not. In the latter group we observed a significantly greater percentage of patients with cognitive deficit (25.3% vs 10.8%, p=0.05). In the same group there was a slightly greater percentage of patients with hypertension (61.9% vs 58.6%), diabetes (43.6% vs 36.9%), GFR<60 ml/min (74.6% vs 67.3%), anemia (52.1% vs 45.6%) and atrial fibrillation (40.8% vs 34.7%), but the differences were not statistically significant.

Conclusions. These results indicate that TT is underutilized in internal medicine wards of Tuscany. Untreated patients had a greater rate of cognitive deficit and were probably sicker, more complex and fragile. ***Clin Ter 2018; 169(6):e287-291. doi: 10.7417/CT.2018.2095***

Key words: *mineralcorticoid receptor antagonists, heart failure, triple therapy*

Introduction

Patients with reduced ejection fraction heart failure (HFrEF) benefit from the addition of mineralcorticoid receptor antagonists (MRAs) to standard therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and beta blockers (BBs) (1-4). This "triple therapy" is strongly recommended by the international guidelines (5-8) when ejection fraction (EF) is ≤35% and the patient is symptomatic. Despite the results of the clinical trials and the guidelines recommendations, several real life studies indicate that TT is underutilized in clinical practice (9-11). However, few data are available on the use of triple therapy (TT) in Italian internal medicine departments and this study was aimed to fill this gap. For this purpose, we assessed the rate of TT use in HFrEF patients enrolled in a large retrospective observational study conducted in 32 internal medicine wards of Tuscany, Italy (12).

Patients and methods

We retrospectively analyzed data from the Scompenso Cardiaco in Medicina Interna in Toscana (SMIT) study, an observational, multicenter 30-day cross-sectional study performed in thirty-two of the 36 Internal Medicine wards of Tuscany, Italy, over one month, from January 30 to February 28 2014. The aim of the SMIT Study was to analyze the epidemiological and clinical data of patients discharged with the main diagnosis of HF in Tuscany. Details of design and main results of the SMIT Study were previously reported (12). The study was approved by the local ethic committees of the participating centers (approval number: 294/13). An informed consent was achieved for each patient. The present sub-analysis focused on the patients with reduced EF (≤ 35%); we separated them into 2 groups, the first consisting of patients discharged with TT and the second constituted by the other patients. Thereafter, we compared the characteristics of the patients of the two groups to identify the reasons for non-prescription of TT. In particular, we considered age, gender, the number and type of co-morbidity, glomerular filtration rate (estimated with the Cockroft-Gault formula), cognitive deficit (assessed with the "Short portable mental status questionnaire" (13); a score > 7 has been considered "cognitive deficit"), the number of pills taken daily and the length of hospital stay.

Diagnosis of HF was performed by clinical, instrumental and laboratory data according to the 2013 American College of Cardiology/American Heart Association guidelines for the management of HF (5).

Statistical analysis: normally distributed quantitative variables were expressed as means ± standard deviations (SD). Categorical variables were presented as frequencies

Correspondence: Alberto Fortini, Internal Medicine, San Giovanni di Dio Hospital, Via di Torregalli 3, Firenze, Italy
E-mail: xfortini@alice.it

Copyright © Società Editrice Universo (SEU)
ISSN 1972-6007

(percentage). In the statistical analysis, categorical variables were compared by using the Chi-square test, whereas continuous data were compared by using t test of Student. A p value < 0.05 was considered statistically significant. Statistical analyses were carried out using SAS software (version 9.1, SAS Institute, Cary, NC, USA).

Results

The SMIT study enrolled 770 consecutive patients admitted during a 1 month period with the main diagnosis of heart failure to 32 of the 36 internal medicine ward of Tuscany (Fig. 1), an Italian region with 3.7 million inhabi-

Fig. 1. territorial distribution of the Tuscany internal medicine units involved in the Smit Study

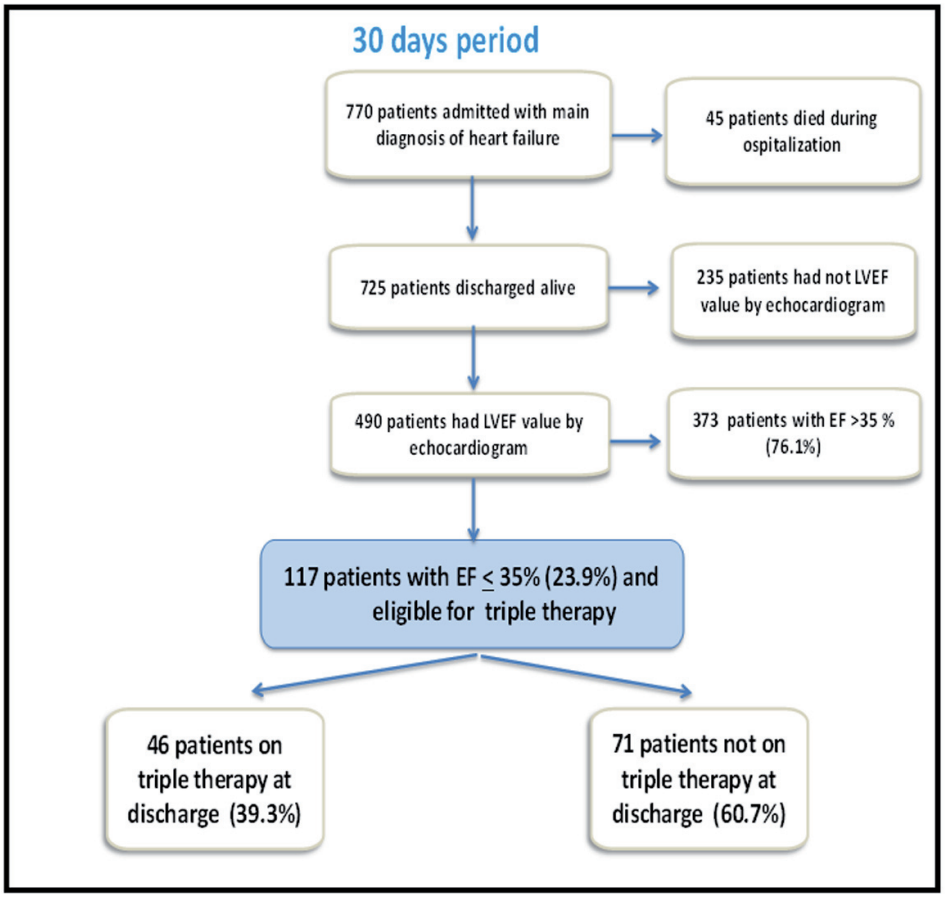

Fig. 2. patients enrolled in the present study

tants. Database analysis showed (Fig. 2) that 725 patients were discharged alive and EF was available from the echocardiographic reports in 490 of these patients (67.6%). EF was ≤ 35% in 117 out of 490 patients (23.9%) and these patients could be eligible for TT with BBs, ACEIs/MRBs and MRAs, according to international guidelines (5-8). At hospital discharge, 46/117 patients (39.3%) were on TT, while the other 71 (60.7%) were treated either with the association of ACEIs/ARBs and BBs (n=29) or with a single drug (n=42).

Table 1 shows the baseline characteristics of the 117 patients potentially eligible for TT, divided according of whether or not they received TT at discharge. Cognitive deficit was over 3 times more frequent in patients not on TT (p=0.05). The other variables taken into consideration were not significantly different in the 2 groups. However, patients on TT were slightly younger and have less comorbidities, such as renal insufficiency, diabetes mellitus, anemia and atrial fibrillation, although none of the differences reached the statistical significance.

Discussion

The main result of the present study indicates that more than half (60.7%) of patients with HFrEF are discharged from the Tuscany internal medicine wards without the prescription of a triple therapy consisting of BB, ACEI/ARB and MRAs. This prescriptive behavior was not consistent with what is recommended by the most authoritative international guidelines (5-8), which strongly indicate the use of triple therapy for symptomatic HFrEF patients with EF ≤ 35% (class of recommendation I and a level of evidence A). The under-utilization of triple therapy is described in several observational real life studies (9,10,14,15) and is mainly due to the lack of addition of MRAs to the standard therapy with ACEI and BB. Recent clinical studies reported a wide variability in the use of MRAs, with a range from 18.2 to 56% of patients eligible for this therapy (9-11,14-16). In our study, TT was prescribed at discharge in 39.3% of patients, a medium-high value compared to what reported in the literature. The causes of the under-prescription of the triple therapy are only partially known. Renal failure (GFR <30 ml / min) and hyperkalemia (K +> 5.0 mEq / L) are correct motivations not to prescribe triple therapy (17), but these controindications explain only a small percentage of cases. Patterson et al. (10), in a recent retrospective observational study, reported that only 24.4% of the patients who were not discharged on an MRA had a contraindication to therapy. In our study, severe renal insufficiency (GFR <30 ml/min) was present in 28% of patients discharged without TT, while we have no data about the values of potassium. Overall, patients discharged without TT appear to be more severely compromised. Compared to patients on TT, they more frequently had a cognitive deficit (p = 0.05); moreover, they were slightly older, had a longer hospital stay and were more frequently affected by more than 3 comorbidities, such as diabetes mellitus, anemia and atrial fibrillation, although none of these differences reached the statistical significance, probably due to the relatively small number of patients under study. In these older and more fragile patients, doctors are likely to have a more cautious attitude in prescribing drugs that can cause side effects, such as hyperkalemia and/or worsening renal function (18), even considering that appropriate monitoring of blood parameters is more difficult to perform in this kind of patients (19). Recent data from 11,215 patients included in the Swedish HF registry (11) indicate that MRAs use does not decrease with elevated potassium and elevated N-terminal pro B-type natriuretic peptide levels but does with impaired renal function, milder HF, older age and follow-up in primary vs specialty care.

An encouraging data that could favor the use of MRAs in the near future comes from a recent analysis of the PARADIGM trial (20). The analysis revealed that among MRA-treated patients with symptomatic HFrEF, severe hyperkalemia is more likely during treatment with enalapril than with sacubitril/valsartan. These data suggest that neprilysin inhibition attenuates the risk of hyperkalemia and that the

Table 1. Baseline characteristics of the study population

Characteristics	Triple therapy		p value
	Yes (n=46)	NO (n=71)	
Age, mean (SD), years	77.5 (10)	78.4 (11.5)	0.65
>80 years, n (%)	25 (54.3)	37 (52.1)	0.81
Men, n (%)	36 (78.3)	44 (62.0)	0.06
Diabetes mellitus, n (%)	17 (37.0%)	31 (43.7%)	0.47
Estimated GFR<60 ml/min	31 (67.4%)	53 (74.6%)	0.39
Estimated GFR<30 ml/min	8 (17.4%)	20 (28.2%)	0.2
Arterial hypertension, n (%)	27 (65.6%)	46 (60.5%)	0.50
Anemia, n (%)	21 (45.7%)	37 (52.1%)	0.46
COPD, n (%)	14 (30.4%)	20 (28.2%)	0.79
Atrial fibrillation n (%),	16 (34.8%)	29 (40.9%)	0.51
Cognitive deficit, n (%)	5 (10.9%)	18 (25.3%)	0.05
≥ 3 comorbidities, n (%)	24 (52.2%)	43 (60.6%)	0.37
Number of dugs taken daily, mean (SD)	7.7 (3.1)	6.6 (2.9)	0.25
Days of hospital stay, mean (SD)	8.5 (4.8)	10.1 (5.5)	0.14

association between an MRA and an angiotensin receptor neprilysin inhibitor (ARNI) could be used more safely than an association between an MRA and an ACEI/ARB.

It must be underlined that the prescription of MRAs at hospital discharge seems to have a relevant and lasting impact on the patients with HFrER, as indicated in the data analysis of the Get With the Guidelines-Heart Failure registry (21). In this study most patients who were prescribed an MRAs at discharge filled the prescription within 90 days and remained on therapy over 1 year follow-up. On the other hand, eligible patients without a discharge prescription seldom initiated therapy as outpatients.

It must be emphasized that the present study has some limitations, such as the relatively small sample of enrolled patients and the lack of potassium values, but overall the data we have observed are consistent with the literature.

What are the possible interventions to increase the rate of treatment with TT of eligible patients? Several solutions have been proposed. The results of an interesting pharmacist-driven aldosterone antagonist stewardship program have recently been reported (22): the pharmacist's involvement led to a significant improvement in the prescription appropriateness of MRAs (from 63 to 95%, p <0.001). Another possible approach is that the doctor, speaking with the patient, emphasizes more the proven benefits of the TT rather than the possible risks (23). The authors' suggestion is to use with the patients the following sentence of high effectiveness: "triple therapy triples lifespan.". We believe that a more widespread awareness of doctors and patients about the real benefits of triple therapy can lead to its more frequent use, increasing adherence to the guidelines recommendations.

Conclusions

The results of the present study indicate that triple therapy (ACEI/ARB+BB+MRA) is underused in HFrEF patients at discharge from Tuscany internal medicine wards. These results are consistent with the data reported in literature for other hospital settings. The explanation of this phenomenon is complex and is probably due, on the one hand, to the extremely fragile characteristics of most of the patients discharged from the internal medicine departments and, on the other, by the doctors' lack of conviction on the real benefits of the TT. To improve the prescriptive appropriateness, it could be useful the involvement of the pharmacist and an educational program to sensitize doctors and patients on the concrete benefits of TT.

References

1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709–17
2. Zannad F, McMurray JJ, Krum H, et al. EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011; 364:11-21
3. Berbenetz NM and Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC Cardiovascular Disorders 2016; 16:246-55
4. Tsutsui H, Ito H, Kitakaze M, et al.-EMPHASIS-HF Study Group. Double-Blind, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Eplerenone in Japanese Patients With Chronic Heart Failure (J-EMPHASIS-HF). Circ J. 2017 Dec 25;82(1):148-158. doi: 10.1253/circj.CJ-17-0323. Epub 2017 Aug 19
5. Mc Murray JJV, Adamopoulos S, Anker SD, et al. ESC. Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J 2012; 33:1787-847
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013 Oct 15;128(16):1810-52. doi: 10.1161/CIR.0b013e31829e8807
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016 Jul 14;37(27): 2129-2200. doi: 10.1093/eurheartj/ehw128
8. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017 Aug 8; 136(6):e137-e161. doi: 10.1161/CIR.0000000000000509. Epub 2017 Apr 28
9. Ferreira JP, Rossignol P, Machu JL, et al. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. Eur J Heart Fail 2017 Oct;19(10):1284-1293. doi: 10.1002/ejhf.900. Epub 2017 Jun 5
10. Patterson SJ, Reaves AB, Tolley EA, et al. Underutilization of Aldosterone Antagonists in Heart Failure. Hosp Pharm 2017 Nov;52(10):698-703. doi: 10.1177/0018578717724886. Epub 2017 Aug 20
11. Savarese G, Carrero JJ, Pitt B, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. European Journal of Heart Failure. First published: 26 March 2018. https://doi.org/10.1002/ejhf.1182
12. Verdiani V, Panigada G, Fortini A, Masotti L, Meini S, Biagi P for the SMIT Study Group. The heart failure in Internal Medicine in Tuscany: the SMIT Study. Italian Journal of Medicine 2015; 9:349-55
13. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. Journal of the American geriatrics Society, Oct.1975; 23 (10): 433-41
14. Albert NM, Yancy CW, Liang L, et al. Use of aldosterone antagonists in heart failure. JAMA. 2009 Oct 21;302(15):1658-65. doi: 10.1001/jama.2009.1493
15. Bress AP, King JB, Brixner D, et al. Pharmacotherapy Treatment Patterns, Outcomes, and Health Resource Utilization Among Patients with Heart Failure with Reduced Ejection Fraction at a U.S. Academic Medical Center. Pharmacothe-

rapy 2016 Feb;36(2):174-86. doi: 10.1002/phar.1701. Epub 2016 Feb 3.
16. Hernandez AF, Mi X, Hammill BG, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. JAMA 2012; 308(20):2097-107. doi: 10.1001/jama.2012.14795
17. Urso C, Canino B, Brucculeri S, et al. Analysis of electrolyte abnormalities and the mechanisms leading to arrhythmias in heart failure. A literature review. Clin Ter 2016; 167(4):e85-91
18. Pitt B, Rossignol P. Impact of Hyperkalemia and Worsening Renal Function on the Use of Renin Angiotensin Aldosterone System Inhibitors in Chronic Heart Failure With Reduced Ejection Fraction. Clin Pharmacol Ther 2017 Sep;102(3):389-391. doi: 10.1002/cpt.746. Epub 2017 Jul 14
19. Sinnott SJ, Mansfield KE, Schmidt M, et al. Biochemical monitoring after initiation of aldosterone antagonist therapy in users of renin-angiotensin system blockers: a UK primary care cohort study. BMJ Open. 2017 Nov 16;7(11):e018153. doi: 10.1136/bmjopen-2017-018153
20. Desai AS, Vardeny O, Claggett B, et al. Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril: A Secondary Analysis of the PARADIGM-HF Trial. JAMA Cardiol 2017 Jan 1;2(1):79-85. doi: 10.1001/jamacardio.2016.4733
21. Curtis LH, Mi X, Qualls LG, et al. Transitional adherence and persistence in the use of aldosterone antagonist therapy in patients with heart failure. Am Heart J 2013 Jun;165(6):979-986.e1. doi: 10.1016/j.ahj.2013.03.007. Epub 2013 Apr 18.
22. Sparks ER, Beavers JC. Evaluation of a Pharmacist-Driven Aldosterone Antagonist Stewardship Program in Patients With Heart Failure. J Pharm Pract. 2017 Jan 1:897190017747083. doi: 10.1177/0897190017747083
23. Cole GD, Patel SJ, Zaman N, et al. "Triple therapy" of heart failure with angiotensin-converting enzyme inhibitor, beta-blocker, and aldosterone antagonist may triple survival time: shouldn't we tell patients? JACC Heart Fail 2014 Oct;2(5):545-8. doi: 10.1016/j.jchf.2014.04.012

Appendix. The SMIT Study Investigators.

Internal Medicine Wards	**Investigators**
Firenze AOU Careggi (FI):	Brunetto Alterini, Regina Maria Lammel AOU
	Alessandro Morettini, Francesco Di Mare AOU
	Carlo Nozzoli, Francesca Bacci
Arezzo 1 (AR):	Mario Felici, Salvatore Lenti, Angela Tufi
Arezzo 2 (AR):	Stefano Arrigucci
Firenze Santa Maria Annunziata (FI):	Raffaele Laureano, Simone Meini, Cinzia Lusini, Maria Teresa Passaleva
Barga (LU):	Guidantonio Rinaldi, Francesca Dini
Borgo San Lorenzo (FI):	Stefano Spolveri, Fuad Amir Tarmum
Carrara (MS):	Monica Uliana, Antonella Venturi
Casentino (AR):	Emilio Santoro, Silvia Manetti
Cecina (LI):	Alessandro Pampana, Gianni Lorenzini
Empoli (FI):	Giuseppe Lombardo, Alessandro Dei
Firenze Santa Maria Nuova (FI):	Giancarlo Landini, Cristiana Seravalle, Luca Masotti
Grosseto (GR):	Valerio Verdiani, Mario Camarda, Andrea Montagnani
Livorno 1 (LI):	Marco Cei, Paolo Pasquinelli
Livorno 2 (LI):	Alberto Camaiti
Lucca (LU):	Giovanni Brunelleschi
Massa (MS):	Lucia Tonarelli
Massa Marittima (GR):	Massimo Alessandri, Graziella Cati
Montepulciano (SI):	Luigi Abate
Pescia (PT):	Grazia Panigada, Irene Chiti, Laila Teghini
Piombino (LI):	Michele Piacentini
Pistoia 1 (PT):	Massimo Giusti, Linda Morosi
Pistoia 2 (PT):	Michela Cameron Smith, Florinda Intilla
Poggibonsi (SI):	Carlo Palermo
Pontedera (PI):	Roberto Andreini, Claudio Belcari, Giuseppa Levantino
Portoferraio (LI):	Plinio Fabiani, Giulia Montorzi
Prato 1 (PO):	Giancarlo Bini, Donatella Bruni
Prato 2 (PO):	Massimo Di Natale, Emanuele Calabrese, Michele Bertoni, Alessandra Giani
S. Marcello Pistoiese (PT):	Marco Frati
Firenze San Giovanni di Dio (FI):	Alberto Fortini, Chiara Angotti, Luca Scarti
Valdichiana (AR):	Rino Migliacci, Giovanni Porciello