Age-related medication adherence in patients with chronic heart failure: A systematic literature review

Katrin Krueger a,⁎, Lea Botermann a, Susanne G. Schorn b, Nina Griese-Mammen a, Ulrich Laufs c, Martin Schulz a,d

a ABDA — Federal Union of German Associations of Pharmacists, Department of Medicine, Berlin, Germany
b German Agency for Quality in Medicine, Berlin, Germany
c Klinik für Innere Medizin III (Kardiologie, Angiologie und Internistische Intensivmedizin), Universitätsklinikum des Saarlandes, Homburg, Germany.
d Department of Pharmacology, Goethe-University Frankfurt, Frankfurt at Main, Germany

A R T I C L E    I N F O

Article history:
Received 11 July 2014
Received in revised form 24 February 2015
Accepted 2 March 2015
Available online 4 March 2015

Keywords:
Chronic heart failure
Medication adherence
Age
Elderly
Systematic literature review

A B S T R A C T

Background: Chronic heart failure (CHF) is prevalent among the elderly and is characterized by high mortality and hospitalization rates. Non-adherence to medications is frequent and related to poor clinical outcomes. It is often assumed that older age is related to poorer medication adherence compared with younger age. We analyzed the existing evidence of age as a determinant of medication adherence in patients with CHF.

Methods: A systematic search of the bibliographic database MEDLINE and all Cochrane databases was performed. Studies were included if they examined medication adherence in adult patients with CHF, evaluated factors contributing to medication adherence, and analyzed the relationship between age and medication adherence. Articles classified as studies with poor quality were excluded.

Results: A total of 1565 titles were found, and ultimately, 17 studies, which provide data for a total of 162,727 patients, were analyzed. Seven studies showed a statistically significant relationship between age and medication adherence: six articles demonstrated that increased age is correlated with higher medication adherence, and one study showed that patients in the age range of 57 to 64 years are affected by non-adherence to angiotensin-converting enzyme inhibitors. Ten studies found no significant relationship.

Conclusions: The results suggest that older age alone is not related to poorer medication adherence compared with younger patients with CHF. More attention should be paid to younger newly-diagnosed patients with CHF. Future studies are required to explore medication adherence in CHF in different, standardized, and specific age groups and should be sufficiently powered to assess clinical endpoints.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

1.1. Chronic heart failure

Chronic heart failure (CHF) is prevalent among the elderly and is characterized by high mortality and hospitalization rates [1]. The EuroHeart Failure survey, for example, identified 11,527 (24% of total 46,788) deaths and hospital discharges of patients with CHF in 24 European countries over a period of six weeks; with 51% of the women and 30% of the men aged over 75 years [2]. The available drugs can improve morbidity and reduce mortality rates in CHF patients [3].

1.2. Medication adherence

The World Health Organization (WHO) defined adherence as the dimension to which a person’s behavior, such as taking medication, corresponds with the agreed recommendations from a health care provider [4]. Adherence to drug therapy is necessary, but poor adherence to treatment for chronic diseases is a worldwide problem. The WHO specified that the average adherence to long-term therapy for chronic diseases is 50% [4]. Effective treatment of CHF improves symptoms and signs, prevents hospital admission, and reduces mortality [3]. Good medication adherence is associated with higher patient survival [5–9].

1.3. Ageing and medication adherence

In general, factors such as multiple co-morbidities, clinical depression and reduced cognitive functioning contribute to poor medication adherence [10–13]. The rate of hospitalization for worsening heart failure increases with patient age [14]; medication non-adherence might be one potential reason [6]. Patient age is one part of the five dimensions...
of the WHO adherence model [4], and is, therefore, indicated as a potential determinant. Haynes [15] and Lorenc and Branthwaite [16] studied the relationship between age and medication adherence in acute and chronic illnesses, and found inconclusive results. Both studies did not differentiate between diseases, indications, or drug classes. Monane et al. investigated the adherence rates of Medicaid beneficiaries who received antihypertensive agents. These researchers included patients aged 65 years and older and found that older age was associated with better adherence [17]. However, patients with hypertension and no obvious symptoms likely exhibit a different adherence profile compared with patients with CHF. CHF is a growing health problem prevalent in the elderly and causes high healthcare costs [18]. In CHF, the lowest adherence rates are often assumed for older patients [19]. Thus, is older age an independent predictor of reduced adherence to CHF medication? In addition, if we develop and implement adherence-promoting interventions into daily practice, should we focus on specific age groups?

The aim of this systematic review was, therefore, to analyze the existing evidence of age as a determinant of medication adherence in patients with CHF.

2. Methods

2.1. Search method

We performed this systematic literature review following the recommendations of the 27-item checklist of the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [20,21]. We systematically searched the bibliographic database MEDLINE and all Cochrane databases from their inception to 9th March 2014 based on the recommendations of the Cochrane Handbook for Systematic Reviews [22]. We placed no restrictions on languages because the authors are able to read and understand German, English, French, Dutch and Spanish and we planned to use a translation service if necessary.

On 9th March 2014, we used the following search strategies (1) in MEDLINE: (((heart failure[MeSH Terms]) AND patient compliance[MeSH Terms]) OR (((heart failu*[Text Word]) OR myocard* failu*[Text Word]) OR cardia* failu*[Text Word])) AND (((((medication compliance[Text Word]) OR patient adherence[Text Word]) OR patient cooperation[Text Word]) OR medication adherence[Text Word]) OR refill compliance[Text Word]) OR refill adherence[Text Word]) OR medication persistence[Text Word]) OR medication concordance[Text Word]) OR patient persistence[Text Word]) OR patient concordance[Text Word]) OR patient cooperation[Text Word]) and (2) in the Cochrane databases: (heart failu* OR myocard failu* OR cardia* failu* AND (medication compliance OR patient adherence OR patient compliance OR medication adherence OR refill compliance OR refill adherence OR medication persistence OR medication concordance OR patient persistence OR patient concordance OR patient cooperation).

2.2. Inclusion/exclusion criteria

The titles were collected, and any duplicates were removed. To select the relevant articles, inclusion and exclusion criteria were predefined. Studies were included if they discussed medication adherence in adult patients with CHF (A in Fig. 1), evaluated factors contributing to medication adherence (B in Fig. 1) and analyzed the relationship between age and medication adherence (C in Fig. 1). Studies related to non-pharmacological adherence, such as recommendations regarding exercise, fluid intake, and diet, or that evaluated guideline adherence were excluded. Descriptions of the methodology used to measure adherence, articles on study design, short summaries, editorials and letters addressed to the editor were also excluded. The search was supplemented by a hand search of the reference lists of all selected full-text articles.

**Fig. 1. Selection process (PRISMA flow diagram [20]). SR = systematic review. Inclusion criteria: A: Examination of medication adherence in patients with CHF. B: Evaluation of factors contributing to medication adherence. C: Analysis of relationship between age and medication adherence.**

2.3. Selection process

The titles were first scanned, and an assessment of the relevant abstracts and full-text articles was then performed (Fig. 1). The relevant articles quoted in the identified systematic reviews were also selected. A quality check of the selected full-text articles was performed based on the Quality in Prognosis Studies (QUIPS) tool [23]. The QUIPS tool contains six categories that assess (1) bias due to patient selection, (2) attrition, (3) measurement of prognostic factors, (4) outcome measurement, (5) confounding on statistical analysis, and (6) confounding on presentation. We used the version modified by Oosterom-Calò et al. [24] who converted the six categories of the QUIPS tool into specific questions (Appendix: Table 4). The quality score for each study was determined in relation to the topic of this review, and this determination was performed independently by two authors (KK and LB). The studies were rated as follows: 2.5–3 as good, 2.0–2.4 as fair and <2.0 as poor quality. If there was a lack of consensus, a third author was consulted (MS). We included those articles that fulfilled the inclusion criteria and were classified as good- or fair-quality manuscripts.

2.4. Best evidence synthesis

We extracted the data from the included studies and used the principles of best evidence synthesis to present (Tables 2 and 3; Appendix: Table 6) and summarize (Table 1) the findings of these studies [25].
Most developed countries consider the age of 65 years, equivalent to the usual retirement age, as a definition of "elderly" or "older person" [26]. We originally planned to define specific age groups, for instance, patients below the age of 65 years, patients aged 65 to 74 years, patients aged 75 to 84 years, and patients aged 85 years and older. The purpose was to clearly differentiate between these age groups. However, the heterogeneity between the studies made it impossible, eventually. Thus, we present published data of the included studies, and followed the comparisons of individually defined age groups in these studies (see Section 3.3, and Appendix: Table 6). We used the harvest plot [27] to synthesize evidence of the relationship between medication adherence and patient age (Fig. 2). Thereby, we classified studies into three groups: the relation of younger age and better medication adherence, no relation, or the relation of older age and better medication adherence. The studies were illustrated, weighted by quality score and sample size — sorted by instrument of measuring medication adherence. The gray ovals indicate good-quality studies, and the uncolored ovals represent the fair-quality studies. The oval height indicates the sample size of the studies (short oval < 1000 participants, and long oval > 1000 participants). The results were classified as consistent when at least 75% of the studies (with comparable instruments) demonstrated results in the same direction [24]. The level of evidence was rated as strong (consistent results from at least two good-quality studies), moderate (consistent results from one good-quality study and at least one fair-quality study or from more than two fair-quality studies), or inconsistent (only one study available or the direction of results were inconsistent) [23,24].

3. Results

3.1. Selection process

The search resulted in 1565 titles: 1081 from MEDLINE and 484 from the Cochrane Library (Fig. 1). We excluded one duplicate publication and selected five new relevant studies that were quoted in four systematic reviews [24,28–30]. After performing a quality assessment in relation to the topic of this review, we excluded four studies due to poor quality (Appendix: Table 5). In these studies, medication adherence and the measurement were not clearly described, or other important quality items were not reported (e.g., items related to the study participants, sampling, study attrition). In the end, we included 17 studies — eight of which were classified as good-quality studies and include 90.2% of the study participants, and nine with fair quality.

3.2. Study characteristics

Tables 1 and 2 provide a descriptive summary of the included studies, which covered a total of 162,727 patients. Nearly 60% of the studies were conducted in the USA, and these included 99.3% of the patients. In addition, 35.3% of the studies were retrospective data evaluations and included 99.1% of the participants. Six studies had a sample size of greater than 300 patients. CHF was an inclusion criterion in all of the studies. The authors considered the total drug regimen, only cardiovascular medication or selected drug classes, such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin-II-receptor antagonists (ARB), β-blockers (BB), spironolactone, diuretics, and digoxin.

3.3. Age characteristics

Six studies defined different age groups and compared medication adherence between these groups (<64, 65–74, 75–84, and ≥85 years [31], ≤60 and >60 years [32], 65–74, 75–84, and >85 years [33], 35–56, 57–64, 65–72, and 73–89 years [34], ≤65 and >65 years [13], <30, 30–49, 50–69, and ≥70 years [35]). Three studies correlated age and medication adherence using a multivariate model but did not provide additional information on the age groups [36–38]. Other studies compared the mean age of the adherent and non-adherent patients [39–46].

Not all of the studies presented complete information on the age characteristics of the participants. Nine studies reported the mean age of specific groups, including 108,196 patients [31,33,39,40,42–46]. Four studies reported the mean age of all of the patients (53–80 years; 62,650 patients). Seven studies reported the age range (20–99 years) for 8134 patients [32–35,38,42,43]. An age of at least 65 years,
respectively 70 years was one of the inclusion criteria in two studies [33, 36]. Six studies reported the characteristics of the different age groups [13,31–35].

3.4. Medication adherence

Three studies directly measured medication adherence (serum digoxin concentration) [43,45,46]. The remaining 14 studies used indirect methods, such as self-reporting (n = 6), proportion of days covered (PDC) with medication (n = 4), pill count (n = 2), or medication possession ratio (MPR; n = 1). Only one study used the Medication Event Monitoring System (MEMS) as an electronic tool [38]. The cut-off points for “good” medication adherence were ≥75% in three [32,34,46] and ≥80% in four studies [31,37,40,41]. In 10 articles, the cut-off points were either not reported [13,33,36,39] or specific definitions were applied [35,38,42–45]. Seven studies reported the mean adherence rates for all of the participants [13,31,32,36–38,43]. Overall, the adherence rate was 73.2% and ranged from 37.6% [37] to 96.3% [32]. Nine of the 17 articles reported the number of non-adherent patients. Three studies directly measured the non-adherence to digoxin in 136 of a total of 484 patients (28.0%) [43,45,46]. Six studies measured medication non-adherence through indirect methods for 4035 of a total of 62,542 participants (6.5%) [35,36,39,41,42,44]. Table 3 shows the definitions and measurements of medication adherence. Table 6 (Appendix) presents all definitions, measurements, and results of medication adherence of studies included in this review.

3.5. Age-related medication adherence

In the best evidence synthesis, we rated the relationship between age and medication adherence as inconsistent (Fig. 2). Ten studies, which included 33.7% of all study participants, found no statistically significant association between age and medication adherence [13,35–38,41,42,44–46]. Six studies stated a statistically significant relationship between older age and better medication adherence [31–33,39,40,43]. One article showed that patients in the range of 57 to 64 years were the group that exhibited the highest non-adherence to angiotensin-converting enzyme (ACE) inhibitors [34]. Of those that found a significant relationship between older age and better medication adherence, three studies, which included 33.0% of all patients studied, reported the mean age of the non-adherent patients: 60.8 [43], 64.2 [39], 67.9, and 68.2 years [40], respectively. The mean age of the adherent patients was 66.3, 73.6, 73.4, and 75.1 years, respectively. One study identified that patients aged at least 60 years presented a better medication adherence than younger patients [32]. Two studies demonstrated that patients aged 65 to 74 years exhibited a higher risk of non-adherence than older patients [31,33]. Fig. 3 presents the main results of the studies with significant results.
4. Discussion

To the best of our knowledge, this study provides the first systematic review of the existing evidence of age as a determinant of medication adherence in CHF patients. We analyzed data from 17 studies and a total of 162,727 patients with CHF. Eight studies, which include 90.2% of the participants, were classified as good-quality studies, and nine were rated as fair-quality studies. The results of the best evidence synthesis were rated as inconsistent: seven articles (including 66.3% of the study participants) reported a significant association between age and medication adherence, and 10 did not. Those with significant results suggest that older age is not related to poorer medication adherence compared with younger CHF patients. This finding is contrary to the assumption that medication adherence is reduced in older patients with CHF [9,19].

Overall, our findings suggest that younger patients have a higher likelihood for medication non-adherence. We found two studies that presented the age range of non-adherent patients as 65–74 years [31, 33], whereas one presented this age range as 57–64 years [34]. Another study identified patients aged 60 years and younger as the higher non-adherent group [32], and three studies showed the mean age of non-adherent patients (as 64.2, 67.9, 68.2, and 60.8 years, respectively [39, 40,43]).

How do our results correspond with the previous literature? Wu et al. found that older CHF patients were more adherent than younger ones, as determined from studies with a large number of participants, multivariate analyses, and objectively measured medication adherence [28]. Wong et al. found the lowest adherence rates from younger age as a predictor of lower medication adherence [17,50–52]. Evangelista et al. reported a higher adherence score in CHF patients aged at least 65 years compared with younger patients [48]. Another study showed that older CHF patients more consistently took their medication as prescribed, in their everyday regimen [49]. Previous studies of patients with hypertension showed younger age as a predictor of lower medication adherence [17,50–52]. Additionally, young-old veterans (65–74 years of age) with multiple drug regimens were less adherent than older ones (≥75 years old) [53]. Our results are confirming these findings.

Cohen et al. found younger age as a predictor of lower medication adherence post-discharge, in patients hospitalized for cardiovascular disease [54]. Non-adherence is common for newly prescribed medications for chronic diseases [55,56]. Younger patients are often less adherent to initial treatment [57–59] because they are newly diagnosed [34].
limited in their disease knowledge [60], burdened with their treatment regimen, and fearful of side effects [17,19,61]. Older patients are thought to receive more support regarding their medication management, and fearful of side effects [17,19,61]. Older patients are limited in their disease knowledge [60], burdened with their treatment regimen, and fearful of side effects [17,19,61].

Six of the included studies regarded medication adherence in different age groups. The classification into different age groups and different sample sizes complicated the comparison [16]. Only a few studies regarded predefined age groups. Therefore, it is difficult to show the influence of age on medication adherence [62]. A previous study showed that less than 5% of the published articles focused on older patients [63]. It can be assumed that older patients included in clinical trials are not representative of the real population, which is markedly more heterogeneous [62,64].

For example, Medicare beneficiaries over 64 years of age and hospitalized for worsening heart failure were compared utilizing the inclusion and exclusion criteria from three large randomized clinical trials. Only 20% of the patients were suitable to be included in these trials, and older patients met fewer inclusion criteria than younger ones [65]. In general, it is a logical assumption that patients with multiple co-morbidities, and complex medication regimens have, therefore, greater difficulties to take their medication [6]. Multimorbidity is prevalent in older patients [66], but it is not a problem in the elderly only. Thus, future research should focus on specific age groups, and include co-morbidities. Increasing life expectancy and the prevalence of CHF demonstrate the importance of research in this area.

Another important challenge is that researchers (1) use different definitions of medication adherence, (2) use different methods to measure adherence, (3) define different cut-off points to describe (non-)adherence, and (4) report different adherence rates (e.g., proportion or number of patients, percentage of adherent days, and adherence scale scores [67]). We found three studies that directly measured medication adherence based on the serum digoxin concentration and 14 that measured it through indirect methods (e.g., self-reporting, proportion of days covered (PDC), pill count, medication possession ratio (MPR), and Medication Event Monitoring System (MEMS)). Systematic reviews have identified approximately 50 unique instruments for the measurement of adherence to antihypertensive medications and (other) medications for chronic diseases [68,69], and the Morisky Medication Adherence Scale (MMAS) [70] was identified as the most frequently used instrument. We found three studies with cut-off points of “good” medication adherence of ≥75%, and four studies with cut-off points of ≥80%. In 10 articles, the cut-off points were either not reported, or specific definitions were applied. Conventionally, medication use rates higher than 80% are accepted as “good/acceptable” adherence [69,71]. But, even this cut-off is selected randomly, and does not characterize the important patient behavior of taking the medication as prescribed [6]. Four of the included studies show an overall mean medication adherence rate higher than 80%, which is in contrast to the general specification of an adherence of 50% to long-term therapy for chronic diseases [4]. It is likely that the comprehensive monitoring of patients and a selection bias in clinical trials have an impact [71].

The results show wide variations in medication adherence rates between 37.6% [37] and 96.3% [32] depending on the measurement of medication adherence and the drug classes studied. In conclusion, it is difficult to summarize the results of previous studies to reach valid statements regarding medication adherence rates [28]. “There is a need for consistency in the adherence-related terms used to allow for comparison of research in this area” [72]. A perfect method to measure medication adherence in patients with CHF is currently unavailable [56,73], but it is necessary to use reliable and validated instruments [68,74].

4.1. Clinical consequences

The aim of measuring medication adherence in daily practice is to predict outcomes. Our results are inconsistent but suggest that medication adherence is not lower in older CHF patients compared with younger patients. The general assumption that the main focus for adherence support is within older patients, may be incomplete. Programs to enhance medication adherence in elderly patients – affected by multiple chronic diseases, complex medication regimes, and cognitive dysfunctions – are important, but younger patients with CHF should not be forgotten [52]. For all CHF patients, the monitoring of medication adherence is recommended. Osterberg et al. noted that a non-judgmental question to evaluate patients’ medication-taking behavior is potentially more appropriate for obtaining honest answers [71,75]. It is still not possible to systematically identify patients with a high risk of non-adherence [34]. All of the presented results show that more information is needed to derive specific recommendations for evidence-based clinical interventions in order to improve medication adherence [19,56].

4.2. Limitations

We searched only two, albeit the most important, electronic libraries, namely MEDLINE and the Cochrane library [21,76]. The Cochrane library consists of the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL) and other resources, including large numbers of citations from EMBASE and
The observed effects are consistent [79, 80]. The used harvest plot was obtained from a literature review. A meta-analysis is only feasible and appropriate if the included studies have a comparable methodological quality and the observed effects are consistent [79, 80]. The used harvest plot (Fig. 2) is a method for illustrating the synthesized evidence if a meta-analysis is not feasible [27].

5. Conclusions

Our results suggest that older age alone is not related to poorer medication adherence compared with younger patients with CHF. Because non-adherence to medication remains an important issue, more focus should be paid to younger newly-diagnosed patients with CHF. This suggestion may help to predict patients who may benefit from further interventions. The continuous monitoring of adherence to medication and the exploration of potential reasons for non-adherence are recommended.

We were unable to identify a single study with the objective of exploring the relationship between (different) age (groups) and CHF medication adherence. Therefore, future studies should explore medication adherence in different, standardized, and predefined age groups and should be sufficiently powered. Ideally, these studies should be conducted in real-life ambulatory-care CHF patients and measure relevant clinical endpoints.

Conflicts of interest

The authors report no relationship that could be construed as a conflict of interest.

Acknowledgments

The authors would like to thank Margit Schmidt, ABDA, Department of Medicine, Berlin, Germany, for the support provided in retrieving the literature included in this review.

Appendix A. Supplementary data

The supplementary material (Appendix covering Tables 4–6) to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.03.042.

References
