Reasons Prompting Digitalis Therapy in the Acute Care Hospital

Raffaele Antonelli Incalzi,¹ Claudio Pedone,¹,² Marco Pahor,³ Luciana Carosella,¹ Roberto Bernabei,¹ PierUgo Carbonin,¹ and the GIFA Investigators

¹Istituto di Medicina Interna e Geriatria, CE.M.I., Università Cattolica del Sacro Cuore, Rome, Italy.
²Center for Gerontology and Health Care Research, Brown University, Providence, Rhode Island.
³Sticht Center on Aging, Wake Forest University, Winston-Salem, North Carolina.

Background. The choice of administering digitalis to older patients with congestive heart failure (CHF) cannot be made on the account of univocally defined criteria because of uncertainty about efficacy and concern about safety of digitalis in this population. The purpose of this study was to verify whether the clinical characteristics on admission to the acute care hospital determine the use of diigitalis therapy in elderly patients.

Methods. A total of 1239 patients (mean age 77.8 ± 7.1 years, range 65–100 years, males 49.8%) consecutively admitted to 69 General Medicine and Geriatrics wards over a 4-month period were grouped by combining two dichotomous factors (Carlson’s score >4: definite or possible diagnosis of CHF; in-hospital adoption of digitalis therapy: yes or no) as follows: Group A: Carlson’s score >4, digitalis (n = 413); Group B: Carlson’s score >4, no digitalis (n = 260); Group C: Carlson’s score <5, digitalis (n = 104); Group D: Carlson’s score <5, no digitalis (n = 462). Variables significantly distinguishing groups were entered into a discriminant analysis aimed at assessing the group specificity of individual clinical profiles.

Results. Use of digoxin at home, atrial fibrillation, older age, and comorbidity (mainly COPD and chronic renal failure) characterized most of the patients given digoxin with or without a definite diagnosis of CHF. Clinical profiles of groups A, B, and C largely overlapped.

Conclusion. Age, historical use of digitalis, and comorbidity might lead to seemingly incongruous digitalis prescription. The choice of adopting digitalis therapy cannot be reliably predicted on the basis of clinical variables only. Presently unexplored physician-related factors, such as cultural background, likely outweigh clinical variables in prompting digitalis prescription.

The rapidly expanding spectrum of therapeutic options for the treatment of congestive heart failure (CHF) has led to a reduction in the use of digitalis. The effectiveness of this drug in reducing mortality is not proven, although a reduction in hospitalizations has been shown (1). Thus, digitalis is no longer considered the mainstay of CHF therapy (2,3) but can be used to improve symptoms of mild to moderate CHF (4).

Age-related increases in the prevalence of risk factors for digitalis toxicity (e.g., polypharmacy, electrolyte imbalance, and renal failure) (5,6) make the decision to use digitalis in elderly CHF patients difficult.

The aim of this study is to verify whether the clinical profile on admission can be used to recognize the reason for the use of digitalis.

Methods

We studied 1239 subjects over the age of 65 consecutively admitted to the Internal Medicine and Geriatric wards participating in the GIFA (Gruppo Italiano di Farmacovigilanza nell’Anziano: Italian Group of Pharmacovigilance in the Elderly) multicenter trial over a 4-month period. Reasons for admission were acute medical problems (63.8%), routine investigation (28.1%), and transfer from other wards (8.1%). The study design has been previously reported in detail (7).

On the day of admission, each patient underwent a multidimensional assessment exploring sociodemographic status and health-related behaviors, functional capabilities as measured by the activities of daily living (ADLs) (8), and mental function as measured by the Abbreviated Mental Test (AMT) (9). Active diagnoses were coded using the International Classification of Disease, 9th revision, Clinical Modification (10). Pharmacological therapy was assessed by requesting the patient and, if necessary, their relatives or caregivers to display drug containers used in the 2 weeks prior to admission or to recall the names of the drugs if containers were not available. Drugs prescribed during the stay were recorded daily and were classified into therapeutic categories according to Anatomical, Therapeutical, and Chemical codes (11).

On the day of admission, the study physician completed a form recording symptoms and signs of CHF according to Carlson (12). This form includes three categories of symptoms and signs in patient history, physical examination, and chest radiography. Each symptom or sign has a score that is directly proportional to its diagnostic importance (i.e., to the contribution that an individual criterion provides to the correlation between the final score and the pulmonary wedge...
pressure). Items explored and their respective point values are reported in Appendix A. The cumulative CHF score of the individual patient can range from 0 to 12. The diagnosis of CHF is considered to be definite if the score is greater than 7, possible for a score of 5 to 7, and unlikely for a score less than 5 (12).

Patients with a possible or definite diagnosis of CHF with or without atrial fibrillation (score >4) were allocated to Group A if they had a digitalis prescription or Group B otherwise. Patients with a score <5, with or without atrial fibrillation, and taking digitalis were allocated to Group C. The remaining patients were allocated to Group D.

Statistical Analysis

The distribution of sociodemographic, medical, functional, and pharmacological data were compared across groups using chi square tests and an ANOVA test corrected for multiple comparisons as appropriate. Variables collected on admission that significantly distinguished groups in univariate analysis were entered into a discriminant analysis to compare clinical profiles of groups and to identify variables with the highest discriminant power. The Wilks’ lambda value was computed to assess the significance of the discriminant function. The Box’s M test was computed to estimate the risk of misclassification of individual clinical profiles (13).

Discriminant analysis allows the characterization of the clinical profiles of individual patients and comparison with the group-specific clinical profile. The final objective of the analysis was to verify whether a well-defined clinical profile characterized patients receiving digitalis (i.e., to recognize the rationale for prescribing digitalis).

Statistical analysis was performed using SPSS Version 9 (SPSS Inc., Chicago, IL) (14).

RESULTS

Table 1 shows baseline characteristics of the groups. Groups A and C were characterized by older age, lower education level, and a higher prevalence of widows than the other groups. Group D patients had better cognitive performance and a higher level of physical independence than the other groups.

Chronic obstructive pulmonary disease (COPD) was highly prevalent in patients with a diagnosis of CHF and among those taking digoxin despite a Carlson’s score less than 5, whereas it was relatively rare among patients with a Carlson’s score less than 5 who were not administered digoxin.

The prevalence of atrial fibrillation was about 30% in patients receiving digitalis regardless of CHF diagnosis and was 2.7% in CHF patients not receiving digitalis. Use of digitalis at home was strongly correlated with subsequent in-hospital use of this drug.

Table 2 compares the use of selected drugs in the four groups of patients. Diuretics, ACE-inhibitors, and other vasodilators were prescribed mainly to patients who had a definite diagnosis of CHF and who were also receiving digitalis.

Tables 3 and 4 show the results of the discriminant analysis. Both functions 1 and 2 could significantly differentiate groups: function 1 explained 88.6% of the cumulative variance and function 2 accounted for a further 10% of the vari-

Table 1. Characteristics of Patients on Admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n = 413)</th>
<th>Group B (n = 260)</th>
<th>Group C (n = 104)</th>
<th>Group D (n = 462)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)†</td>
<td>79.2 (6.9)</td>
<td>76.6 (7.1)</td>
<td>79.9 (6.7)</td>
<td>76.6 (7.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Males†</td>
<td>208 (50.4)</td>
<td>143 (55.0)</td>
<td>46 (44.2)</td>
<td>220 (47.6)</td>
<td>.169</td>
</tr>
<tr>
<td>Formal education (y)†</td>
<td>5.1 (3.0)</td>
<td>5.6 (3.7)</td>
<td>5.1 (3.3)</td>
<td>5.6 (3.2)</td>
<td>.043</td>
</tr>
<tr>
<td>Widows‡</td>
<td>187 (45.6)</td>
<td>100 (38.6)</td>
<td>50 (48.1)</td>
<td>168 (36.6)</td>
<td>.018</td>
</tr>
<tr>
<td>Drugs used at home‡</td>
<td>4.1 (2.3)</td>
<td>3.4 (2.2)</td>
<td>3.6 (2.2)</td>
<td>2.7 (2.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use of digitalis at home‡</td>
<td>265 (66.6)</td>
<td>37 (14.2)</td>
<td>62 (59.6)</td>
<td>47 (10.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Type of wards§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General medicine</td>
<td>155 (37.5)</td>
<td>118 (45.4)</td>
<td>24 (23.1)</td>
<td>163 (35.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>258 (62.5)</td>
<td>142 (54.6)</td>
<td>80 (76.9)</td>
<td>299 (64.7)</td>
<td>.001</td>
</tr>
<tr>
<td>AMT, correct answers‡</td>
<td>6.8 (3.0)</td>
<td>7.2 (3.1)</td>
<td>7.2 (3.0)</td>
<td>7.5 (3.1)</td>
<td>.015</td>
</tr>
<tr>
<td>ADLs, deficits on admission‡</td>
<td>1.8 (2.4)</td>
<td>1.5 (2.3)</td>
<td>1.5 (2.4)</td>
<td>1.1 (2.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum albumin, g/dl‡</td>
<td>3.6 (0.5)</td>
<td>3.5 (0.6)</td>
<td>3.6 (0.6)</td>
<td>3.6 (0.5)</td>
<td>.067</td>
</tr>
<tr>
<td>Serum sodium, meq/l‡</td>
<td>140.1 (4.1)</td>
<td>139.7 (4.6)</td>
<td>139.1 (3.8)</td>
<td>140.1 (4.0)</td>
<td>.084</td>
</tr>
<tr>
<td>Serum potassium, meq/l‡</td>
<td>4.1 (0.6)</td>
<td>4.2 (0.6)</td>
<td>4.0 (0.6)</td>
<td>4.1 (0.6)</td>
<td>.023</td>
</tr>
<tr>
<td>Osmolarity, mosm/l‡</td>
<td>312.1 (13.4)</td>
<td>310.9 (12.6)</td>
<td>306.5 (12.8)</td>
<td>309.5 (11.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Atrial fibrillation‡</td>
<td>124 (30.0)</td>
<td>7 (2.7)</td>
<td>27 (26.0)</td>
<td>9 (1.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Active medical problems‡</td>
<td>3.9 (2.3)</td>
<td>3.6 (2.4)</td>
<td>3.7 (2.3)</td>
<td>3 (2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>COPD‡</td>
<td>96 (23.2)</td>
<td>58 (22.3)</td>
<td>16 (15.4)</td>
<td>28 (6.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAD‡</td>
<td>124 (30.0)</td>
<td>59 (22.7)</td>
<td>28 (26.9)</td>
<td>79 (17.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronic renal failure‡</td>
<td>29 (7.0)</td>
<td>20 (7.7)</td>
<td>4 (3.8)</td>
<td>15 (3.2)</td>
<td>.03</td>
</tr>
<tr>
<td>Diabetes mellitus§</td>
<td>78 (18.9)</td>
<td>44 (16.9)</td>
<td>15 (14.4)</td>
<td>75 (16.2)</td>
<td>0.636</td>
</tr>
</tbody>
</table>

Notes: Group A: Carlson’s score >4, digitalis prescribed; Group B: Carlson’s score >4, digitalis not prescribed; Group C: Carlson’s score <5, digitalis prescribed; Group D: Carlson’s score <5, digitalis not prescribed. ADLs = Activities of Daily Living; AMT = Abbreviated Mental Test; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease.

†Values are means ± SD.
‡Values are number of patients with percentage in parentheses.
ance, whereas function 3 did not substantially contribute to discriminate groups. Among discriminant variables, use of digoxin at home was the main determinant of function 1; atrial fibrillation, COPD, and comorbidity further contributed to this function. A secondary diagnosis of COPD, atrial fibrillation, age, and chronic renal failure were the main determinants of discriminant function 2.

Table 5 shows a cross-tabulation of actual group membership, defined by selected criteria, versus functional group membership resulting from a clinical profile. A high degree of concordance between actual and predicted group membership was found in Group D, whereas a low degree of concordance characterized the remaining groups. Thus, only a minority of patients belonging to Groups B or C and 60.3% of group A patients were recognized as having a clinical profile typical of their actual group. The significant value of the Box’s M (862.5, $F = 4.15, p < .001$) indicates a negligible risk of misclassification of individual clinical profiles, meaning that the dispersion of clinical profiles reflects the heterogeneity of clinical conditions.

**DISCUSSION**

Our study shows that previous use of digitalis, history of atrial fibrillation, older age, and comorbid diseases (especially COPD) predict the adoption of digitalis therapy in the hospital; clinical profiles of patients receiving digitalis with or without a definite diagnosis of CHF largely overlap.

The practice of confirming home use of digitalis is likely to contribute to the preservation of the leading role this drug shares with diuretics in the treatment of CHF in general medicine and geriatrics wards. This practice has been associated with inappropriate prescription in a consistent proportion of patients (12,15), but present findings do not support this conclusion: only 77 out of the 517 patients who were administered digitalis neither met the Carlson’s criteria for CHF nor had atrial fibrillation. Nevertheless, a 15% prevalence of possibly inappropriate use should not be considered negligible, because these patients had mean age of 80 years and, thus, were at high risk of experiencing digitalis toxicity.

The association between older age and use of digitalis was not accounted for by the association of age and CHF or atrial fibrillation: 76.5% of subjects over 75 years receiving digitalis in the absence of a definite diagnosis of CHF did not suffer from atrial fibrillation; thus, aging might be a confounding factor leading to inappropriate digitalis prescription, and the high prevalence of noncardiogenic dyspnea and leg edema in elderly patients might be a clue to understanding this finding (15).

The association between COPD and in-hospital use of digitalis deserves some comment. The available evidence suggests that digitalis can benefit only COPD patients with a clinically significant left ventricular systolic dysfunction due to a coexisting disease (16). Given that the prevalence of such a dysfunction even in advanced COPD is quite low, the fact that 56.6% of our patients with COPD were given digitalis seems to indicate that COPD leads to incongruous digitalis prescription (17).

Only patients with a Carlson’s score less than 5, and who were not given digitalis, had a clinical profile with a high degree of group specificity. This means that these patients are easily recognized on admission, whereas the same is not true of patients in the other groups. The poor degree of group specificity of clinical profiles suggests that patient-related variables cannot completely explain differences in group location and that physician-related variables, such as personal judgment and therapeutic practice in individual

**Table 3. Results From Discriminant Analysis 1: Canonical Discriminant Functions**

<table>
<thead>
<tr>
<th>Function</th>
<th>Eigenvalue</th>
<th>Percent of Variance</th>
<th>Wilks’s Lambda</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.722</td>
<td>88.6</td>
<td>.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>.082</td>
<td>10.0</td>
<td>.91</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Note: Canonical discriminant function 3, accounting for 1.4% of the whole variance, has not been reported.*
wards, might help in predicting whether a patient will or will not be prescribed digitalis.

This study has some limitations. Some variables that may be potentially explanatory, such as type of specialty of the prescribing physician, were not collected, and no gold-standard criteria can be recommended for the diagnosis of CHF (18). This difficulty in diagnosing CHF could account, to some extent, for the large overlap of clinical profiles of Group A to C. Furthermore, the age-related increasing prevalence of factors apt to confound the clinical presentation of CHF supports the conclusion that the complex discriminant model really reflects the difficulty in predicting which patient will be prescribed digitalis on the basis of the patient’s clinical characteristics on admission.

In conclusion, the choice of adopting digitalis therapy cannot be reliably predicted on the account of clinical variables only, although some of these characterize patients who will be prescribed digitalis in the absence of a definite diagnosis of CHF. Exploring the cultural background of the prescriber could help limit the possible overuse of digitalis as well as promote the presently limited use of ACE inhibitors and beta blockers.

Acknowledgment

Address correspondence to Claudio Pedone, MD, PhD, Center for Gerontology and Health Care Research, Brown University, 171 Meeting Street, Providence, RI 02912. E-mail: Claudio_Pedone@Brown.edu

References


Appendix A

Carlson’s Score

Items explored in individual categories of the Carlson’s score for Congestive Heart Failure and, in parentheses, their respective point values.

- Category “History”: rest dyspnea (4), orthopnea (4), paroxysmal nocturnal dyspnea (3), dyspnea on walking on level (2), dyspnea on climbing (1).
- Category “Physical Examination”: heart rate >90 bpm (1), heart rate >110 bpm (2), jugular venous pressure >6 cm H2O (2), jugular venous pressure >6 cm H2O plus hepatomegaly or edema (3), basilar lung crackles (1), more than basilar lung crackles (2), wheezing (3), third heart sound (3).
- Category “Chest Radiography”: alveolar pulmonary edema (4), interstitial pulmonary edema (3), bilateral pleural effusion (3), cardiothoracic ratio ≥0.5 (3), and upper-zone flow redistribution (2).

The maximum obtainable subscore in each category cannot exceed 4. To provide an example, a patient with interstitial pulmonary edema (p. 3), and cardiothoracic ratio ≥0.5 (p. 3) produces a total subscore of 4 in the category “Chest Radiography.”

Appendix B

GIFA Investigators

Coordinating Center

Chief Investigator: P.U. Carbonin

Investigators: M. Pahor, L. Carosella, R. Bernabei, C. Pedone, A. Sgadari, G. Onder

Software: M. Carli, M. Pavon

Technical support: G. Vagni

1. Acquaviva delle Fonti - Divisione di Gerontologia, Ospedale “Miulli” - V. Aloeia, G. Baldassarre
2. A. Andreoni, P. Angelini, L. Gigli, P. Tomassini
3. A. Sgadari, G. Onder
4. J. Crampe, M. Pavon
5. A. Andreoni, P. Angelini, L. Gigli, P. Tomassini
6. P. Pescetelli