Cumhuriyet Tıp Derg 2011; 33: 293-298
Cumhuriyet Med J 2011; 33: 293-298

Original research-Orijinal araştırma

Factors influencing treatment preferences in the patients with acute heart failure with depressed ejection fraction

Düşük ejeksiyon fraksiyonu olan akut kalp yetmezliği hastalarında tedavi seçeneklerini etkileyen faktörler

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Abstract

Aim. Systolic heart failure (HF) is an important health problem with considerable mortality and morbidity. We aimed to investigate factors influencing initiation (prescription) of HF drugs within the hospital. **Method.** Hospital records of consecutive 456 patients, hospitalized (first hospitalizations) and treated for acute HF (ejection fraction <40%) were retrospectively reviewed. In-hospital treatments were considered irrespective of previous or discharge treatments. **Results.** Patients with impaired renal function were administered beta blockers more frequently compared to those without impaired GFR. Functional class did not seem to influence starting of ACE inhibitors or beta blockers. Those with ischemic HF were given ACE inhibitors less frequently compared to those with nonischemic HF. Those with permanent AF were less frequently administered aspirin and ACE inhibitors compared to those without. Elderly patients (≥65 years) were not different from younger ones in terms of prescription choices including ACE inhibitor, beta blocker, and spironolactone. Patients with anemia were not different from those without anemia in terms of prescription of ACE inhibitors, beta blockers and spironolactone. **Conclusion.** We think that recognizing factors that drive physicians to initiate or continue drugs in systolic HF is important in making risk stratification accurately and in modifying prognosis.

Keywords: Acute systolic heart failure, drugs, subgroup

Özet

Amaç. Sistolik kalp yetmezliği mortalite ve morbidite açısından önemli bir sağlık problemidir. Çalışmanın amacı, kalp yetmezliği nedeni ile hastaneye başvuran hastalarda kalp yetmezliği ilaçlarının başlanmasını etkileyen faktörleri araştırmaktı. **Yöntem.** Akut kalp yetmezliği nedeni ile ilk kez hastaneye başvuran ejeksiyon fraksiyonu < % 40 altında olan 456 ardışık hastanın hastane kayıtları retrospektif olarak incelendi. Hospitalizasyon sırasındaki tedaviler, daha önceki tedavilerden ve taburculuk sırasındaki tedavilerden bağımsız olarak değerlendirildi. **Bulgular.** Beta bloker kullanımı renal fonksiyonları bozuk olan hastalarda GFR si normal olan hastalara kıyasla daha fazla idi. ACE inhibitörleri ile beta blokerlerin başlanmasında fonksiyonel kapasitenin bir etkisi yoktu. İskemik kalp yetmezliği olan hastalarda ACE inhibitörü kullanımı iskemik olmayan kalp yetmezlikli hastalara göre daha azdı. Permanent AF si olan hasta grubunda olmayan hastalara kıyasla aspirin ve ACE inhibitörlerinin kullanımı daha düşüktü. ACE inhibitörü, beta bloker ve spiranalakton kullanımı açısından yaşlı (≥ 65 yaş) ve genç hastalar arasında fark yoktu. ACE inhibitörü, beta blokör ve spiranalakton reçete edilmesinde anemisi olan ve olmayan hastalar arasında fark saptanmadı. **Sonuç**. Sistolik kalp yetmezliğinde ilaç başlanmasını ve tedavinin devamını etkileyen faktörlerin fark edilmesi hastaların risklerinin belirlenmesinde ve prognozun değiştirilmesinde önemli bir etken olabilir.

Anahtar sözcükler: Akut sistolik kalp yetmezliği, ilaçlar, altgruplar

Geliş tarihi/Received: April 07, 2010; **Kabul tarihi/Accepted:** August 3, 2011

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Introduction

Systolic heart failure (HF) is associated with increased morbidity and mortality in the general population, particularly in the elderly [1-3]. Despite significant improvements in morbidity and mortality via several agents [4], optimal therapy in real life practice is far from ideal. Several reasons such as age, sex, accompanying diseases, hypertension, congestion, physician's perception, and racial differences may have an impact on it [5].

On the other hand, age seems to influence therapeutic choices. Since, older patients with HF are more likely to have other comorbid conditions that may interact with prescribed medications, older patients with HF seems to be undertreated compared to their younger counterparts [6]. Furthermore, several disease states frequently complicate the course of HF and hence modify therapeutic choices such as renal failure, anemia [7-9].

In this study, we investigated the factors influencing initiation (or continuation) of in-hospital treatment among patients who were hospitalized with acute systolic heart failure for the first time in their lives in a retrospective cohort.

Material and methods

Hospital records of consecutive 456 patients (329 male, 127 female) with a mean age of 57.5±15.5 years, hospitalized (first hospitalizations) and treated for acute HF (ejection fraction <40%) were retrospectively reviewed. In-hospital administration of drugs (initiation or continuation) was considered irrespective of previous or discharge treatments. All patients were under the care of a cardiologist. Hypertension (HT) was defined as having blood pressure >140/90 mmHg or being on treatment, diabetes mellitus (DM) was defined as having fasting blood glucose of >125 mg/dL or being on antidiabetic medication, current smoking was accepted to indicate smoking status. Patients having left ventricular (LV) ejection fraction (EF) >40%, creatinine level >3 mg/dl, severe dysfunction of liver function tests (>3 times upper limit of normal), asthma, patients having myocardial infarction or acute coronary syndrome within the last month and patients who were previously hospitalized with acute decompensation of HF were excluded from the study. Besides, patients who were designated to have NYHA Class I symptoms at admission were excluded due to the possibility of misleading results. Patients with incomplete and/or complete bundle branch block were considered as having bundle branch block. Ejection fraction was measured by echocardiography via Modified Simpson's method by blinded authors within 48 hours of admission. Patients were classified into two as those with permanent atrial fibrillation (AF) and those who were not. Concerning in-hospital prescriptions, patients were subclassified into two as those who were started a specific drug (intravenous diuretic, oral beta blocker, oral ACE inhibitor, spironolactone, intravenous nitrate, and digoxin) or who were not during in-hospital follow up irrespective of dose of each drug. Patients were subclassified into two according to daily intravenous dose of furosemide (only available loop diuretic, above and below 80 mg/day). Patients were classified into two according to age as those ≥ 65 years and those below 65 years of age. Estimated glomerular filtration rate (GFR) was calculated according to MDRD formula [9], and patients were classified into two as those with impaired GFR (<60 ml/min/m^2) and those with normal GFR. Discharge medications or outpatient medications were not considered. Hence, reasons of starting one medication were searched.

Statistical analysis

Parametric data were expressed as mean±standard deviation, and categorical data as percentages. SPSS 10.0 was used to perform statistical procedures. Independent parameters were compared according to independent sample's t test. Categorical data were evaluated by Chi square test as appropriate. A p value of ≤0.05 was accepted as significant.

Results

Mean age was 57.5±15.5 years, and was not different according to sex (males, n=325, 57.9±14.8 years vs. females, n=127, 56.4±17.1 years p=0.374). Mean NYHA was 3.4±0.5, mean ejection fraction was 28.8±4.6% (min=14, max=35) in the whole group. Actually there were only 4 patients with NYHA Class II symptoms during admission, 242 patients had NYHA Class III, and 210 patients had NYHA Class IV symptoms at admission to the hospital. Hence, relatively severely symptomatic patients were under evaluation. Considering the whole group; 49.1% had ischemic HF, 27.9% had HT, 18.6% had DM, 27.4% were current smoker, 23.7% had AF, 11.2% had left bundle branch block, 31.6% had impaired GFR. Considering drugs started in the hospital, 88.2% were administered aspirin, 89.5% were given ACE inhibitors, 81.4% were given digoxin, 67.5% were given beta blocker, 89.3% were administered intravenous loop diuretic, 77.6% were given spironolactone, and 12.9% were administered warfarin.

Impaired GFR: Patients with impaired GFR were (initiated or continued) administered beta blockers more frequently compared to those without impaired GFR (75.7% vs. 63.8%, p=0.012). There was no difference concerning use of loop diuretics (88.2% vs. 89.7%, p=0.632). However, those with impaired GFR were administered high dose loop diuretics more frequently compared to those without impaired GFR (22.9% vs. 13%, p=0.008). Those with impaired GFR tended to be given ACE inhibitors less frequently compared to those without impaired GFR (86.8% vs. 91.7%, p=0.106). Whereas, those with impaired GFR were given angiotensin receptor blockers more frequently compared to those without impaired GFR (11.8% vs. 5.6%, p=0.036). Those with impaired GFR were given digoxin less frequently compared to those without (70.8% vs. 87.4%, p<0.001). It was interesting to see that those with and without impaired GFR were not different from each other concerning administration of spironolactone (75.7% vs. 79.4%, p=0.375). Those with impaired GFR were not different from those without impairment in terms of presence of hypertension, diabetes mellitus, smoking status (p=0.906, p=0.412, p=0.573). Impaired GFR was not related with severe functional class (41.7% vs. 48.5%, p=0.176).

Poor NYHA functional class: Those with NYHA Class IV were not different from those with NYHA Class ≤3 concerning starting of beta blockers and ACE inhibitors (66.7% vs. 68.3%, p=0.712; 87.1% vs. 91.5%, p=0.134). However, those with NYHA Class IV were less frequently given aspirin (83.3% vs. 92.3%, p=0.005) and more frequently given spironolactone (82.4% vs. 73.6%, p=0.025). Though, two subgroups were similar in terms of intravenous loop diuretic use (90% vs. 88.6%, p=0.635), those with NYHA Class IV were given high dose loop diuretics more frequently compared to those with NYHA Class ≤3 (20.5% vs. 12.2%, p=0.016). There was no significant difference in terms of administration of digoxin and nitrate (84.8% vs. 78.5%, p=0.085; 27.1% vs. 34.1%, p=0.107). Functional class was not related with HT, DM and smoking status (p=0.250, p=0.782, p=0.905).

Ischemic HF: Those with ischemic HF were similar to those with nonischemic HF in terms of administration of beta blocker, digoxin (66.1% vs. 69%, p=0.509; 81.2% vs. 81.5%, p=0.953). Those with ischemic HF were given nitrates more often compared to those with nonischemic HF (46.9% vs. 15.5%, p<0.001). On the other hand, those with ischemic HF were administered more frequently aspirin compared to those with nonischemic HF (96.4% vs. 80.2%, p<0.001). Besides, those with ischemic HF were

given high dose intravenous loop diuretics more often than those with nonischemic HF (22.3% vs. 9.9%, p<.001), though they were not different in terms of use of intravenous diuretic (90.6% vs. 87.9%, p=0.353). Those with ischemic HF were given ACE inhibitors less frequently compared to those with nonischemic HF (86.6% vs. 92.2%, p=0.05). Those with ischemic HF were not different from those with nonischemic HF in terms of HT, smoking status (p=0.450, p=0.166). Whereas, DM was more frequent among those with ischemic HF compared to those with nonischemic HF (23.7% vs. 13.8%, p=0.007). Ischemic etiology was not related with more frequent severe functional class (IV) at admission (45.5% vs. 46.6%, p=0.828).

Atrial fibrillation: Those with permanent AF were administered more frequently beta blockers compared to those without (75.9% vs. 65.9%, p=0.033). Those with permanent AF were less frequently administered aspirin and ACE inhibitors compared to those without (82.4% vs. 89.9%, p=0.041; 84.3% vs. 91.1%, p=0.049). Both groups were similar in terms of administration of intravenous loop diuretic and digoxin (90.7% vs 88.8%, p=0.694; 79.6% vs. 81.9%, p=0.597). Those with permanent AF were given less frequently nitrates (23.1% vs. 33.3%, p=0.045), and more frequently received warfarin in the hospital (32.4% vs. 6.9%, p<0.001) compared to those without permanent AF. Presence of permanent AF was not related with HT, DM and smoking status (p=0.089, p=0.083, p=0.255).

Elderly patients: Elderly patients (≥65 years) were not different from younger ones in terms of prescription choices including ACE inhibitor, beta blocker, and spironolactone (89.5% vs. 89.4%, p=0.974; 69.8% vs. 66.2%, p=0.430; 75.6% vs. 78.9%, p=0.414). However, they were more frequently administered intravenous nitrate compared to younger counterparts (39% vs. 26.1%, p=0.004). Intravenous loop diuretic administration was similar between two age groups (90.1% vs. 88.7%, p=0.644). There were less NYHA Class IV patients in the elderly patients compared to younger ones (37.8% vs. 51.1%, p=0.006). Besides, as it was expected, impaired GFR was related with being older (53.5% vs. 46.5%, p<0.001).

Patients with anemia: Patients with anemia were not different from those without in terms of prescription of ACE inhibitors, beta blockers and spironolactone (86.9% vs. 90.3%, p=0.421; 70.1% vs. 66.8%, p=0.520; 72% vs. 79.4%, p=0.108). Though, both groups were similar in terms of prescription of intravenous loop diuretic, those with anemia were more frequently administered high dose compared to those without anemia (22.4% vs. 14%, p=0.038). Anemia was significantly associated with older age (>75 years) and impaired renal function in our study group (p<0.001, p=0.010).

Discussion

Systolic HF has a considerable mortality and morbidity [4]. Undertreatment seems quite common among some subgroups yielding increased mortality. Hence, it might be important to recognize them in order to produce timely and rational drug use, particularly with those having prognosis modifying capacity [4]. Renal dysfunction frequently complicates the course of HF in varying degrees, hence, the term "cardiorenal syndrome" was established recently [8]. In our study, we showed that those with impaired GFR were prescribed beta blockers more frequently. This might seem hopeful, however, hepatic metabolism of commonly used drugs seems to enable this. Because, use of ACE inhibitors tended to be less in this group. On the other hand, it seems easy to understand less frequent preference of digoxin due to its renal clearance. However, no avoidance from spironolactone seemed interesting to note. It was also interesting to see that poor functional class did not seem to dissuade ACE inhibitor and beta blocker prescription contrary to Koshack et al. [11]. In their study, beta blocker prescription was decreased with increased functional class despite similar rates in ACE inhibitors. On the other hand, it was relatively easy to understand more preference for spironolactone in poor functional class, as indicated by guidelines [4]. Ischemic heart disease is one of the most frequent

risk factors associated with systolic HF [12]. It was unexpected to see less frequent preference of ACE inhibitors in this group, which has a poorer prognosis, and hence, requires drugs with mortality benefit more often. Atrial fibrillation is also a frequent accompany of systolic HF. It worsens HF. In our study group, use of beta blockers was more frequent among those with permanent AF as it was expected. However, less frequent prescription of ACE inhibitors as shown by Nieuwlaat et al recently [13] is important to rethink on it. On the other hand, less frequent use of aspirin may be due to more frequent use of warfarin in this group.

Finding of no difference in rates of prescription of prognosis modifying drugs of HF in elderly patients compared to younger ones might seem satisfactory even in the presence of significant association between age and impaired renal function. In another study, elderly patients were less prescribed beta blockers compared to younger ones [14]. This difference might be due to different attitudes at discharge prescriptions. Furthermore, worsening status of the patient might influence decreased trend at discharge, though it was initiated. On the other hand, similarity may be lost as the age limit is increased to very elderly [11].

Anemia, which is accepted as a prognostic factor in HF did not seem to affect prescription patterns at least at the cut off level of 12 gr/dL of hemoglobin. On the other hand, lowering the threshold might yield different results [7]. In our study, anemia was related to age and renal function as indicated by a recent review [7]. As a whole, it seems some factors influence initiation of certain drugs. However, whatever the reason, prescription rates for digoxin, diuretic and antiaggregants seem considerably high despite they do not have mortality reducing properties as indicated by a previous study from our country [15] and, there is still window for improvement for beta blockers and nitrates even with high doses having ancillary effects [4, 16].

There are several limitations of the current study. First of all, retrospective nature brings about several confounders in establishing relationships. First of all, we do not have the data concerning discontinuation of specific drugs. Hence, prescription findings did not mean that they were used continuously till discharge. Changing status of the patient i.e., worsening symptoms, worsening renal function, may change actual rates of prescriptions. Hence, our study just gives clues which drive physicians to initiate (or continue if already present) a specific drug. Besides, we did not have accurate data for previous drugs, which could possibly influence prescription pattern. However, presence or absence of any drug previously does not justify making prescriptions in the hospital. Due to acute nature of the clinical picture, many drugs could be suspended or reinitiated particularly in a group of severely ill patients. Our study just draws the picture in the hospital without taking prehospital and post hospital status. Besides, oral drugs, given in-hospital in our study, were low doses in contrast to prognosis modifying doses. Hence, we had shown only an instantaneous picture of patients with acute systolic heart failure during the first hospitalization along with its associations with some subgroups.

We think that there are many factors influencing in-hospital prescription (initiation or continuation) of drugs in the clinical picture of acute systolic heart failure. Accurate identification of subgroups, deriving large benefit might help risk stratification and rational treatment.

References

1. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation 1993; 88: 107-15.
2. McAlister FA, Teo KK, Taher M, Montague TJ, Humen D, Cheung L, Kiaii M, Yim R, Armstrong PW. Insights into the contemporary epidemiology and outpatient management of congestive heart failure. Am Heart J 1999; 138: 87-94.
3. Rodeheffer RJ, Jacobsen SJ, Gersh BJ, Kottke TE, McCann HA, Bailey KR, Ballard DJ. The incidence and prevalence of congestive heart failure in Rochester, Minnesota. Mayo

Clin Proc 1993; 68: 1143-50.
4. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008; 10: 933-89.
5. Mortality risk and patterns of practice in 4606 acute care patients with congestive heart failure. The relative importance of age, sex, and medical therapy. Clinical Quality Improvement Network Investigators. Arch Intern Med 1996; 156: 1669-73.
6. Leibundgut G, Pfisterer M, Brunner-La Rocca HP. Drug treatment of chronic heart failure in the elderly. Drugs Aging 2007; 24: 991-1006.
7. Tang YD, Katz SD. The prevalence of anemia in chronic heart failure and its impact on the clinical outcomes. Heart Fail Rev 2008; 13: 387-92.
8. Ronco C, Cruz DN, Ronco F. Cardiorenal syndromes. Curr Opin Crit Care 2009; 15: 384-91.
9. Coresh J, Stevens LA. Kidney function estimating equations: where do we stand? Curr Opin Nephrol Hypertens 2006; 15: 276-84.
10. Braun E, Landsman K, Zuckerman R, Berger G, Meilik A, Azzam ZS; American Heart Association; American College of Cardiology; European Society of Cardiology. Adherence to guidelines improves the clinical outcome of patients with acutely decompensated heart failure. Isr Med Assoc J 2009; 11: 348-53.
11. Koschack J, Jung HH, Scherer M, Kochen MM. Prescriptions of recommended heart failure medications can be correlated with patient and physician characteristics. Int J Clin Pract 2009; 63: 226-32.
12. Flaherty JD, Bax JJ, De Luca L, Rossi JS, Davidson CJ, Filippatos G, Liu PP, Konstam MA, Greenberg B, Mehra MR, Breithardt G, Pang PS, Young JB, Fonarow GC, Bonow RO, Gheorghiade M, Acute Heart Failure Syndromes International Working Group. Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. J Am Coll Cardiol 2009; 53: 254-63.
13. Nieuwlaat R, Eurlings LW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, López-Sendòn JL, Meeder JG, Pinto YM, Crijns HJ. Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation. J Am Coll Cardiol 2009; 53: 1690-8.
14. Yilmaz MB, Refiker M, Guray Y, Guray U, Altay H, Demirkan B, Caldir V, Korkmaz S. Prescription patterns in patients with systolic heart failure at hospital discharge: why beta blockers are underprescribed or prescribed at low dose in real life? Int J Clin Pract 2007; 61: 225-30.
15. Ergin A, Eryol NK, Unal S, Deliceo A, Topsakal R, Seyfeli E. Epidemiological and pharmacological profile of congestive heart failure at Turkish academic hospitals. Anadolu Kardiyol Derg 2004; 4: 32-8.
16. Breidthardt T, Noveanu M, Potocki M, Reichlin T, Egli P, Hartwiger S, Socrates T, Gayat E, Christ M, Mebazaa A, Mueller C. Impact of a high-dose nitrate strategy on cardiac stress in acute heart failure: a pilot study. J Intern Med 2010; 267: 322-30.