Chronic heart failure diagnostics and application of neuropeptides in residential elderly

Barents, Maaike

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Chapter 6

SUMMARY, DISCUSSION, RECOMMENDATIONS AND FUTURE PERSPECTIVES
Chapter 6.1

SUMMARY

A drawback of the improved survival from cardiovascular diseases (CVD) (1) is that cardiovascular morbidities have grown. As we have emphasized in the introduction of this thesis, the number of people living with heart failure (HF) has increased impressively in conjunction with a tremendously improved life expectancy of the Dutch population (www.cbs.nl; www.nationaalkompas.nl), during the last century. Since HF is mainly a problem of advanced age, subjects diagnosed with chronic HF (CHF) often concern elderly. However, there is a wide lack of knowledge with regard to data on HF when age progresses and elderly become frail and more care dependent. The most care dependent elderly are committed to a care or nursing home. In this thesis, those elderly persons are indicated as residential elderly. The shortage of (research) data is mainly caused by excluding residential elderly from studies because of high age and multimorbidities, such as CVD.

Since there is a deficiency of data, no specific guidelines are available to diagnose and to treat HF in residential elderly. From this perspective, there is debate on the applicability of existing HF guidelines developed for CHF patients in general, to residential elderly with CHF. However, guidelines for residential elderly with CHF are sorely missing because diagnosing CHF is notoriously difficult: elderly tend to subscribe complaints to aging instead of CHF or other diseases. Subsequently, CHF treatments are often incorrectly applied, or not applied at all. The consequences of these caveats may be loss of quality of life and increase of costs.

Therefore, we sought to study CHF in the residential elderly.

In Chapter 2.1 we have explored the epidemiological scale of CHF, by determining the prevalence of CHF in residential elderly. Based on the recent literature, when general guidelines on CHF (2;3;4) were applied to residential elderly, diagnosing CHF was less accurate due to poor predictive values of signs and symptoms, medical history, and electrocardiogram (ECG).
From medical files of residential elderly in a single nursing home in Groningen, we inventoried signs, symptoms, medical history and registered the number of subjects with CHF. Then we performed a physical examination and an ECG of all residents. Next we estimated the accuracy of both, former CHF diagnostic (natriuretic peptides (NPs) not used) and current CHF diagnostic procedures (including NPs), since, in contrast to the broad recognition of NPs as a screening test for CHF, their use as biomarkers in residential elderly has remained limited. The restricted use in elderly is caused by lack of validation of cut-off values for NPs in this group of subjects. Finally, we studied ECGs of all residents.

A panel of cardiologists decided on the presence or absence of CHF by assessment of NPs and the result of echocardiography, successively. Echocardiographic investigations were feasible in 98%. As a result of the present study, CHF was established in 24/103 (23%) residential elderly. Fifteen (15/24) residents were not previously detected with CHF. Before the study, 22 were identified with CHF. Out of the 22 residents with CHF before the study, in only 9 residents CHF was confirmed and of 13 residents with CHF the diagnosis was rejected.

The diagnostic accuracy of NT-proBNP at 450 pg/mL was 0.71 sensitivity, 0.67 specificity, 0.42 positive predictive value (PPV) and 0.91 negative predictive value (NPV). The diagnostic accuracy of BNP at 100 pg/mL was: 0.71 sensitivity, 0.70 specificity, 0.41 PPV and 0.88 NPV.

In brief, the most striking results of the present study were that more than half the CHF diagnoses were missed (i.e. 15/24) or incorrectly made (i.e. 13/22). Hence we concluded that the overall accuracy of identifying CHF is limited. However, given the high NPVs, the use of natriuretic peptides as additional diagnostic instrument seems promising, even in nursing home residents but requires further evaluation. The CHF prevalence in residential elderly was estimated at 23%.

In Chapter 2.2 we studied whether the outcomes of chapter 2.1 were consistent with the CHF prevalence in Aruban nursing homes. Aruban nursing homes were chosen since we were interested in a comparable population with Dutch nationality living in a different environment and
having another lifestyle. The same design as in Chapter 2.1 was utilized to study the prevalence of CHF in Aruban residential elderly. The other aim was to validate whether employment of natriuretic peptides could improve identification of CHF in residential elderly in another part of the Dutch Kingdom. The main difference with the chapter 2.1 study was that we were unable to obtain echocardiograms of all residential elderly, due to logistic reasons. Therefore, we could not meet the diagnostic standards for CHF (2-4).

As a result, 51 out of 235 elderly Aruban residents were included with a mean age of 78±8 years. According to the medical files 7/51 residents were acknowledged with CHF. However, two out of the 7 residents did not have CHF. Furthermore, CHF was established in 16 out of 51 (31%) residents. Out of the 16 residents with CHF, 11 were not previously diagnosed with CHF and of 5/16 residents identified with CHF, the diagnosis was confirmed.

In brief, the general guidelines for HF are applied to Aruban residential elderly, infrequently. When compared to residential elderly in Groningen, the prevalence of CHF may be at least as high in Aruban residential elderly. In conclusion, recognition of CHF appears to be severely underestimated in Aruban residential elderly. The detection of CHF will be improved by implementing an appropriate guideline, including the determination of BNP.

In Chapter 2.3 we addressed the problem of the large intra-individual variations [individual coefficient of variation (CV$_i$)] of NT-proBNP in plasma, since large CV$_i$s limit the applicability of NT-proBNP for among others, guided therapy optimization in individual patients with CHF (5).

In search of more reliable CV$_i$s we compared concentrations of urine NT-proBNP (NT-proBNP$_u$) to concentrations of plasma NT-proBNP (NT-proBNP$_p$), in HF patients living in Curaçao.

Urine and blood samples were taken on a single day (“within-day”): six blood samples every 2 hours and spontaneously voided urines during 24-hours. On five consecutive days (“day-to-day”): five blood samples, five enforced urine samples, and five full 24-h urines were taken. On the same day of six consecutive weeks (“week-to-week”): one blood sample, one enforced
urine sample and one full 24-h urine was collected. Out of these blood and urine samples the
total CVs (CVs), CVs and reference change values (RCVs) were calculated.

In this study 25 CHF patients were included with a mean age of 61 (range 36-80) years, 60% was male and the average left ventricular ejection fraction was 36±15%. Median CVs for NT-proBNPp were 9% (within-day), 18% (day-to-day) and 30% (week-to-week). For NT-proBNP_u the CVs were 34%, 21% and 28%, respectively. The reference change value (RCV) of NT-proBNP_u was higher than, or equal to, the RCV for NT-proBNP_p, even after correction for creatinine and the time period (in hours) in which the urine accumulated in the bladder.

Our data of day-to-day and week-to-week samples suggest that (immunoreactive) concentrations of NT-proBNP in urine do not unequivocally correlate with (immunoreactive) NT-proBNP concentrations in plasma, up to an NT-proBNP_p threshold of about 310 pg/mL (Figure 1). In addition, we found that beyond this threshold the higher NT-proBNP concentrations, as expressed in Figure 1, are not explained by an increase in blood pressure, during the day (results not shown). We hypothesise that filtration of natriuretic peptides may be considered as the dominant factor beyond the threshold and that at lower NT-proBNP levels filtration and reabsorption are more dynamically interacting.

In conclusion, measurements of NT-proBNP in urine have no advantages in stable patients with chronic heart failure.
Figure 1. Relation between NT-proBNP in plasma and NT-proBNP in the enforced urine voidings collected in the day-to-day and week-to-week protocols.

Data derive from 22 patients and in total 182 comparisons of NT-proBNP in plasma and urine. Day-to-day and week-to-week samples were used. For urine we have used the enforced voidings.

In Chapter 3 we have investigated the prognostic value of natriuretic peptides on one-year mortality in the same cohort of residential elderly as studied in chapter 2.1. The clinical relevance is that if natriuretic peptides are related to prognosis of residential elderly with CHF, these biomarkers may be exploited for advance care planning. Advance care planning is related to quality of life and becomes important when life expectancy is restricted (www.Verenso.nl).

To investigate one-year mortality, survival and death of residential elderly was tracked, during one year. Since ten residential elderly could not be followed up, because they moved to unknown destinations, we studied the remaining 93 residential elderly.
Eighteen out of 93 residents (mean age 81 ± 3 years, 66% female) died within one year (non-survivors).

A mutually adjusted Cox proportional hazard regression analysis was performed. Adjustments were made for six predefined chronic diseases, immobilization, age, sex, NT-proBNP and BNP. The results found were that both natriuretic peptides (NT-proBNP and BNP) significantly predicted one-year mortality (HR 1.02 and p=0.001, and HR 1.16 and p=0.003, respectively). In addition, the one-year mortality risk increases exponentially in concert with higher BNP and NT-proBNP levels. For instance, an NT-proBNP increase up to 2,000 pg/mL was associated with a 60% higher risk of dying, within one year.

In conclusion, both BNP and NT-proBNP are independent predictors of one-year mortality for residential elderly with CHF. In addition, the mortality risk increases at natriuretic peptide concentrations elevated far beyond the diagnostic cut-off values of the guidelines (2;3;4).

In Chapter 4 we studied the relation between CHF and the support that is needed for residential elderly with CHF during their activities of daily life (ADL). To this end, the same cohort of residential elderly was examined as in chapter 2.1. The rationale for this study question was to draw attention of care teams to the need of support among those residents with CHF.

For this study the same group of residential elderly was assessed as in chapter 2.1. To collect data on ADL the Minimal Data Set (MDS)-items of the Resident Assistant Instrument was used. The MDS consists of systematic observations on dependency and delivered support and aims to quantify dependence and aid (6). The MDS instrument consists of a software program for entering the observations of the individual residential elderly, during predefined activities of daily living (ADL). An example of such an activity is walking. The care taker observes and scores (quantifies) whether the individual is able to walk predefined distances independently and needs help during walking. Of 103 residents with and without CHF, the ADL-dependence and ADL-help scores were compared and adjusted for differences between the two groups by means of
logistic multivariate regression. CHF was associated with ADL-help (OR 4.68 and p=0.015) however, CHF was not related to ADL-dependence.

In conclusion, CHF is associated with a necessary increase of ADL-help for nursing home residents. In this regard, CHF is of importance for both residents (loss of autonomy and life satisfaction) and organization (workforce planning).

In Chapter 5 we assessed a physical exercise program in residential elderly with CHF. The rationale for this study was the discrepancy between the sedentary lifestyle adhered to by residential elderly and the recommendations for physical activity from HF guidelines (2;3;4). Also family members are stimulating their parents in care homes to become physically active. However, for a variety of reasons, residential elderly prefer to remain sedentary. Furthermore, because of fear of falling, also caretakers prefer residential elderly to maintain their sedentary lifestyle. On the other hand, a sedentary life style is related to an increased risk on (progression of) atherosclerosis and CV-metabolic diseases, such as CHF and metabolic syndrome (7).

To investigate whether regular exercise is safe and has beneficial effects on CV-metabolic indices for residential elderly, we evaluated effects of exercise on CHF symptoms, NT-proBNP and metabolic syndrome.

A pilot single-blinded, randomized controlled feasibility trial in four care homes was performed. In collaboration with other investigators (8), we studied whether a standardized exercise program affects CHF symptoms, NT-proBNP and the metabolic syndrome. The other investigators (8) studied whether the same standardized exercise program affects functional endpoints in comparable groups.

The exercise intervention included a guided moderate-to-high intensity training of one hour twice weekly, during 16 consecutive weeks. Exercise consisted of progressive resistance training of upper and lower extremities, and of the trunk, static and dynamic balance training, and functional training. The control group intervention contained a guided non-physical social program of similar frequency, duration, length and location. The study endpoints consisted of
symptoms of CHF (fatigue, dyspnea), NT-proBNP, and body measurements and laboratory results, together known as parameters of the "metabolic syndrome". The syndrome is defined as the presence of three out of five measurements and laboratory results. These measurements include waist, blood pressure, fasting glucose, triglycerides and high-density lipoprotein (HDL)-cholesterol. We substituted glucose for glycated hemoglobin (HbA1c), since fasting blood collection was not feasible for logistic reasons.

As a result, out of 434 residential elderly 163 were eligible. Unfortunately, only 52 (12%) were willing to participate in the study. Of these 52, six dropped out during the study for reasons not related to the exercise. The remaining 46 participants were 85±6 years, 65% females and all had been randomized to exercise (n=24) or control groups (n=22). The intention-to-treat analysis showed no significant change of any of a variable in the exercise groups compared to controls. The as-treated group completed half or more of the 32 training sessions. The females of the latter group had a significant reduction in waist size [-8 (range -15 - -2) cm]. The controls showed a significant triglycerides decrease [-8 (-17-0) mg/dL] and an NT-proBNP increase [67 (7-126) pg/mL]. The attendance of the residents was inversely related to the non-fasting triglycerides in the exercise group (p=0.024).

We concluded that over a short period of time guided physical exercise, performed by residential elderly, had neither beneficial effects on symptoms and a biomarker of CHF, nor on cardiovascular-metabolic indices. We have explained the neutral results with the high age (85 years on average) accompanied by loss of muscle endurance, and with a training offer that is not enough personalized.
In brief, the outcomes of this thesis are:

- the prevalences of CHF in residential elderly are 23% in Groningen, which is consistent with literature (9), and >30% in Aruba (chapters 2.1 and 2.2).

- in Dutch residential elderly, undetected diagnoses of CHF often occur. The use of natriuretic peptides, as an additional test for CHF, needs to be further studied. In residential elderly in Groningen, the incorrect diagnoses of CHF can be reduced by applying natriuretic peptides (chapter 2.1 and 2.2).

- determination of NT-proBNP concentrations in the urine of CHF patients is not more favourable compared to NT-proBNP plasma levels. This finding results from the large intraindividual variabilities of urine NT-proBNP which is comparable to that in plasma NT-proBNP (chapter 2.3).

- in residential elderly, natriuretic peptide testing has prognostic values [HR of NT-proBNP 1.02 and BNP 1.16 (vs. HR (10) of BNP is 2.2)], of which the outcome of BNP is consistent with the literature (10) (chapter 3).

- residential elderly with CHF need more ADL-help, when compared to those without CHF (chapter 4).

- a short-term period of guided exercise performed by residential elderly has neither effect on CHF nor on cardiovascular indices (i.e. the metabolic syndrome). There are no studies to compare with (chapter 5).
Chapter 6.2

DISCUSSION
We assessed our hypothesis (Introduction) according to which general HF guidelines (2-4) are not applicable to residential elderly with regard to diagnostics. Therefore, we applied natriuretic peptides (NPs) threshold values, derived from HF guidelines (2-4) to the residential elderly cohort in Groningen (chapter 2.1). It should be noticed that both, the ESC and Multidisciplinary HF guidelines (2;3) advise to use the same cut-off values (NT-proBNP 125 and BNP 35 pg/mL), which values are lower compared to the NICE HF guideline (i.e. NT-proBNP 400 and BNP 100 pg/mL) (4). Using these cut-off values from the guidelines, we calculated the predictive values for the CHF diagnosis in residential elderly of a single nursing home in Groningen (Table 1). We also calculated the predictive values at higher thresholds such as at NT-pro BNP 900 pg/mL and BNP 100 pg/mL. Years after our study, Mason et al. (11) published a paper on predictive values of NPs for CHF. The cut-off values of their study in British residential elderly were slightly different from those chosen in our study. In accordance with the NICE HF guideline (4) Mason et al. validated their findings for NT-proBNP and BNP cut-off points (Table 1).

The Mason group (11) and we not only evaluated isolated natriuretic peptides but also combinations of medical history, symptoms and signs, ECG, and natriuretic peptides to predict the presence of CHF. We both found that any combination of studied parameters did not improve the predictive values, as determined by natriuretic peptides either (Table 1). The outcomes of Mason’s study, specifically with regard to PPV, correspond well with our findings.
Table 1. Predictive values of NT-proBNP and BNP for the heart failure diagnosis in two populations of residential elderly (RE): the Groningen (NL) (Chapter 2.1) and the British population (11).

<table>
<thead>
<tr>
<th></th>
<th>Cut-off value pg/mL</th>
<th>sensitivity</th>
<th>specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groningen (NL) RE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP¹</td>
<td>125</td>
<td>1.00</td>
<td>0.28</td>
<td>0.29</td>
<td>1.00</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>450</td>
<td>0.71</td>
<td>0.67</td>
<td>0.42</td>
<td>0.91</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>900</td>
<td>0.67</td>
<td>0.85</td>
<td>0.56</td>
<td>0.89</td>
</tr>
<tr>
<td>BNP¹</td>
<td>35</td>
<td>0.88</td>
<td>0.39</td>
<td>0.30</td>
<td>0.91</td>
</tr>
<tr>
<td>BNP</td>
<td>50</td>
<td>0.88</td>
<td>0.63</td>
<td>0.31</td>
<td>0.89</td>
</tr>
<tr>
<td>BNP²</td>
<td>100</td>
<td>0.71</td>
<td>0.70</td>
<td>0.41</td>
<td>0.88</td>
</tr>
<tr>
<td>British RE (11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP²</td>
<td>400</td>
<td>0.56</td>
<td>0.69</td>
<td>0.35</td>
<td>0.84</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>760</td>
<td>0.62</td>
<td>0.75</td>
<td>0.42</td>
<td>0.87</td>
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<tr>
<td>BNP</td>
<td>115</td>
<td>0.67</td>
<td>0.68</td>
<td>0.38</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Residential elderly, RE; PPV, positive predictive value; NPV, negative predictive value; NT-proBNP, N-terminal amino pro B-type natriuretic peptide; B-type natriuretic peptide.

1 ESC HF guideline (2) and multidisciplinary HF guideline (3)
2 NICE HF guideline (4).

In addition, both groups report that when applying HF guidelines (2-4) to Dutch and British residential elderly (11), more than half of the initial CHF diagnoses are missed (too many false negatives). Also lowering the threshold values (2;3), when compared to the NICE (4) HF guideline, does not provide any substantial improvements. We and Mason et al. further estab-
lished that in residential elderly, the calculated predictive values are not reliable for ruling-in but only for ruling out CHF.

In this thesis, we thus adapt the algorithm of the Multidisciplinary HF guideline (3) to residential elderly (Figure 1). These modifications include the use of NPs for excluding CHF only, the use of echocardiography for ruling in CHF, the use of NICE cut-off values (4), and utilization of echocardiography in primary care laboratories (www.Certe.nl).

However, Oudejans et al. (12) demonstrated in geriatric outpatients with a prevalence of >40% CHF, that natriuretic peptide testing in combination with other diagnostic tests, are very accurate for both, ruling out and ruling in CHF. Therefore, the PPV of CHF in our group might have been lower due to a lower a priori chance on having CHF based on the lower CHF prevalence (23%) when compared to the a priori chance of CHF in outpatients (CHF prevalence >40%). In contrast to the results of the Oudejans group, but in concert with those of Mason and our study group [Chapter 1.2 and reference (11)], we have revised our recommendations for residential elderly.

We had to reject our hypothesis in part, since CHF cannot be diagnosed in residential elderly by making use of HF guidelines. In addition, our hypothesis was fair in part because CHF can be ruled out using natriuretic peptides according to the HF guidelines.

Based on our new insights, we advise to make an echocardiogram for diagnosing CHF in residential elderly. Theoretically, NPs are recommended to rule out CHF although we realize that excluding CHF does not comply with daily practice. Further, We processed these recommendations into an algorithm for CHF diagnostics (i.e. non-acute HF) for residential elderly (Figure 1).
Chapter 6.3

RECOMMENDATIONS AND FUTURE PERSPECTIVES
In the discussion, we have concluded that general HF guidelines cannot be used for diagnosing CHF in residential elderly. Furthermore, echocardiography is warranted to establish the diagnosis of CHF in the individual residential elderly.

To that end, we have customized the Dutch diagnostic algorithm for CHF (3) to that particular group (Figure 1). In the future, it is crucial to assess this adjusted CHF diagnostic algorithm on accuracy and costs. We therefore recommend to validate the customized CHF diagnostic algorithm in new populations of residential elderly.

In the introduction, the paragraph on HF diagnostics, we emphasized that access to echocardiography was limited. Since recently, echocardiography has become available for primary care patients in The Netherlands, that barrier to accurately diagnose CHF seems to be removed. We subsequently argue for the option of on-site echocardiography for those (residential) elderly who are immobile.

To editors of the Multidisciplinary HF guideline (3), we give in consideration to adapt the algorithm (3) to residential elderly. The adaptations concern non-acute HF exclusively. They include the use of echocardiography for ruling in CHF, the use of NPs only for excluding CHF, and referral for echocardiography also in primary care laboratories (www.Certe.nl).

In Chapter 3, we showed the prognostic values of NPs for one-year mortality of residential elderly with an established diagnosis of CHF. We therefore advise to add natriuretic peptide testing to “advance care planning” for those (residential) elderly facing a limited life expectancy.

In Chapter 4, we demonstrated the relation between CHF and the needs for more ADL-help, compared to residential elderly without CHF. This relation made us to advise care teams to recognise higher requirements for ADL-help, in residential elderly with CHF.

In Chapter 5, we observed that residential elderly who performed exercise during four months, changed neither their CHF nor their CV-metabolic indices. We have explained the absence of improvements to the high age and subsequent loss of muscular endurance. In addition, the
training frequency and duration were too modest contributing to the absence of improvements as well. Based on these findings, we recommend in future to study residential elderly with CHF during and after a personalized exercise program of three times a week in the long-run. An example of a personalized program is the option for the aged to select his type of training himself. Such programs may be more effective compared to programs imposed (13). Besides, we emphasize to pay attention regularly to the motivation of residential elderly to exercise, since we found low participation rates in our study.

As a consequence of our results partly processed in the diagnostic CHF algorithm specific for residential elderly (Chapter 6.2), we recommend the following:

To editors of continuing medical education (e.g. www.CME-scholing.nl), we suggest to record our new insights into CHF in education programs for physicians elderly medicine (SO). The insights include the found CHF prevalence of at least 23% in residential elderly. Those also include that CHF can be better diagnosed according to the diagnostic CHF algorithm that we customized to residential elderly (Figure 1). Furthermore, that advance care for residential elderly, can be improved by the determination of natriuretic peptides also. Importantly, neither CHF symptoms and a marker nor CV-metabolic indices may not improve in residential elderly, after exercise during a four months period. However, in the long-run, beneficial effects of exercise in residential elderly may not be impossible, when using personalized conditions. This includes that the resident chooses himself whether he starts walking, home-training, swimming or visits the fitness club.
Residential elderly with complaints and symptoms suspected for non-acute heart failure (HF) in a long-term care facility or primary care medicine

- **Patient diagnosed with HF**
  - Physical examination, ecg, lab.
  - Consider comorbidity or HF decline consider further steps

- **Patient not diagnosed with HF**
  - Physical examination, ecg, NT-proBNP or BNP (Hb, eGFR, TSH, K+, glucose)
  - If NT-proBNP <400 pg/mL or BNP <100 pg/mL, ecg undisturbed

**Residential elderly medicine in primary care**

- **Yes**
  - Patient not diagnosed with HF
    - Physical examination, ecg, NT-proBNP or BNP (Hb, eGFR, TSH, K+, glucose)
    - If NT-proBNP <400 pg/mL or BNP <100 pg/mL, ecg undisturbed

- **No**
  - Echocardiography
    - **Pos.**
      - HF is unlikely. Consider other causes
    - **Neg.**
      - HF is unlikely. Consider other causes

- **Further diagnostics by the SO/GP**

**HF outpatients’ clinic**

- **Cause analysis / treatable HF cause.**
  - Consultation with SO /GP
  - Treatment

- **Cause analysis / no treatable cause for HF.**
  - Referral back to SO/GP with treatment advice.

**Figure 1. Diagnostic algorithm for non-acute heart failure in residential elderly.**
BNP, B-type natriuretic peptide; NT-proBNP, nitrogen-terminal-proBNP; SO, specialist ouder-engeneeskunde; GP, general practitioner.

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2 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33(14):1787-1847.


