European Journal of Internal Medicine 21 (2010) 439–443

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Mild heart failure is a mortality marker after a non-ST-segment acute myocardial infarction

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ARTICLE INFO

Article history:
Received 23 November 2009
Received in revised form 2 June 2010
Accepted 9 June 2010

Keywords:
Myocardial infarction
Heart failure
Killip class
Non-ST-segment elevation acute coronary syndrome

ABSTRACT

Background: The Killip classification categorizes heart failure (HF) in acute myocardial infarction, and has a prognostic value. Although non-ST-elevation myocardial infarction (NSTEMI) is increasing steadily, little information is available about the prognostic value of low Killip class in this scenario. Our aim was to assess the prognostic value of mild HF in NSTEMI.

Methods: 835 patients with NSTEMI between 2005 and 2007 were prospectively recruited. Patients in Killip-1 (K1 = 684) or Killip-2 class (K2 = 113) were selected (38, with K>2, excluded). Clinical, angiographic, treatment strategies, and 30-day all-cause mortality, together with other cardiovascular outcomes were recorded.

Results: K2 patients were mostly women (K1 27.9% vs K2 48.0%, $p<0.001$) and older (K1 66.6 years vs K2 73.8 years, $p<0.001$) with a higher frequency of diabetes mellitus ($p<0.001$) and hypertension ($p<0.001$). Smoking was less frequent in the K2-group ($p=0.003$). A previous infarction/revascularization history was similar in both groups. The infarction size, assessed by Troponin I/Creatin kinase, did not differ between groups ($p=0.378$ and $p=0.855$). Multivessel coronary disease and revascularization procedures were less common in group K2 ($p=0.015$ and $p=0.005$ vs group K1, respectively). Patients in K2 had a worse prognosis in terms of maximum Killip class, death and major adverse cardiovascular events ($p<0.001$). After multivariate analysis, mild HF at presentation was an independent risk factor for mortality (OR = 6.50; IC 95%: 2.48–16.95; $p<0.001$).

Conclusion: Mild HF at presentation in NSTEMI is linked to a poor prognosis, with increased short-term mortality. Thus, a more aggressive approach including early cardiac catheterization and revascularization should be considered.

1. Introduction

Heart failure is a common complication after a myocardial infarction, and it is linked to other complications and higher mortality [1–5]. The Killip–Kimball classification categorizes the presence and severity of heart failure in acute myocardial infarction using data obtained from the physical examination [6]. Patients are classified into I to IV classes (no heart failure, signs of mild heart failure, pulmonary edema-S3 and cardiogenic shock, respectively). Its simplicity and prognostic value are well known, and it is widely used as a readily achievable tool in daily practice [2,7,8]. Traditionally, only the highest Killip classes (III and IV) have been considered in studies focusing on the prognosis of this group of patients [9,10]. The proportion of patients with non-ST-elevation myocardial infarction (NSTEMI) proportion increased from 14.2% to 59.1% from 1990 to 2006 in the United States [11]. However, little information exists in the literature regarding the prognostic value of low Killip class in this scenario.

Keeping all these considerations in mind, we conducted the present study with the aim to assess the prognostic value of mild heart failure in patients with NSTEMI.

2. Methods

2.1. Patients

Between January 2005 and December 2007, 835 consecutive patients admitted to the coronary care unit of San Carlos Hospital Cardiovascular Institute in Madrid, Spain, with the diagnosis of NSTEMI [12] were assessed for the present study. The diagnosis of

Abbreviations: MACE, Major adverse cardiovascular events; NSTEMI, Non-ST-elevation myocardial infarction; PCI, Percutaneous coronary intervention; Tn I, Troponin I.

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doi:10.1016/j.ejim.2010.06.003

NSTEMI was based on the criteria of the European Society of Cardiology at that time [12]. Patients were divided according to Killip classification at presentation, as following: K1 = 684 (81.9%), K2 = 113 (13.5%), and K3–4 = 38 (4.5%). The attending physicians were unaware of the purposes of this study. Patients were considered K3 when pulmonary edema was depicted on chest x-ray [6], and cardiogenic shock or Killip IV was defined by the clinical criteria of the SHOCK trial [13]. K3 and 4 patients were excluded, and the remaining 797 patients constituted the study group.

Baseline characteristics, therapeutic approach, in-hospital and 30-day outcomes were collected. The main end-points were death, maximum Killip class and new myocardial infarction. A combined event included all the previous end-points (MACE).

2.2. Statistical methods

SPSS 13.0 for Windows (SPSS 2006, Illinois) was used for statistical analysis and unless otherwise indicated, data are expressed as the mean value ± standard deviation or percentages. They are shown as median and inter-quartile range when necessary. Comparisons between groups were made with Pearson's chi-square test for categorical variables and the Student *t*-test or Mann–Whitney U-test for continuous variables. The following variables were assessed: age, gender, diabetes mellitus, arterial hypertension, smoking, dyslipemia, peak troponin value, multivessel disease (three vessel or left main plus right coronary artery involvement), gpIIb/IIIA inhibitors, beta-blockers, statins, early initiation of ACEIs/ARB and PCI/CABG during CCU stay. Linearity assumption was assessed using the residual analysis. This assumption was satisfied by every continuous variable. Comparisons were considered significant when two-sided p value <0.05.

3. Results

Baseline features showing different patient profiles are displayed in Table 1. Patients with heart failure at admission (K2) were more frequently women (K1 27.9% vs K2 48.0%, p<0.001), older (K1 66.6 vs K2 73.8 years, p<0,001) and had significantly more comorbidities such as DM (p<0,001) and hypertension (p<0,001). Nonetheless, smoking habit was less common between them (p = 0,003). A previous history of myocardial infarction or coronary revascularization was equally frequent in both groups (p = 0.124). The infarct size, measured by Tn I or CK, was similar between groups, as well (p = 0.378 and p = 0.855, respectively). However, an extensive coronary involvement with multivessel disease was more commonly found in K2 group than it was in K1 patients (p = 0.015, Table 1). Cardiac catheterization was performed more frequently in K1 group. The initial medical treatment at the coronary care unit displayed some differences between groups. Of note, more K1 than K2-patients received gpIIb/IIIa inhibitors (70.3% vs 54.9%, p = 0.003), beta-blockers (77.6% vs 46.0%, p = 0.000), and statins (87.1% vs 76.1%, p = 0.002). However, angiotensin converting enzyme inhibitors or angiotensin receptor blockers were more commonly administrated to K2-patients (60.5% vs 74.3%, p = 0.005). Revascularization procedures during CCU stay were significantly more common among K1 patients (72.2% K1 vs 61.2% K2, p = 0.005). After a 30-day follow up, worse outcomes were found in K2 group (Table 2), in terms of maximum Killip class (Fig. 1), MACE and exitus (1.8% vs 14.2%, p<0.001). Fig. 2 displays the complication percentages in every group. Of note, only 7% of the patients in K1 group developed adverse events, compared to 27% of the patients in K2 group (p<0.001).

In order to identify the existence of independent risk factors for mortality, a multivariable analysis was conducted including age, gender, diabetes mellitus, hypertension, smoking habit, dyslipidemia, Killip class at admission, peak troponin value, multivessel disease, use of gpIIb/IIIA inhibitors, beta-blockers, statins, ARB/ACEIs and revascularization procedures (none/PCI/CABG) during CCU stay (Table 3). Mild heart failure at admission was found to be an independent risk factor for 30-day mortality (OR = 6.50; IC 95%:2.48–16.99; p<0.001). Early initiation of ACEIs and statins displayed a protective short-term effect on mortality (p<0.05).

Then, an additional multivariable analysis addressing independent risk factors for MACE was performed. Again, Killip-II class retained its prognostic significance, along with multivessel disease, use of statins, previous events and infarct size (Table 3).

Table 1
Baseline characteristics.

	No HF (K1)	HF (K2)	p
n	684 (85.8%)	113 (14.2%)	–
Mean age (years)	66.6	73.8	**0.000**
Male (%)	72.1%	52%	**0.000**
Hypertension (%)	62.4%	78.8%	**0.001**
DM n, (%)	28.7%	49.6%	**0.000**
Dyslipidemia n, (%)	54.2%	49.6%	0.355
Smoking n, (%)	29.2%	15.2%	**0.003**
Previous diagnosis of CAD	27.5%	27.4%	0.991
Previous coronary revascularization	23.5%	27.4%	0.124
Myocardial markers			
Peak CK	472.2	459.3	0.855
Peak troponin I	14.6	18.1	0.378
LVEF[a] (CCU, echocardiography)	52.49 ± 10.96	39.11 ± 13.24	**0.000**
Coronary angiography during hospitalization (%)	96.3%	86.7%	**0.000**
Location of severe coronary lesions			
LMA	7.6%	8.8%	**0.647**
LAD	44.4%	48.7%	0.403
RCA	37.6%	40.7%	0.525
Cx	38.6%	46.0%	0.135
Multivessel disease (3 vessel or LMA + RCA)	22.8%	33.6%	**0.018**
Patients undergoing revascularization procedures (CCU)			
None (conservative)	27.5%	39.8%	**0.005**
Only PCI	58.6%	43.5%	
CABG (± PCI[b])	13.9%	17.7%	

CABG: Coronary artery bypass grafting. CCU: coronary care unit. CK: creatin kinase. Cx: circumflex coronary artery. DM: diabetes mellitus. LAD: left anterior descendent coronary artery. LMA: left main coronary artery. LVEF: left ventricular ejection fraction. PCI: percutaneous coronary intervention. RCA: right coronary artery.
[a] LVEF, when available at CCU (314 and 62 patients, respectively).
[b] Including mixed procedures and CABG after PCI failure (0.5% overall).

4. Discussion

To our knowledge, this is the first study focusing on the prognostic influence of mild heart failure alone in patients with NSTEMI.

The Killip classification is a validated and a simple way to assess the patient's heart failure-status after all kind of infarctions in daily practice. Its validity and usefulness have been maintained since it was first described in 1967 over 250 patients. In the original study, a 3 fold higher mortality in AMI was noted in Killip-II class compared to Killip-I class patients. Nowadays it is still considered “state of the art” [7] in full. That is because heart failure is a frequent, well known complication after an acute coronary syndrome [1]. In our study, it was present in 18% of our patients. Heart failure during an acute coronary event has been consistently related with other complications

Table 2
Outcomes during short-term follow up (30 days).

	No HF (K1)	HF (K2)	p
In hospital stay (mean, days)	6.98	13.84	**0.011**
Pulmonary edema	1.2%	8.8%	**0.000**
Reinfarction	4.1%	4.4%	0.870
Death	1.8%	14.2%	**0.000**
MACE	6.1%	20.4%	**0.000**

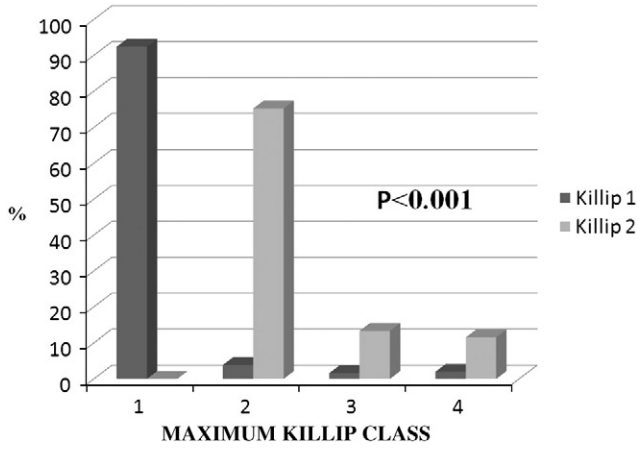

Fig. 1. Maximum evolutive Killip class according to Killip class at admission.

Table 3
Multivariable analysis for mortality and the combined event (MACE). Variables included in the model are explained on the text. Only variables which showed statistical influence are displayed (p<0.11).

Mortality	OR	CI, 95%	p
K2	6.50	2.48–16.99	**0.000**
gpIIb/IIIa	0.73	0.50–1.06	0.102
Onset ACEI/ARB use.	0.38	0.15–0.95	**0.040**
Statins	0.25	0.09–0.69	**0.001**
Multivessel disease[a]	5.66	1.95–16.37	**0.008**
MACE	**OR**	**CI, 95%**	**p**
Previous revascularization	1.44	1.00–2.07	**0.045**
K2	2.93	1.46–5.91	**0.002**
Troponin	1.01	1.00–1.019	**0.001**
Statins	0.34	0.16–0.70	**0.004**
Multivessel disease[a]	2.55	1.30–5.00	**0.006**

[a] Triple vessel disease or left main plus right coronary artery involvement.

and higher mortality [4,5,7,14,15]. Therefore, its proper and early management is warranted. Being extensively addressed in previous studies, Killip class as a marker of worrisome prognosis has been classically considered in its highest degrees (Killip-III or IV class) [16]. Some authors have pointed out its overall relevance. Khot analyzed information from 26090 patients with non-ST-elevation acute coronary syndromes enrolled in the GUSTO IIb, PURSUIT, PARAGON A, and PARAGON B trials, between 2001 and 2003, concluding Killip classification was a powerful independent predictor of all-cause mortality, as well [8].

Here, our data exhibit the current great importance of even mild signs of heart failure in NSTEMI, in terms of 30-day survival, and adverse events such as pulmonary edema and cardiogenic shock.

The optimal management of this group of patients has not been completely established yet. The current ESC guidelines, do not advise an early catheterization (<72 h) [17] for all NSTEMI, as they do for ST-segment elevation acute myocardial infarction. In non-ST-segment elevation MI, an invasive strategy has shown to improve outcomes in high-risk patients, as recognized in the current AHA and ESC guidelines. But optimal timing for catheterization remains controversial. Probably, currently available evidence is incomplete. This is particularly true for catheterization within 12 h of presentation [18] and, as it has been recognized by the CRUSADE authors, a significant risk reduction may have not been excluded in this subgroup of patients.

In spite of that, an early invasive strategy is recommended for high NSTEMI risk patients, primarily based on three large randomized trials: the Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease (FRISC)-II trial, the Treat Angina with Agrastrat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 (TACTICS–TIMI-18) trial and the third Randomised Intervention Treatment of Angina (RITA 3) trial [19,20]. That is why K2 patients should probably receive particular attention in the initial risk assessment, bearing in mind the possibility of an invasive management [17].

Other authors have previously pointed out other factors which may carry a worse outcome after such an increasingly frequent condition as NSTEMI, and several prognostic scoring systems have been proposed [3,5,8,9,21,22]. Thus, other clinical parameters such as age [22], gender [11,23], race [24], diabetes [25,26], depression [27], peripheral vascular disease [28], kidney failure [22], previous infarctions [22], type of infarction [26], electrocardiographic and echocardiographic parameters [29] including ischemic mitral regurgitation [15,30], laboratory parameters including troponin, NT proBNP or PCR levels [31], leucocytes [22], anemia [32] or even circulating endothelial cell levels [33], medical treatment (beta-blockers) or influence of coronary revascularization [17], etc.

We were not able to identify an independent influence of beta-blockers on the short-term course, although they were more commonly prescribed to K1. Conversely, we did find ACEIs and statins to exert an independent protective effect, which is congruent with previous reports [5,17,34].

5. Study limitations

The observational non-randomized design of this study warrants that our results must be assumed carefully. Not every patient in our series had coronary arteriography or revascularization, but it is of note that this study is not an intervention study. The management of these patients was the standard management at that time in our Institution

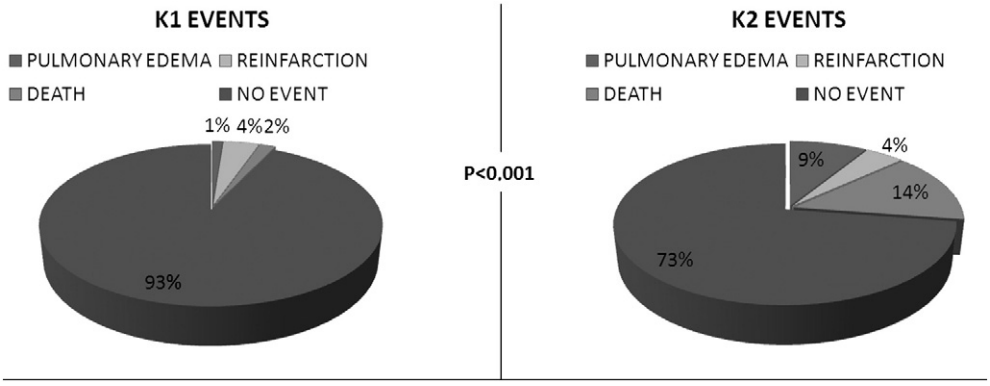

Fig. 2. Event distribution in K1 and K2 groups.

and it depended on the physician's preferences, following current recommendations at the moment. So, in this way, our results reflect more closely the daily clinical practice and the short-term evolution after a NSTEMI. Although we did not consider properly the timing to angiography in our study, we felt that an invasive strategy of early cardiac catheterization would be beneficial based on previous data about high-risk patients [17,19,20].

6. Conclusions

Heart failure is a frequent complication after an NSTEMI. Its presence in this clinical scenario provides independent prognostic significance that must be considered along with other risk factors. Even in its mild degree, heart failure is still associated with increased mortality, as it was in the original description given by Killip and Kimball in 1967. Thus, patients with Killip-II class, should be managed as high-risk patients; heart failure must be promptly addressed and earlier invasive strategy should be considered. Further studies focusing on the matter, providing additional data and evidence, are needed to support our findings.

7. Learning points

- Heart failure is a common complication following myocardial infarction.
- The presence and severity of heart failure at the time of initial presentation have been formally categorized into the Killip classification.
- The proportion of non-ST-elevation myocardial infarction increased from 14.2% to 59.1% from 1990 to 2006 (American National Registry of Myocardial Infarction), compared to ST elevation infarctions.
- Despite the new state of the art treatments, Killip classification is still a powerful independent predictor of mortality in patients with non-ST-elevation acute coronary syndromes.
- The exact timing for cardiac catheterization remains unclear for non-ST-elevation myocardial infarction. However, patients with $K \geq 2$ could benefit from early invasive management.
- Meeting the current practice guidelines improve outcomes.

Disclosures

There is no conflict of interest concerning this manuscript.

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