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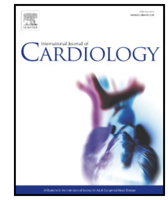

Age-related medication adherence in patients with chronic heart failure: A systematic literature review☆

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ABSTRACT

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.

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 11,327 (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

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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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 compliance[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.

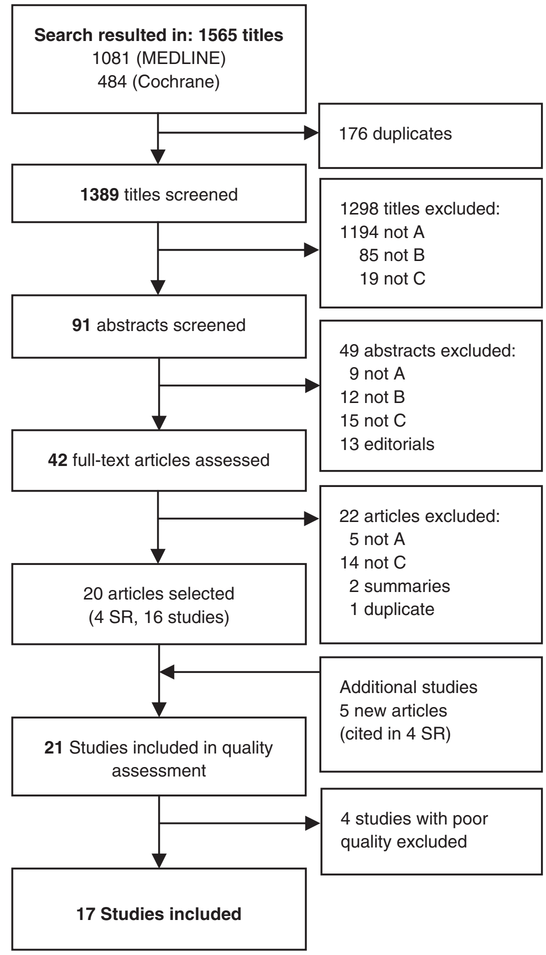

Fig. 1. Selection process (PRISMA flow diagram [20]). SR = systematic review. *Inclusion criteria:* A: Examination of medication adherence in patients with CHF. B: Evaluation of factors contributing to medication adherence. C: Analysis of relationship between age and medication adherence.

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-Calo 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].

Table 1
Summary of characteristics of included studies.

	Studies (n)	(%)	Participants (n)	(%)
Total	17	100.0	162,727	100.0
Participants				
Male (sex not reported for n = 325)			59,560	36.7
Study region				
Asia	02	11.8	444	0.3
Australia	01	5.9	115	0.1
Europe	03	17.6	402	0.2
USA	10	58.8	161,663	99.3
West-Africa	01	5.9	103	0.1
Data source				
Prospective	11	64.7	1526	0.9
Retrospective	06	35.3	161,201	99.1
Adherence measurement				
Direct method	03	17.6	484	0.3
Indirect method	14	82.4	162,243	99.7
Non-adherent patients				
Direct method (n = 484 participants)	03	17.6	136	28.0
Indirect method (n = 62,542 participants)	06	35.3	4035	6.5
Relation of age and medication adherence				
Significant association	07	41.2	107,821	66.3
No significant association	10	58.8	54,906	33.7
Quality assessment				
Good quality	08	47.1	146,801	90.2
Fair quality	09	52.9	15,926	9.8

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

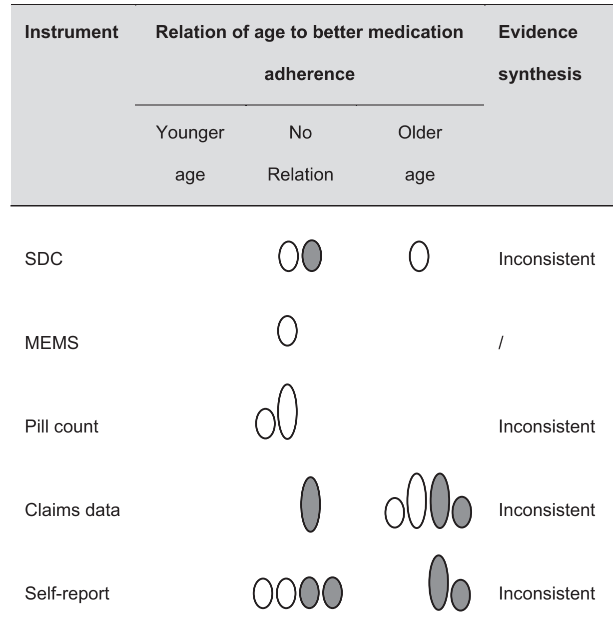

Fig. 2. Harvest plot [27], illustrating the evidence about the relation of medication adherence and patient age. Each oval shows one study, weighted by the quality score, and by the sample size — sorted by the instrument of measuring medication adherence: SDC (serum digoxin concentration), MEMS (Medication Event Monitoring System), pill count, claims data (MPR — medication possession ratio, PDC — proportion of days covered, NDC — number of days covered (in which no CHF medication was available to the patient (during 12 months)), percent acquisition method), self-report. ◯ = study size < 1000 participants. ⬯ = study size > 1000 participants. ▭ = fair quality score. ▬ = good quality score.

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 participants. 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]. 14 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,

Table 2
Characteristics of included studies.

Reference	Region	Participants			Data source	Statistical method	Quality
		N	Mean age, years (SD)	Age range, years			
Older age significantly related to better medication adherence							
Ambardekar et al. [39]	USA	54,322	/	[>18][a]	Retrospective GWTG-HF	Multivariate logistic regression analysis	Good
Bagchi et al. [31]	USA	45,572	/	/	Retrospective Medicaid data	Regression analysis	Good
Dunlay et al. [40]	USA	209	73.7 (13.5)	/	Prospective Refill data	t-Test	Good
Evangelista et al. [32]	USA	82	54.1 (12.9)	(22–90)	Prospective HF clinic	Multivariate linear regression	Good
Miura et al. [43]	Japan	325	59.3[b]	(33–89)[b]	Prospective Hospital	Multiple regression analysis	Fair
Monane et al. [33]	USA	7247	77.2 (7.7)	[65–99][a]	Retrospective Medicaid data	Linear regression model	Fair
Rodgers and Ruffin [34]	USA	64	65	(34–89)	Prospective Clinic	Odds ratio	Fair
No significant relation between age and medication adherence							
Granger et al. [41]	25 countries	7599	66 (11)	[>18 y][a]	Retrospective (CHARM study)	Multivariable regression model	Fair
Michalsen et al. [42]	Germany	179	75.4 (9.9)	(49–95)	Prospective Hospital	t-Test	Fair
Mockler et al. [44]	Ireland	183	/	/	Retrospective DMP	t-Test	Good
Modares-Mosadegh and Sadr Bafghi [45]	Iran	119	53.2 (14.8)	/	Prospective Clinic	t-Test	Fair
Muzzarelli et al. [46]	Switzer-land	40	69 (12)	/	Prospective Hospital	t-Test	Good
Rich et al. [36]	USA	156	79.4 (6.0)	/	Prospective Hospital	Multiple regression	Fair
Schweitzer et al. [13]	Australia	115	63	/	Prospective Hospital	t-Test	Good
Setoguchi et al. [37]	USA	46,278	80 (10)	/	Retrospective Medicare data	Multivariate regression	Good
Wu et al. [38]	USA	134	61.2 (11.5)	(24–87)	Prospective Clinic	Hierarchical multiple regression	Fair
Yayehd et al. [35]	Togo	103	54 (36)	(25–89)	Prospective Hospital	Univariate analysis	Fair

CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity.
DMP = Disease Management Program.
GWTG-HF = Get With The Guidelines-Heart Failure registry.
HF = heart failure.
[a] Inclusion criteria.
[b] All observed participants (N = 834).

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.

Table 3
Medication adherence — definitions and instruments of included studies.

Reference	Medication adherence: definition	Instrument	Adherence, mean % (SD)
Older age significantly related to better medication adherence			
Ambardekar et al. [39]	/	Clinician interview and patient self-report	/
Bagchi et al. [31]	Good drug adherence: ≥80% of days a patient was supplied with more than one CHF drug, related to the first and the last prescription date.	MPR and medication persistence [81]	71.9 (44.4)
Dunlay et al. [40]	Poor adherence: PDC < 80% adherence.	PDC, pharmacy records [5]	/
Evangelista et al. [32]	A score ≥ 75% categorized the patient as adherent.	Modified version of the Compliance Questionnaire [82]	96.3 (8.9)
Miura et al. [43]	Non-adherent if the SDC was below the detection limit for all three measurements.	SDC	77.8 (outpatients)
Monane et al. [33]	/	Number of days during the 12 months period after an initial digoxin prescription in which no CHF medication was available to the patient.	/
Rodgers and Ruffin [34]	Non-adherence was defined as a cumulative percent acquisition of <75%.	Percent acquisition method (validated) [83]	/
No significant relation between age and medication adherence			
Granger et al. [41]	Proportion of time patients took more than 80% of study medication as prescribed.	Patients report, pill bottles check, pill count	/
Michalsen et al. [42]	Non-adherent, if patient reported taking drugs only intermittently or not at all.	Standardized interview	/
Mockler et al. [44]	Discontinuation of disease-modifying therapy for any period since recruitment to the program was classified as non-persistence ("indirect measurement of adherence").	Comparing the patient-reported medication profile with the physician-prescribed medication profile and identifying episodes of non-persistence.	/
Modares-Mosadegh and Sadr Bafghi [45]	Non-adherent: SDC more than 50% greater or 50% lower than the predicted level.	SDC	/
Muzzarelli et al. [46]	Poor adherence of digoxin: SDC during follow-up < 0.4 ng/mL and/or a medication intake ≤ 75%.	SDC, CARDIA-Questionnaire [67]	/
Rich et al. [36]	/	Pill count	84.6 (15.1) range 23.1–100
Schweitzer et al. [13]	/	HFCQ [32]	91.2
Setoguchi et al. [37]	Full adherence: PDC ≥ 80%.	PDC	55.9 (RAAS) 54.5 (BB) 37.6 (SL)
Wu et al. [38]	Patient medication taking behavior corresponded with the prescribed medication regimen.	MEMS (dose count, dose-day, dose-time)	89 (12–102) 81 (0–100) 67 (0–100)
Yayehd et al. [35]	Classified as "mauvaise observance" if ≥3 times of answering yes to six questions.	Questionnaire de Girerd [84]	/

CARDIA = cardiovascular risk factors in young adults.
CHF = chronic heart failure.
HFCQ = Heart Failure Compliance Questionnaire.
MEMS = Medication Event Monitoring System.
MPR = medication possession ratio.
PDC = proportion of days covered.
SDC = serum digoxin concentration.

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 the study of the angiotensin-II-receptor antagonist (ARB) candesartan in the youngest age group [47]. 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],

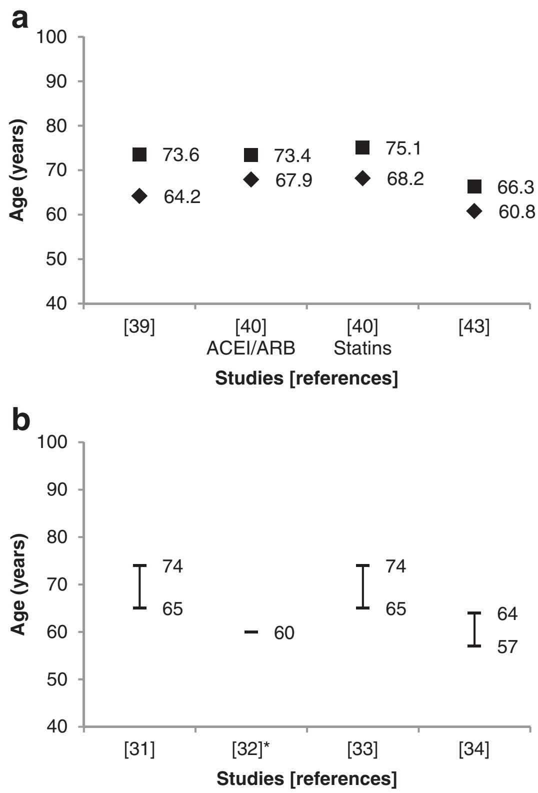

Fig. 3. Age (mean or most affected age-range) of the non-adherent CHF patients, presented in the seven studies with statistically significant results [31–34,39,40,43]. (For details see Appendix: Table 6.) **a.** ■ Mean age of adherent CHF patients. ♦ Mean age of non-adherent CHF patients. Ambardekar et al. [39] $p = 0.0001$, Dunlay et al. [40] ACEI/ARB: $p = 0.05$; statins: $p = 0.03$, Miura et al. [43] $p = 0.001$. ACEI = angiotensin-converting enzyme inhibitors. ARB = angiotensin-II-receptor antagonists. CHF = chronic heart failure. The mean age of adherent versus non-adherent patients was not reported in [31–34]. **b.** | Most affected age range of non-adherent CHF patients. Bagchi et al. [31] $p = 0.01$, Evangelista et al. [32] $p < 0.001$, Monane et al. [33] $p = 0.05$, Rodgers and Ruffin [34] odds ratio 17.83. *Evangelista et al. [32] identified patients ≤60 years as most affected by non-adherence. The most affected age range of non-adherent patients was not reported in [39,40,43].

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 [33] and comply due to visible symptoms of progressed disease [17]. Older patients may have a greater belief in the importance of disease management and have more experience with their medications [54,60,61].

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 citations not covered by either MEDLINE or EMBASE [77]. In addition, during the initial screening process of the titles, relevant articles may have been excluded prematurely. Mateen et al. showed, however, that screening of titles only compared to screening of titles and abstracts resulted in the same set of articles for their systematic literature review. Hence, this method appears acceptable [78].

The absence of a gold standard for the measurement of medication adherence, inconsistent definitions of medication adherence, and different cut-off points complicate the comparison of the results of previous studies. Hence, a meta-analysis was not justified for our systematic 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 unsuitable [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.

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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

[1] W.B. Kannel, Incidence and epidemiology of heart failure, Heart Fail. Rev. 5 (2000) 167–173.
[2] J.G. Cleland, K. Swedberg, F. Follath, M. Komajda, A. Cohen-Solal, J.C. Aguilar, R. Dietz, et al., The EuroHeart Failure survey programme — a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis, Eur. Heart J. 24 (2003) 442–463.
[3] J.J. McMurray, S. Adamopoulos, S.D. Anker, A. Auricchio, M. Böhm, K. Dickstein, V. Falk, 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. 33 (2012) 1787–1847.
[4] E. Sabaté, Adherence to Long-term Therapies: Evidence for Action, World Health Organization, Geneva, 2003.
[5] B.B. Granger, K. Swedberg, I. Ekman, C.B. Granger, B. Olofsson, J.J. McMurray, S. Yusuf, et al., Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial, Lancet 366 (2005) 2005–2011.
[6] B. Riegel, G.J. Knafl, Electronically monitored medication adherence predicts hospitalization in heart failure patients, Patient Prefer. Adherence 8 (2013) 1–13.
[7] P. Muntner, J.H. Halanych, K. Reynolds, R. Durant, S. Vupputuri, V.W. Sung, J.F. Meschia, et al., Low medication adherence and the incidence of stroke symptoms among individuals with hypertension: the REGARDS study, J. Clin. Hypertens. 13 (2011) 479–486.
[8] J. Wu, T.A. Lennie, R.L. Dekker, M.J. Biddle, D.K. Moser, Medication adherence, depressive symptoms, and cardiac event-free survival in patients with heart failure, J. Card. Fail. 19 (2013) 317–324.
[9] A.A. Fitzgerald, J.D. Powers, P.M. Ho, T.M. Maddox, P.N. Peterson, L.A. Allen, F.A. Masoudi, et al., Impact of medication nonadherence on hospitalizations and mortality in heart failure, J. Card. Fail. 17 (2011) 664–669.
[10] P.S. Corotto, M.M. McCarey, S. Adams, P. Khazanie, D.J. Whellan, Heart failure patient adherence: epidemiology, cause, and treatment, Heart Fail. Clin. 9 (2013) 49–58.
[11] M.L. Alosco, M.B. Spitznagel, M. van Dulmen, N. Raz, R. Cohen, L.H. Sweet, L.H. Colbert, et al., Cognitive function and treatment adherence in older adults with heart failure, Psychosom. Med. 74 (2012) 965–973.
[12] D.K. Moser, P.L. Worster, Effect of psychosocial factors on physiologic outcomes in patients with heart failure, J. Cardiovasc. Nurs. 14 (2000) 106–115.
[13] R.D. Schweitzer, K. Head, J.W. Dwyer, Psychological factors and treatment adherence behaviour in patients with chronic heart failure, J. Cardiovasc. Nurs. 22 (2007) 76–83.
[14] A. Skalska, B. Wizner, A. Więcek, T. Zdrojewski, J. Chudek, A. Klich-Rączka, K. Piotrowicz, et al., Reduced functionality in everyday activities of patients with self-reported heart failure hospitalization—population-based study results, Int. J. Cardiol. 176 (2014) 423–429.
[15] R.B. Haynes (Ed.), Compliance in Health Care, Johns Hopkins Univ. Press, Baltimore, 1979.
[16] L. Lorenc, A. Branthwaite, Are older adults less compliant with prescribed medication than younger adults? Br. J. Clin. Psychol. 32 (Pt 4) (1993) 485–492.
[17] M. Monane, R.L. Bohn, J.H. Gurwitz, R.J. Glynn, R. Levin, J. Avorn, Compliance with antihypertensive therapy among elderly Medicaid enrollees: the roles of age, gender, and race, Am. J. Public Health 86 (1996) 1805–1808.
[18] M.R. Cowie, A. Mosterd, D.A. Wood, J.W. Deckers, P.A. Poole-Wilson, G.C. Sutton, D.E. Grobbee, The epidemiology of heart failure, Eur. Heart J. 18 (1997) 208–225.
[19] M.H.L. van der Wal, T. Jaarsma, Adherence in heart failure in the elderly: problem and possible solutions, Int. J. Cardiol. 125 (2008) 203–208.
[20] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Int. J. Surg. 8 (2010) 336–341.
[21] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P. Ioannidis, M. Clarke, et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, PLoS Med. 6 (2009) e1000100.
[22] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
[23] J.A. Hayden, P. Côté, C. Bombardier, Evaluation of the quality of prognosis studies in systematic reviews, Ann. Intern. Med. 144 (2006) 427–437.
[24] R. Oosterom-Calo, A.J. van Ballegooijen, C.B. Terwee, S.J. te Velde, I.A. Brouwer, T. Jaarsma, J. Brug, Determinants of adherence to heart failure medication: a systematic literature review, Heart Fail. Rev. 18 (2013) 409–427.
[25] R.E. Slavin, Best evidence synthesis: an intelligent alternative to meta-analysis, J. Clin. Epidemiol. 48 (1995) 9–18.
[26] J. Roebuck, When does "old age begin?": the evolution of the English definition, J. Soc. Hist. 12 (1979) 416–428.
[27] D. Ogilvie, D. Fayter, M. Petticrew, A. Sowden, S. Thomas, M. Whitehead, G. Worthy, The harvest plot: a method for synthesising evidence about the differential effects of interventions, BMC Med. Res. Methodol. 8 (2008) 8.
[28] J. Wu, D.K. Moser, T.A. Lennie, P.V. Burkhart, Medication adherence in patients who have heart failure: a review of the literature, Nurs. Clin. North Am. 43 (2008) 133–153.
[29] C. Kongkaew, I. Sakunrag, P. Jianmongkol, Non-compliance with digoxin in patients with heart failure and/or atrial fibrillation: a systematic review and meta-analysis of observational studies, Arch. Cardiovasc. Dis. 105 (2012) 507–516.
[30] M.H.L. van der Wal, T. Jaarsma, D.J. van Veldhuisen, Non-compliance in patients with heart failure; how can we manage it? Eur. J. Heart Fail. 7 (2005) 5–17.
[31] A.D. Bagchi, D. Esposito, M. Kim, J. Verdier, D. Bencio, Utilization of, and adherence to, drug therapy among Medicaid beneficiaries with congestive heart failure, Clin. Ther. 29 (2007) 1771–1783.
[32] L.S. Evangelista, J. Berg, K. Dracup, Relationship between psychosocial variables and compliance in patients with heart failure, Heart Lung 30 (2001) 294–301.
[33] M. Monane, R.L. Bohn, J.H. Gurwitz, R.J. Glynn, J. Avorn, Noncompliance with congestive heart failure therapy in the elderly, Arch. Intern. Med. 154 (1994) 433–437.
[34] P.T. Rodgers, D.M. Ruffin, Medication nonadherence: part II—a pilot study in patients with congestive heart failure, Manag. Care Interface 11 (1998) 67–69 (75).
[35] K. Yayehd, F. Damorou, M.P. N'cho Mottoh, T. Tchérou, A. Johnson, S. Pessinaba, Y. Tété, et al., Observance thérapeutique de l'insuffisant cardiaque à Lomé, Ann. Cardiol. Angeiol. (Paris) 62 (2013) 22–27.
[36] M.W. Rich, D.B. Gray, V. Beckham, C. Wittenberg, P. Luther, Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure, Am. J. Med. 101 (1996) 270–276.
[37] S. Setoguchi, N.K. Choudhry, R. Levin, W.H. Shrank, W.C. Winkelmayer, Temporal trends in adherence to cardiovascular medications in elderly patients after hospitalization for heart failure, Clin. Pharmacol. Ther. 88 (2010) 548–554.
[38] J. Wu, D.K. Moser, M.L. Chung, T.A. Lennie, Predictors of medication adherence using a multidimensional adherence model in patients with heart failure, J. Card. Fail. 14 (2008) 603–614.

[39] A.V. Ambardekar, G.C. Fonarow, A.F. Hernandez, W. Pan, C.W. Yancy, M.J. Krantz, Characteristics and in-hospital outcomes for nonadherent patients with heart failure: findings from Get With The Guidelines-Heart Failure (GWTG-HF), Am. Heart J. 158 (2009) 644–652.
[40] S.M. Dunlay, J.M. Eveleth, N.D. Shah, S.M. McNallan, V.L. Roger, Medication adherence among community-dwelling patients with heart failure, Mayo Clin. Proc. 86 (2011) 273–281.
[41] B.B. Granger, I. Ekman, C.B. Granger, J. Ostergren, B. Olofsson, E. Michelson, J.J. McMurray, et al., Adherence to medication according to sex and age in the CHARM programme, Eur. J. Heart Fail. 11 (2009) 1092–1098.
[42] A. Michalsen, G. König, W. Thimme, Preventable causative factors leading to hospital admission with decompensated heart failure, Heart 80 (1998) 437–441.
[43] T. Miura, R. Kojima, Y. Sugiura, M. Mizutani, F. Takatsu, Incidence of noncompliance and its influencing factors in patients receiving digoxin, Clin. Drug Invest. (2000) 123–130.
[44] M. Mockler, C. O'Loughlin, N. Murphy, M. Ryder, C. Conlon, K.M. McDonald, M.T. Ledwidge, Causes and consequences of nonpersistence with heart failure medication, Am. J. Cardiol. 103 (2009) 834–838.
[45] M. Modares-Mosadegh, S.M. Sadr Bafghi, Digoxin compliance: a pharmacokinetic quantification, Med. J. I.A.S. (2001) 117–122.
[46] S. Muzzarelli, H. Brunner-La Rocca, O. Pfister, P. Foglia, G. Moschovitis, G. Mombelli, H. Stricker, Adherence to the medical regime in patients with heart failure, Eur. J. Heart Fail. 12 (2010) 389–396.
[47] C.M. Wong, N.M. Hawkins, P.S. Jhund, M.R. MacDonald, S.D. Solomon, C.B. Granger, S. Yusuf, et al., Clinical characteristics and outcomes of young and very young adults with heart failure: the CHARM programme (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity), J. Am. Coll. Cardiol. 62 (2013) 1845–1854.
[48] L. Evangelista, L.V. Doering, K. Dracup, C. Westlake, M. Hamilton, G.C. Fonarow, Compliance behaviours of elderly patients with advanced heart failure, J. Cardiovasc. Nurs. 18 (2003) 197–206 (quiz 207–8).
[49] N.T. Artinian, M. Magnan, M. Sloan, M.P. Lange, Self-care behaviours among patients with heart failure, Heart Lung 31 (2002) 161–172.
[50] J.E. Bailey, M.D. Lee, G.W. Somes, R.L. Graham, Risk factors for antihypertensive medication refill failure by patients under Medicaid managed care, Clin. Ther. 18 (1996) 1252–1262.
[51] Gabrielle K.Y. Lee, Harry H.X. Wang, Kirin Q.L. Liu, Yu Cheung, Donald E. Morisky, Martin C.S. Wong, Determinants of medication adherence to antihypertensive medications among a Chinese population using Morisky Medication Adherence Scale, PLoS One 8 (2013) e62775.
[52] P. Assawasuwannakit, R. Braund, S.B. Duffull, A model-based meta-analysis of the influence of factors that impact adherence to medications, J. Clin. Pharm. Ther. 40 (2015) 24–31.
[53] E.A. Graveley, C.S. Oseasohn, Multiple drug regimens: medication compliance among veterans 65 years and older, Res. Nurs. Health 14 (1991) 51–58.
[54] M.J. Cohen, S. Shaykevich, C. Cawthon, S. Kripalani, M.K. Paasche-Orlow, J.L. Schnipper, Predictors of medication adherence postdischarge: the impact of patient age, insurance status, and prior adherence, J. Hosp. Med. 7 (2012) 470–475.
[55] M.A. Fischer, M.R. Stedman, J. Lii, C. Vogeli, W.H. Shrank, M.A. Brookhart, J.S. Weissman, Primary medication non-adherence: analysis of 195,930 electronic prescriptions, J. Gen. Intern. Med. 25 (2010) 284–290.
[56] R. Nieuwlaat, N. Wilczynski, T. Navarro, N. Hobson, R. Jeffery, A. Keepanasseril, T. Agoritsas, et al., Interventions for enhancing medication adherence, Cochrane Database Syst. Rev. 11 (2014) CD000011.
[57] W.H. Shrank, T. Hoang, S.L. Ettner, P.A. Glassman, K. Nair, D. DeLapp, J. Dirstine, et al., The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions, Arch. Intern. Med. 166 (2006) 332–337.
[58] T.H. Wroth, D.E. Pathman, Primary medication adherence in a rural population: the role of the patient–physician relationship and satisfaction with care, J. Am. Board Fam. Med. 19 (2006) 478–486.
[59] A. Ekedahl, N. Månsson, Unclaimed prescriptions after automated prescription transmittals to pharmacies, Pharm. World Sci. 26 (2004) 26–31.
[60] L.H. Huang, Medication-taking behaviour of the elderly, Kaohsiung J. Med. Sci. 12 (1996) 423–433.
[61] M.H.L. van der Wal, T. Jaarsma, D. Moser, N. Veeger, W.H. van Gilst, D.J. van Veldhuisen, Compliance in heart failure patients: the importance of knowledge and beliefs, Eur. Heart J. 27 (2006) 434–440.
[62] D.M. Zulman, J.B. Sussman, X. Chen, C.T. Cigolle, C.S. Blaum, R.A. Hayward, Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials, J. Gen. Intern. Med. 26 (2011) 783–790.
[63] M.E. McMurdo, M.D. Witham, N.D. Gillespie, Including older people in clinical research, BMJ 331 (2005) 1036–1037.
[64] I.A. Scott, G.H. Guyatt, Cautionary tales in the interpretation of clinical studies involving older persons, Arch. Intern. Med. 170 (2010) 587–595.
[65] F.A. Masoudi, E.P. Havranek, P. Wolfe, C.P. Gross, S.S. Rathore, J.F. Steiner, D.L. Ordin, et al., Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure, Am. Heart J. 146 (2003) 250–257.
[66] S. Banerjee, Multimorbidity-older adults need health care that can count past one, Lancet 385 (2015) 587–589. PMID:25468155.
[67] M.J. Leventhal, B. Riegel, B. Carlson, S. de Geest, Negotiating compliance in heart failure: remaining issues and questions, Eur. J. Cardiovasc. Nurs. 4 (2005) 298–307.
[68] S.A. AlGhurair, C.A. Hughes, S.H. Simpson, L.M. Guirguis, A systematic review of patient self-reported barriers of adherence to antihypertensive medications using the world health organization multidimensional adherence model, J. Clin. Hypertens. (Greenwich) 14 (2012) 877–886.
[69] A. Lehmann, P. Aslani, R. Ahmed, J. Celio, A. Gauchet, P. Bedouch, O. Bugnon, et al., Assessing medication adherence: options to consider, Int. J. Clin. Pharm. 36 (2014) 55–69.
[70] D.E. Morisky, L.W. Green, D.M. Levine, Concurrent and predictive validity of a self-reported measure of medication adherence, Med. Care 24 (1986) 67–74.
[71] L. Osterberg, T. Blaschke, Adherence to medication, N. Engl. J. Med. 353 (2005) 487–497.
[72] R. Ahmed, P. Aslani, What is patient adherence? A terminology overview, Int. J. Clin. Pharm. 36 (2014) 4–7.
[73] H. Smith, M. Hankins, A. Hodson, C. George, Measuring the adherence to medication of elderly patients with heart failure: is there a gold standard? Int. J. Cardiol. 145 (2010) 122–123.
[74] M. Viswanathan, C.E. Golin, C.D. Jones, M. Ashok, S.J. Blalock, R.C. Wines, E.J. Coker-Schwimmer, et al., Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review, Ann. Intern. Med. 157 (2012) 785–795.
[75] J. Wu, D.A. DeWalt, D.W. Baker, D. Schillinger, B. Ruo, K. Bibbins-Domingo, A. Macabasco-O'Connell, et al., A single-item self-report medication adherence question predicts hospitalisation and death in patients with heart failure, J. Clin. Nurs. 23 (2013) 2554–2564. PMID:24355060.
[76] M. Egger, G.D. Smith, D.G. Altman, Systematic Reviews in Health Care: Meta-analysis in Context, 2nd ed. BMJ Books, London, 2001. (©).
[77] K.S. Khan, Systematic Reviews to Support Evidence-based Medicine: How to Review and Apply Findings of Healthcare Research, 2nd ed. Hodder Annold, London, 2011.
[78] F.J. Mateen, J. Oh, A.I. Tergas, N.H. Bhayani, B.B. Kamdar, Titles versus titles and abstracts for initial screening of articles for systematic reviews, Clin. Epidemiol. 5 (2013) 89–95.
[79] K.F. Schulz, I. Chalmers, R.J. Hayes, D.G. Altman, Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials, JAMA 273 (1995) 408–412.
[80] L.L. Kjaergard, J. Villumsen, C. Gluud, Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses, Ann. Intern. Med. 135 (2001) 982–989.
[81] R. Sikka, F. Xia, R.E. Aubert, Estimating medication persistency using administrative claims data, Am. J. Manage Care 11 (2005) 449–457.
[82] G.A. Hilbert, Accuracy of self-reported measures of compliance, Nurs. Res. 34 (1985) 319–320.
[83] J.F. Steiner, T.D. Koepsell, S.D. Fihn, T.S. Inui, A general method of compliance assessment using centralized pharmacy records. Description and validation, Med. Care 26 (1988) 814–823.
[84] X. Girerd, O. Hanon, K. Anagnostopoulos, C. Ciupek, J.J. Mourad, S. Consoli, Evaluation de l'observance du traitement antihypertenseur par un questionnaire: mise au point et utilisation dans un service spécialisé, Presse Med. (Paris) 30 (2001) 1044–1048.