Clinical research

Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey

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Aims The impact on outcome of the implementation of European guidelines for the treatment of chronic heart failure (CHF) has not been evaluated. We investigated the consequences of adherence to care by cardiologists on the rate of CHF and cardiovascular (CV) hospitalizations and time to CV hospitalization.
Methods and results We constructed class adherence indicators for angiotensin-converting enzyme (ACE)-inhibitors, beta-blockers, spironolactone, diuretics, and cardiac glycosides and GAIs (GAI3 adherence to first three classes of heart failure medication, GAI5 adherence to five classes). In the study, 1410 evaluable patients (mean age 69, 69% males, New York Heart Association (NYHA) II: 64%, III: 34%, IV: 2%) were enrolled and followed up for 6 months by 150 randomly selected cardiologists/cardiology departments from six European countries (France, Germany, Italy, The Netherlands, Spain, and UK).
Overall, adherence to treatment guidelines was 60 (GAI3) and 63% (GAI5) and was better for ACE-I (88%) or diuretics (82%) than for cardiac glycosides (52%), beta-blockers (58%), and spironolactone (36%). In the three tertiles of the population defined by a decreasing mean adherence score value, CHF and CV hospitalization rates were, respectively, 6.7, 9.7, and 14.7% and 11.2, 15.9, and 20.6% ($P < 0.002$ and $P < 0.001$, respectively). Global adherence indicator GAI3 was an independent predictor of time to CV hospitalization in a multi-variable model together with NYHA Class, history of CHF hospitalization, ischaemic aetiology, diabetes mellitus, and hypertension.
Conclusion We demonstrate that adherence of physicians to treatment guidelines is a strong predictor of fewer CV hospitalizations in actual practice. There is a need to develop further quality improvement programmes in this condition.

Introduction

Chronic heart failure (CHF) is a condition characterized by unpleasant symptoms, high mortality, and recurrent and lengthy hospitalizations. It is a burden for health care systems.[1] Major improvement in the medical management of CHF has been achieved in the past decades. Angiotensin-converting enzyme (ACE) inhibition and beta blockade have both been demonstrated to be of benefit in mild, moderate, and severe heart failure due to left ventricular systolic dysfunction, whereas, aldosterone antagonists have proven efficacy in more severe stages of CHF.[2–7] More recently, angiotensin receptor blockers have shown benefit as an alternative to or on top of ACE-inhibitors.[8,9] The results of large placebo-controlled, randomized trials published till 2001 have been integrated into the 'Guidelines for the diagnosis and the treatment of chronic heart failure' published by the European Society of Cardiology (ESC).[10]

However, both national and European surveys consistently suggest that there is a suboptimal utilization of recommended medications in outpatients as well as in hospital situations.[11–13] In particular, the Euro heart failure survey performed in 116 hospitals across 24 ESC countries shows a suboptimal utilization of ACE-inhibitors and particularly of beta-blockers.[11]

We evaluated the impact of implementation or non-implementation of ESC treatment guidelines on disease outcome measured by CV hospitalizations in a large prospective international observational survey performed from November 2001 to September 2002 in six European countries, the MAHLER survey (Medical Management of Chronic Heart Failure in Europe and Its Related Costs).

Methods

The MAHLER Study is a multi-centre, observational study on the medical management and cost of CHF in six European countries (France, Germany, Italy, The Netherlands, Spain, UK).

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The primary objective was to describe the medical management, healthcare resource utilization, and the direct or indirect costs of this condition in each participating country and will be reported elsewhere. The second objective was to evaluate the impact of the implementation of the recommendations for the diagnosis and treatment of CHF on outcome and is reported in the present manuscript.

Inclusion criteria were (i) age $\geq$ 40; (ii) prevalent CHF in New York Heart Association (NYHA) Class II–IV; (iii) diagnosis of CHF on the basis of the presence of signs and symptoms suggestive of CHF and objective evidence of cardiac dysfunction as recommended by the ESC guidelines.[10] Patients presenting with acute pulmonary oedema, recent myocardial infarction (<1 month), cardiogenic shock, significant valvular disease, or planned surgery in the next 6 months were excluded.

A target recruitment of 250 patients was planned in each country. Thus, total target recruitment was 1500 patients. MAHLER was powered to examine relationships between overall CV hospitalization rates and key clinical variables. The recruitment goal was considered sufficient to detect a 40% difference in hospitalization rates between NYHA Class II and III patients with 80% power. This assumed an average of one hospitalization per patient-year and a drop-out rate of 20%.

Three visits were performed at baseline 3 and 6 months. At baseline, social and demographic data were recorded together with lifestyle, risk factors, cardiovascular (CV) history, clinical profile, diagnostic procedures, and medical treatment. All changes in the baseline characteristics as well as visits and outcome variables including death, CV and heart failure hospitalizations were recorded at 3 and 6 months.

Physicians reported the primary cause of hospitalizations and these were classified as CHF, other CV hospitalizations, or non-CV hospitalizations on the basis of their diagnoses.

Ethical approval was obtained in each country. The survey was under the supervision of an independent Steering Committee (Appendix I). At inclusion, patients were followed as outpatients by office or hospital-based cardiologists.

Selection of cardiologists

In all countries except UK, cardiologists were randomly selected from lists provided by national medical institutions. Twenty-five cardiologists were selected in each country and were asked to recruit 20 consecutive patients. If they declined, they were replaced by the same random procedure. In UK, a random sample of 25 hospitals with a cardiology department was selected and stratified by region and hospital size. The investigator was then identified by the head of the department of cardiology. The list of investigators is provided in Appendix II.

We based the assessment of adherence to the ESC guidelines on the criteria/procedures recommended by the ESC for the use of ACE-inhibitors, beta-blockers, spironolactone, diuretics, and cardiac glycosides.[10]

Indicators of adherence to guidelines

An adherence indicator was developed using a two-step procedure on the basis of the five pharmacological classes mentioned previously. First, it was determined whether, according to the individual patient's profile, a recommended drug was prescribed. Algorithms used to determine whether a patient is adherent or non- adherent to the ESC guidelines for each medication are given in *Table 1*.

For each of the five therapeutic classes of interest, we computed a class adherence indicator defined as the proportion of patients whose physicians prescribed according to the guidelines. We also computed a global adherence indicator (GAI) by calculating for each patient the proportion of indicated care (across all five therapeutic classes) that was prescribed. Our term 'adherence' in this study related solely to physicians following guidelines, not to patient compliance or persistence.

Owing to the fact that evidence-based benefit on outcome is much stronger for ACE-inhibitors, beta-blockers, and spironolactone than for cardiac glycosides or diuretics, we also calculated a separate GAI on the basis of first three classes (GAI3). Then, the pre-specified GAIs, GAI3 and GAI5, were included with other clinical variables in Cox proportional hazard models designed to predict CHF and CV hospitalizations. GAI3 and GAI5 were continuous variables.[14] It was anticipated that higher GAI values would be associated with longer times to re-hospitalization. A Cochrane–Armitage test was performed in order to evaluate whether the rate of CV hospitalization was different among three adherence groups. These were perfect adherence (100%), moderate adherence (50–67%), and low adherence (0–33%). Kaplan–Meier estimates for the time to CV hospitalization on the basis of adherence measures were obtained and a log-rank test was used to test differences between the three adherence groups.

Univariate analyses were performed using variables including age, gender, NYHA Class, presence of co-morbidity (atrial fibrillation, diabetes mellitus, myocardial infarction, hypertension), history of CHF hospitalization in the 12 months prior to inclusion, and country. The outcome variable was time to any CV hospitalization (including both CHF and other CV causes). All factors which were significant at the 5% alpha level in univariate analysis were used in a multi-variate model.

All analyses of quality of care were pre-specified. The aim was to examine the relationship between quality of care and outcomes and not to interpret the significance of other variables in the multi-variable model. Analyses were centred on the pooled set of patients from all six countries, and there was no goal of comparing results from different countries. Therefore, no adjustments were made for multiple comparisons. All tests were two-sided. Graphical methods were used to assess model assumptions and all were satisfied.

Statistical analysis used the statistical package software SAS for windows™ version 8.02.

Results

Patients

In the MAHLER Study, 1410 evaluable patients were included: 248 in France, 251 in Germany and Italy, 246 in the Netherlands, 249 in Spain, and 165 in UK between November 2001 and April 2002. The lower number of patients enrolled in UK was related to a late start of recruitment. There were 971 male (69%) and 439 female (31%) subjects with no significant difference across countries. Mean age was 68.6 years [standard deviation (SD), 10.4].

On inclusion, 902 patients (64%) were in NYHA Class II, 485 (34%) in class III, and 23 (2%) in Class IV. Of these, 496 patients (35%) had experienced at least one previous CHF hospitalization. This proportion was higher in Italy (44%) and in The Netherlands (43%) than in Spain (39%), UK (36%), France (29%), or Germany (21%). The predominant aetiology was ischaemic and more than half of the population had an history of hypertension (*Table 2*).

Most patients complained of breathlessness or fatigue, whereas, only less than half of them had symptoms of peripheral congestion. First-line assessment was made by ECG and X-ray in majority of patients. BNP plasma determination was made only in a minority. Doppler echocardiography was the method of choice for the confirmation of cardiac dysfunction in >80% of patients except for patients of UK. On average, the adherence to ESC guidelines for diagnosis of CHF in the six countries was high with slight variations

Table 1 Algorithms for adherence to guidelines indicators computation

Therapeutic class	Guidelines conditions for therapeutic class use	Criteria for guidelines enforcement
(A) ACE inhibitor/AIIRA	IF (NYHA class III OR IV at baseline) THEN guidelines apply; ELSE IF NYHA class II at baseline AND ('YES' to symptoms of breathlessness, ankle swelling or fatigue) THEN guidelines apply; ELSE IF diuretic prescribed THEN guidelines apply.	IF Guidelines applies AND patient is on ACE inhibitor or AIIRA at baseline THEN guidelines are met.
(B) Diuretics	IF NYHA class II at baseline AND 'YES' to symptoms of ankle swelling THEN guidelines apply; ELSE IF NYHA class III or IV at baseline THEN guidelines apply.	IF Guidelines applies AND patient is on diuretics at baseline THEN guidelines are met.
(C) Beta-blockers	IF 'NO' to diagnoses of asthma/COPD THEN guidelines apply.	IF Guidelines applies AND patient is on beta-blocker at baseline THEN guidelines are met.
(D) Spironolactone	IF NYHA class III or IV at baseline THEN guidelines apply.	IF Guidelines applies AND patient is on spironolactone at baseline THEN guidelines are met.
(E) Glycosides	IF 'YES' to atrial fibrillation OR (NYHA class III or IV at baseline) THEN guidelines apply.	IF Guidelines applies AND patient is on glycosides at baseline THEN guidelines are met.

Table 2 Cardiovascular status and baseline medication

	n	(%)
NYHA II	902	64
NYHA III	485	34
NYHA IV	23	2
Male/female	971/439	69/31
Previous myocardial infarction/ischaemic heart disease	956	68
Hypertension	779	55
Diabetes mellitus	331	23
Stroke/TIA	169	12
Coronary bypass	264	19
PTCA/stent	147	10
Valve replacement	102	7
Baseline medication		
ACE-inhibitors	974	69
Angiotensin II receptor antagonist	248	17.6
Beta-blocker	752	53
Diuretics	1108	79
Cardiac glycoside	581	41
Spironolactone	396	28
Nitrates	457	32
Aspirin/clopidogrel	505	36
Statin	478	34
Anticoagulant	492	35

There were 1421 patients included in the MAHLER study, of whom 1410 were evaluable. Of these, 1333 (94%) patients completed the final visit and there were 63 (4.4%) patients who died during follow-up. Twenty-five patients withdrew their consent or were lost to follow-up prior to the end of the study or could not be included in the statistical analysis because of missing data even though they had completed the final visit.

Two hundred and thirty three patients (17%) were hospitalized for a CV reason during follow-up; worsening heart failure was the most common reason (128 patients, 9.1%) followed by arrhythmias ($n = 36$, 2.6%), myocardial infarction ($n = 14$, 1%), stroke ($n = 13$, 0.9%), and ischaemia ($n = 12$, 0.9%).

Guideline adherence indicators

GAIs were 63 (GAI5) and 60% (GAI3). They were rather homogenous across the six countries. Class adherence indicator was high for ACE-inhibitors (85.4%) and diuretics (83%) but was much lower for beta-blockers (58%), cardiac glycosides (52%), and spironolactone (36%) with variations across countries.

GAIs as predictors of hospitalization

Table 3 shows the CHF and CV hospitalization rates in the overall population divided into three homogeneous groups according to the adherence score (perfect adherence, moderate adherence, and low adherence as determined by GAI3). CV and CHF hospitalization are significantly lower in groups with a better adherence score. Similar trends were not seen for GAI5 (data not shown) suggesting that the indicator based on robust evidence was more strongly associated with the hospitalization rates. *Figure 1* shows Kaplan–Meier estimates for CV hospitalization according to GAI3 tertiles.

across countries. The overall adherence to diagnosis guidelines was 74%.

Baseline medications are given in *Table 2*. A total of 69% of patients were taking an ACE-inhibitor, 87% either an ACE-inhibitor or an angiotensin type-II receptor blocker, 53% a beta-blocker, 79% a diuretic agent, 41% a cardiac glycoside, and 28% spironolactone.

The average follow-up was 175 days (median 182, interquartile range 170–188). It was homogenous across countries except in UK where it was 155 days because of the late start of recruitment in this country.

Table 3 Hospitalization rates among tertiles of selected adherence measure (GAI3)

Patients groups	n	Mean adherence score GAI3	CHF hospitalization rate (%)	Cardiovascular hospitalization rate (%)
Perfect adherence (GAI3 = 100%)	643	1.000	6.7	11.2
Moderate adherence (GAI3 = 50–67%)	548	0.55	9.7	15.9
Low adherence (GAI3 = 0–33%)	218	0.15	14.7	20.6
Total	1409		9.1	14.5
P-value (two-sided Cochran–Armitage test)		—	0.0004	0.0003
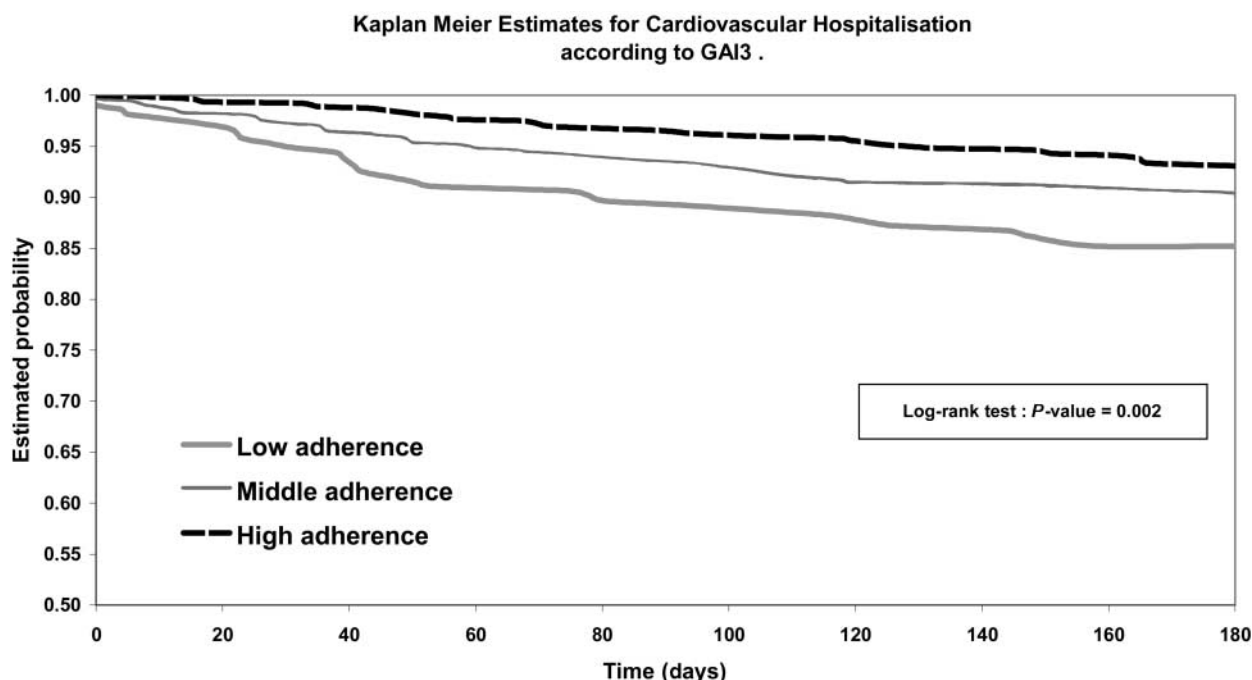
Figure 1 Kaplan–Meier curve of cardiovascular hospitalizations according to GAI3 tertiles. See Supplementary material online for a colour version of this figure.

Table 4 gives the statistically significant factors predicting time to CV hospitalizations that were included in the multivariate model. The relationships between covariates and outcome were clinically relevant. Time to CV hospitalization was influenced by severity of CHF (NYHA Class III), an history of previous CHF hospitalization, ischaemic aetiology, presence of hypertension or diabetes mellitus, and adherence to care measured by GAI3 which was a strong and independent predictor of delayed hospitalization.

Discussion

Population profile and adherence to diagnosis guidelines

We enrolled a large European population with mild-to-moderate heart failure. Unlike previous surveys, we carefully selected investigators by randomization and not on a voluntary basis in the six countries involved in the study in order to avoid both patients and physicians profile bias. The

clinical profile of our patients is consistent with previous surveys performed in outpatients or in hospital in terms of age and predominance of ischaemic aetiology.[11–13] The extrapolated 1 year mortality rate (8.8%) and cause-specific hospitalizations with more than half CHF hospitalizations were also consistent with previous surveys or trials[4–6] performed in this group of patients with mild/moderate heart failure.

Physician adherence to ESC diagnosis guidelines was high overall (75%). This reflects the fact that MAHLER was performed among cardiologists and not general practitioners with a high rate of prescription of first line tests such as electrocardiogram or X-ray. The very low rate of use of BNP plasma determination might result from the fact that many investigators were in private practice where BNP availability was low at the time of the survey. Doppler echocardiography was by far the most common second line test for the confirmation of cardiac dysfunction with some variations across countries, whereas other imaging techniques were used marginally. This is consistent with previous European surveys.[11]

Table 4 Predictors of time to cardiovascular (CV) hospitalization—multivariable Cox model

Factors	Time to CV hospitalization		
	Hazard ratio	95% CI	P-value
NYHA III	1.72	1.29–2.30	0.0002
CHF hospitalizations in last 12 months	1.84	1.38–2.44	<0.0001
GAI3	0.64	0.41–1.00	0.048
Ischaemic aetiology	1.44	1.08–1.91	0.013
Atrial fibrillation	1.34	1.01–1.78	0.045
Diabetes mellitus	1.43	1.05–1.93	0.022
Hypertension	0.70	0.53–0.93	0.012

Treatment profile, adherence to treatment guidelines, and impact on outcome

We found that the overall physician adherence to ESC treatment guidelines was 63%. Treatment profile was characterized by a high rate of prescription of diuretics and ACE-inhibitors similar to that reported in recent European surveys.[11,12] Prescription of beta-blockers was observed in only half of the patients who should be receiving them according to ESC guidelines. MAHLER confirms that a number of patients with symptomatic systolic dysfunction are still not treated or cannot be treated with beta-blockers despite a high level of evidence in favour of beneficial effect on morbidity and mortality. In contrast, a substantial proportion of our patients received cardiac glycosides despite the fact that this treatment is only recommended for symptomatic improvement.[10] This finding is also consistent with previous European surveys.[11,12] Overall, the analysis of class adherence indicators suggests a high level of compliance to guidelines for ACE-inhibitors or diuretics but a rather low level for beta-blockers, suggesting that there is still room for improving practice in Europe.

We found that adherence to treatment guidelines was independently and strongly correlated to outcome measured by rate of CHF or CV hospitalization and time to CV hospitalization.

To our knowledge, this is the first report of the direct impact of a global prescribing score on the outcome in an outpatient heart failure population in actual practice. In a cohort study performed in US, it was observed that both 1 year mortality and rehospitalizations were favourably influenced by ACE-inibitor treatment and that ACE-inhibitor prescription was predicted by cardiology consultation.[15] However, this survey was retrospective and conducted in 1994 before the introduction of beta-blockers as a major therapeutic concept in CHF. Two other more recent surveys in elderly or advanced elderly patients have also demonstrated a relationship between ACE-inhibitor prescription and outcome but the sample size was small.[16,17] In another US study, the rate of prescription of ACE-inhibitors was high in the white population > 65 years of age, but these results differ from those reported in the large ADHERE database of patients hospitalized for decompensated heart failure where the rate of ACE-inhibitors was only 44% prior to hospitalization and 54% at discharge.[18,19] It has been shown that the prescriber's specialty influences the rate of prescription of ACE-inhibitors.[11,20] Indeed, the high ACE-inhibitor prescription adherence observed here is probably due to the fact that MAHLER was conducted with cardiologists.

For beta-blockers, surveys show a constant under use both in terms of prescriptions and daily dosage. Here again, the rate of prescription is increased significantly among cardiologists vs. non-cardiologists,[11,20] and we observed in MAHLER a greater adherence to beta-blocker therapy than in the previous surveys. No previous survey has tried to evaluate the impact of beta-blocker prescription on outcome, on a background of other major heart failure medications on outcome, in actual practice and in outpatients. Recently, an Italian survey suggested that implementation of beta-blocker therapy could be improved in hospital and was associated with lower mortality and reduced hospital admission rates.[21]

Several quality improvement programmes including a limited number of patients have been developed over the past years in order to improve daily care in CHF. US and European programmes have demonstrated that specialized or 'aggressive' settings result in a significant improvement in the use of drugs such as ACE-inhibitors and beta-blockers which are associated with reduced morbidity or mortality and are cost effective.[22–24] New programs aiming at improving the standard of heart failure care in the hospital and outpatient settings are currently under development.[25] The present study shows a clear relationship between adherence to guidelines and subsequent CV hospitalizations in a large heart failure population treated by cardiologists. This should encourage development of integrated approaches including nurses, dieticians, generalists, and cardiologists in order to improve the management of CHF in clinical practice.

Strengths of MAHLER

We believe that by design, including careful random investigator selection, large sample size, and conduct of the survey across six European countries, MAHLER is representative of cardiology practice in western Europe. Unlike other surveys, we used a longitudinal design with few patients lost to follow-up at 6 months. We did not use only class-specific adherence to care indicators and a dichotomic approach (prescription or non-prescription) of a given class but also comprehensive indicators including the main therapeutic heart failure medications. GAIs were analysed in a multi-variablemodel together with other important clinical, demographic, and co-morbid factors increasing, therefore, the clinical relevance of our results.

Limitations

We measured only 'positive' adherence to care but could not evaluate the reasons why there was non-adherence. In particular, MAHLER did not record non-prescription of recommended classes for poor tolerance or contraindication. Thus, it is not suggested that 'non-adherence' is not appropriate for an individual patient. Accordingly, non-adherence could be either a cause or a marker of poor outcome. As many ambulatory CHF patients can be controlled without long-term use of diuretic agents, this may have impacted on the 'non-adherence' score of GAI5 despite appropriate therapy. Also, we did not measure dosage of the different

heart failure medications and, therefore, cannot take under dosage into consideration for our analysis.

The present database has enough subjects to examine the relationship between a GAI (integrating several classes of medication) and short-term outcomes. However, it is not large enough to compare and contrast the relationships between individual classes of medication and these outcomes. Although we note that GAI3 (on the basis of ACE-inhibitors, beta-blockers, and spironolactone) was more closely related to CV hospitalization than GAI5, we cannot draw from this observation any firm conclusions discouraging the use of diuretics or spironolactone in quality measurement efforts.

The follow-up duration was also limited, and we could not, therefore, evaluate the long-term impact of adherence to care on outcome and particularly all-cause mortality or CHF mortality.

Finally, the relatively young age of the population together with the high proportion of male subjects is not necessarily representative of real life heart failure patients.

Conclusion

We have demonstrated in a large European population of patients with mild/moderate heart failure that global indicators of adherence to the ESC guidelines are associated with decreased rates of heart failure and CV hospitalization and delayed time to rehospitalization. This observation made in actual practice among cardiologists in a pan European survey suggests that there is a need to develop further quality improvement programmes in this condition.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

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