Appendix

Table 4

Quality check: Quality in Prognosis Studies (QUIPS) tool [23], modified by Oosterom-Calo et al. [24]. (Y=yes, N=no, NR=not reported)

Methodological issue	Question addressed	Scoring
Theoretical background	1. Is a theoretical background presented, to which the motivation for conducting the study and/or the hypotheses are linked?	Y=3, NR=2, N=1
Study participation	2. Is the study population clearly described in terms of age, gender, and important HF characteristics?	Y=3, NR=2, N=1
	3. Is the percentage of eligible subjects who participated in the study (response rate) adequate?	Y=3, NR=1, N=2
Sampling	4. Are patients who participated in the study similar to eligible non-participants, in terms of age, gender, and important disease characteristics?	Y=3, NR=1, N=2
Study attrition	5. Is the percentage of subjects available for analysis adequate (i.e., 70%)?	Y=3, NR=1, N=2
	6. Were reasons for loss to follow-up presented and assessed during the study for possible systematic attrition?	Y=3, NR=1, N=2
Determinant/ correlate(s) measurement	7. Are clear definitions of each determinant and/or correlate provided?	Y=3, NR=2, N=1
	8. Are clear operationalizations of each determinant and/or correlate provided?	Y=3, NR=2, N=1
	9. Are the measurement instruments used for the measurement of the determinants and correlates reliable and valid?	Y=3, NR=1, N=2
	10. Were the measurement approach, time and place of measurement of the determinants and/or correlates standardized or conducted in a way that limits systematically different measurement?	Y=3, NR=2, N=1
Outcome variable measurement	11. Are clear definitions of each outcome variable provided?	Y=3, NR=2, N=1
	12. Are clear operationalizations of each outcome variable provided?	Y=3, NR=2, N=1
	13. Are the measurement instruments used for the measurement of the outcome variable(s) reliable and valid?	Y=3, NR=2, N=1
	14. Were the measurement approach, time and place of measurement of the outcome variable(s) standardized or conducted in a way that limits systematically different measurement?	Y=3, NR=2, N=1
Statistical analyses	15. Is the percentage of missing values adequate (i.e. <30%)?	Y=3, NR=1, N=2
	16. Were multivariable analyses performed? If yes, was it clearly described which variables were included in the (multivariable) model(s)?	Y=3, NR=1, N=2
General question	17. Were there any other important flaws in the design or analyses of the study?	Y=1, NR=2, N=3

Table 5
Quality check of 21 studies considered for inclusion.

Selected articles	Questions																	Quality score	Quality rating
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
Ambardekar et al.[39]	3	3	/	/	/	/	3	/	/	/	1	3	2	/	/	3	3	2.6	**good**
Artinian et al.[49]	3	3	1	1	/	/	3	/	/	/	1	1	1	3	/	2	1	1,8	**poor**
Bagchi et al.[31]	3	3	/	/	/	/	3	/	/	/	3	3	2	3	/	3	3	2,9	**good**
Dunlay et al.[40]	3	3	2	1	3	3	3	/	/	/	3	3	2	3	3	2	3	2,6	**good**
Evangelista et al.[48]	3	3	/	1	1	1	3	/	/	/	1	3	3	2	1	1	2	1,9	**poor**
Evangelista et al.[32]	3	3	3	1	3	3	3	/	/	/	3	3	3	3	3	3	2	2,8	**good**
González et al.[85]	3	3	1	1	1	1	3	/	/	/	1	3	2	2	1	2	2	1,9	**poor**
Granger et al.[41]	3	2	/	/	1	1	3	/	/	/	3	3	2	3	1	3	2	2,3	**fair**
Liekens et al.[86]	3	3	/	1	1	1	3	/	/	/	3	2	2	3	1	1	1	1,9	**poor**
Michalsen et al.[42]	3	3	1	3	1	1	3	/	/	/	3	3	2	2	1	2	2	2,1	**fair**
Miura et al.[43]	3	3	1	1	1	1	3	/	/	/	3	3	3	3	1	3	2	2,2	**fair**
Mockler et al.[44]	3	3	/	/	3	/	3	/	/	/	3	3	2	3	3	3	3	2,9	**good**
Modares-Mosadegh et al.[45]	3	2	1	1	1	1	3	/	/	/	3	3	3	3	1	2	2	2,1	**fair**
Monane et al.[33]	3	1	/	/	/	/	3	/	/	/	3	3	2	/	/	3	1	2,4	**fair**
Muzzarelli et al.[46]	3	3	1	1	3	3	3	/	/	/	3	3	3	3	3	2	1	2,5	**good**
Rich et al.[36]	3	3	1	1	1	1	3	/	/	/	3	3	2	3	1	3	3	2,2	**fair**
Rodgers et al.[34]	2	3	/	/	2	3	3	/	/	/	1	3	3	/	/	2	1	2,3	**fair**
Schweitzer et al.[13]	3	3	1	1	3	1	3	/	/	/	3	3	3	3	3	2	3	2,5	**good**
Setoguchi et al.[37]	3	3	/	/	/	/	3	/	/	/	3	3	3	/	/	3	3	3,0	**good**
Wu et al.[38]	3	3	1	1	1	1	3	/	/	/	3	3	3	3	1	3	2	2,2	**fair**
Yayehd et al.[35]	3	3	1	3	1	1	3	/	/	/	3	3	2	3	1	3	2	2,3	**fair**

/ = not applicable. The quality score presents the average value of the questions. Studies were rated as follows: 2.5-3 as good, 2.0-2.4 as fair and <2.0 as poor quality. Additional references, not cited in the original article: [85] González B, Lupón J, Parajón T, Urrutia A, Altimir S, Coll R, Prats M et al. Nurse evaluation of patients in a new multidisciplinary Heart Failure Unit in Spain. Eur. J. Cardiovasc. Nurs. 2004;3:61–9. [86] Liekens S, Hulshagen L, Dethier M, Laekeman G, Foulon V. L'observance thérapeutique des traitements chroniques: problématique pour les patients belges aussi! J. Pharm. Belg. 2013:18–27.

Table 6
Medication adherence: definitions, measurement and results of included studies.

Reference	Medication adherence: definition	Instrument	Adherence, mean, % (SD)	Results (statistic)	Result (conclusion)	Result (age-related)
Ambardekar et al. [39]	/	Clinician interview and patient self-report	/	Non-adherent patients **64.2 y** vs. patients without non-adherence 73.6 y, univariate, p<0.0001 Odds Ratio (OR) 1.022 (95% confidence interval 1.019-1.026), multivariate, p<0.0001	Patients with Heart Failure-admission because of non-adherence were younger than those without non-adherence. Younger age was independently associated with non-adherence.	Significant Younger age and non-adherence
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 last prescription date.	MPR and medication persistence [81]	**71.9 (44.4)**	MPR p<0.01; standard error (SE) ≤64 y – omitted category **65-74** y ß=2.14 (SE 0.489) 75-84 y ß=4.45 (SE 0.563) ≥85 y ß=5.27 (SE 0.644)	Regression results indicate that patient medication adherence increases with age.	Significant Younger age and non-adherence
Dunlay et al. [40]	Poor adherence: PDC < 80% adherence.	PDC, Pharmacy records [5]	/	Poor adherence ACEI/ARB **67.9 y** (SD 11.0) vs. good adherence 73.4 y (SD 13.5), p=0.05 Poor adherence statins **68.2 y** (SD 13.9) vs. good adherence 75.1 y (SD 11.1), p=0.03 (t-test)	Patients with poor adherence to ACEI/ARB and statins were younger than those with good adherence. No age-related differences found for BB.	Significant Younger age and non-adherence
Evangelista et al. [32]	A score ≥ 75% categorized the patient as adherent.	Modified version of the Compliance Questionnaire [82]	**96.3 (8.9)**	Pearson correlation ratio (PCR) r=0.442, p<0.001, R^2=0.185, F 19.189, p=0.000	Medication adherence was higher for older patients (two groups aged **≤ 60 y** and > 60 y).	Significant Younger age and non-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	/	B=0.001, p=0.997, α=0.01	Age was not significantly associated with adherence (women, particularly those < 74 y, were less likely to be adherent).	Not significant

Reference	Medication adherence: definition	Instrument	Adherence, mean, % (SD)	Results (statistic)	Result (conclusion)	Result (age-related)
Michalsen et al. [42]	Non-adherent, if patient reported taking drugs only intermittently or not at all.	Standardized interview	/	Adherent patients 77.4 y (9.7) vs. non-adherent patients 72.2 y (10.5), not significant	The non-adherent group tended to be younger than the adherent group.	Not significant
Miura et al. [43]	Non-adherent if the SDC was below the detection limit for all three measurements.	SDC	**77.8** (outpatients)	Adherent patients 66.3 (SD 11.7) vs. non-adherent patients **60.8** (SD 10.0), p<0.0001 (t-test) Relation between SDC and age partial regression coefficient 0.0053, partial correlation coefficient 0.149, p=0.008	Younger age was significant associated with non-adherence to digoxin.	Significant Younger age and non-adherence
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.	/	Non-persistent 70.9 y (SD 10.3) vs. persistent patients 69.4 y (SD 11.6), p=0.40 (t-test) Hazard ratio (HR)=1.013 (95% confidence interval 0.984-1.043), p=0.41	There was no age-related difference in those patients who stopped therapy.	Not significant
Modares-Mosadegh et al. [45]	Non-adherent: SDC more than 50% greater or 50% lower than the predicted level.	SDC	/	Adherent patients 54.67 y (SD=14.75) vs. non-adherent patients 51.45 y (SD 14.78), p=0.24	No significant difference in relation to age and adherence to digoxin between adherent and non-adherent groups.	Not significant
Monane et al. [33]	/	Number of days during the 12 months period after an initial digoxin prescription in which no CHF medication was available.	/	Oldest group ≥ 85 y had 17.0 fewer days (range -23.7 to -10.3) without therapy than the youngest group **65-74** y (p≤0.05)	Adherence rates were higher in patients aged ≥85 years.	Significant Younger age and non-adherence

Reference	Medication adherence: definition	Instrument	Adherence, mean, % (SD)	Results (statistic)	Result (conclusion)	Result (age-related)
Muzzarelli et al. 2010 [46]	Poor adherence of digoxin: SDC during follow-up < 0.4 ng/mL and/or a medication intake ≤ 75%.	SDC, CARDIA-(Cardiovascular risk factors in young adults) Questionnaire [67]	/	Adherent patients 67 y (SD 12) vs. non-adherent patients 71 (SD 11), p=0.4	Age was not significantly associated with adherence to digoxin.	Not significant
Rich et al. 1996 [36]	/	Pill count	**84.6 (15.1)** range 23.1-100	Multiple regression models. Method 1: age r=0.032 (p=0.692), method 2: age r=0.021 (p=0.797)	No significant correlation between age and medication adherence.	Not significant
Rodgers et al. 1998 [34]	Non-adherence was defined as a cumulative percent acquisition of < 75%.	Percent acquisition method (validated) [83]	/	Odds ratio (OR) 35-56 y: 1.00 57-64 y: 17.83 65-72 y: 1.91 73-89 y: 3.25	Increased risk of non-adherence in the 56-64 y age group.	Significant 56-64 y age group non-adherent
Schweitzer et al. 2007 [13]	/	HFCQ [32]	**91.2**	Model 1: SE 0.00 ß=0.01 Model 2: SE 0.00 ß=-0.04	No significant relation between age and medication adherence was found.	Not significant
Setoguchi et al. 2010 [37]	Full adherence: PDC ≥ 80%.	PDC	**55.9** (RAAS) **54.5** (BB) **37.6** (SL)	Risk ratio (RR) RAAS: 1.02 (1.00-1.04), p=0.0175 BB: 1.02 (1.00-1.05), p=0.099 SL: 1.05 (0.97-1.15), p=0.214	No significant relationship between age and full medication adherence.	Not significant
Wu et al. 2008 [38]	Patient medication taking behaviour corresponded with the prescribed medication regimen.	MEMS	**89 (12-102)** **81 (0-100)** **67 (0-100)**	p(dose-count)=0.101 p(dose-day)=0.107 p(dose-time)=0.135 Spearman´s rho (not significant)	Age was not related to medication adherence.	Not significant
Yayehd et al. 2013 [35]	Classified as "mauvaise observance" if ≥ 3 times of answering yes to six questions.	Questionnaire de Girerd [84]	/	p=0.37	No significant relation between medication adherence (“mauvaise observance”) and age.	Not significant

ACEI = angiotensin-converting enzyme inhibitors
ARB = angiotensin-II-receptor antagonists
BB = ß-blockers
HFCQ = Heart Failure Compliance Questionnaire
MEMS = Medication Event Monitoring System
MPR = medication possession ratio
PDC = proportion of days covered
RAAS = renin angiotensin aldosteron system
SD = standard deviation
SDC = serum digoxin concentration
SL = spironolactone
y = year