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A tool for assessment of heart failure prescribing quality: a systematic review and meta-analysis.

A tool for assessment of heart failure prescribing quality: a systematic review and meta-analysis.

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Abstract:

Introduction: Heart failure (HF) guidelines aim to standardise patient care. Internationally, prescribing practice in HF may deviate from guidelines and so a standardised tool is required to assess prescribing quality. A systematic review and meta-analysis were performed to identify a quantitative tool for measuring adherence to HF guidelines and its clinical implications.

Methods: Eleven electronic databases were searched to include studies reporting a comprehensive tool for measuring adherence to prescribing guidelines in HF patients aged ≥18 years. Qualitative studies or studies measuring prescription rates alone were excluded. Study quality was assessed using the GRACE Checklist.

Results: In total, 2,455 studies were identified. Sixteen eligible full-text articles were included (n=14,354 patients, mean age 69±8 years). The Guideline Adherence Index (GAI), and its modified versions, was the most frequently cited tool (n=13). Other tools identified were: the Individualised Reconciled Evidence Recommendations, the Composite Heart Failure Performance, and the Heart Failure Scale. The meta-analysis included the GAI studies of good-high quality. The average GAI-3 was 62%. Compared to Low GAI, High GAI patients had lower mortality rate (7.6% vs. 33.9%) and lower rehospitalisation rates (23.5% vs. 24.5%); *both* $p \leq 0.05$. High GAI was associated with reduced risk of mortality (HR = 0.29, 95% CI 0.06 - 0.51) and rehospitalisation (HR = 0.64, 95% CI 0.41 - 1.00). No tool was used to improve prescribing quality.

Conclusion: The GAI is the most frequently used tool to assess guideline adherence in HF. High GAI is associated with improved HF outcomes.

Introduction

Landmark clinical trials [1-3] revealed the benefits of evidence-based therapies on mortality, hospitalisation and quality of life in heart failure (HF). However, international reports suggest that prescribers do not optimally adhere to the recommendations of HF prescribing guidelines[4-6]. It has been shown that under-prescribing of evidence-based therapies is associated with worsening HF and higher rates of HF hospital admissions and mortality [7-9]. Furthermore, where these disease-modifying agents are prescribed but at lower than target dose, patients may not obtain the full beneficial effect of the agent [5, 10]. Thus, HF care could be vastly improved with optimal use of guideline-directed therapy [10, 11].

Guideline adherence refers to the adoption of clinical guidelines by clinicians, rather than to the patient's own adherence. There remains a wide variation in HF prescribing patterns and quality internationally [5, 12, 13] and several barriers to guideline adherence have been described. Prescribing for patients with multiple comorbidities [5], polypharmacy [14], or advanced age [14] can affect prescriber's adherence to guidelines. Furthermore, lack of resources in the healthcare setting or lack of knowledge on the behalf of the prescriber may also play a role in poor guideline adherence [15].

Given the complexity of HF management, prescription rates alone are not sufficient to judge prescribing quality as they do not consider factors such as a patient's eligibility for or contraindication to therapy or achievement of target dose. Innovative methods to measure prescription quality in an objective manner and to assess the impact of guideline adherence on clinical outcomes are required in order to optimise HF care [14, 15].

Therefore, a systematic review and meta-analysis were performed in order to identify objective tools for assessing adherence to guideline-led prescribing in HF and to assess the clinical outcomes associated with guideline adherence measured by such tools.

Methods

Search Strategy

The systematic review was performed in line with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [16]. A database search was performed and duplicate results were removed. Two reviewers (SE, MB) independently reviewed the titles and abstracts of studies identified in the search. Studies that were eligible for full-text review were identified and reviewed by the two reviewers (SE, MB) for final determination of study inclusion in the systematic review and meta-analysis.

Information Sources

The following electronic databases were searched in April 2016: Medline PubMed, Scopus, Web of Knowledge, Science Direct, CINAHL, PsycInfo, EMBASE, Cochrane Library, Campbell Collaboration, Open Grey and Grey Lit. No restriction was placed on publication date or language.

Search method

The following search terms were combined as appropriate across each database: heart failure, care indicator, global prescribing score, guideline adherence indicator,

guideline adherence index, GAI, guideline compliance, guideline implementation, implementation of guidelines, process indicator, quality circle, strategies for guideline implementation, underutilisation of evidence-based therapies in heart failure. The search terms were used as single terms or combined via Boolean logic (AND, OR) in each of the aforementioned databases.

Eligibility criteria

The inclusion criteria for the systematic review were studies (i) specific to chronic or acute HF patients aged ≥18 years, (ii) measuring adherence to a national or international chronic or acute HF guideline; (iii) using a quantitative tool to assess adherence to prescribing guidelines. The exclusion criteria for this systematic review were (i) studies reporting drug utilisation rates in the absence of a quantitative or comprehensive tool and (ii) qualitative studies. Risk of bias assessment was performed using the Good ReseArch for Comparative Effectiveness (GRACE) Checklist for observational studies [(17)].

Meta-analysis

A meta-analysis was performed on studies identified in the systematic review that used the Guideline Adherence Index (GAI) tool to assess guideline adherence. Studies of good to high quality according to the GRACE Checklist were included in the meta-analysis. The following GAI-based measures [(18)] were reported in the meta-analysis: i) overall GAI is a mean score of the guideline adherence levels (range from 0% - 100%) of all the eligible

patients prescribed HF medications as recommended by the relevant guideline; ii) GAI-3 is the proportion of eligible patients prescribed the three principle HF disease-modifying therapies: renin-angiotensin system inhibitor (RASi), beta-blocker and mineralocorticoid receptor antagonist (MRA) according to the indications of the relevant guideline; iii) GAI-5 is the proportion of eligible patients prescribed the recommended five standard HF medications: RASi, beta-blocker, MRA, loop diuretic and cardiac glycoside according to the indications of the relevant guideline. Furthermore, GAI score could be reported as tertiles [18]: (a) Perfect GAI is prescription of the three principle HF medications; (b) Medium GAI is prescription of two out of the three HF medications; c) Poor GAI is prescription of one or zero HF medications. However, in this study, GAI scores are categorised into dichotomous levels only (i) High GAI that is prescription of ≥2 recommended HF agents and (ii) Low GAI that is prescription of <2 recommended HF agents. GAI could also be calculated for each pharmacological substance class individually as the proportion of eligible patients to the proper pharmacological substance class. This is usually compared to the drug utilisation rate (DUR) that is the percentage of patients prescribed a medication out of the total population regardless of the patient's eligibility.

Meta-analysis of patient outcomes associated with guideline adherence

Data were extracted from the studies identified using a structured form in Microsoft Office Excel® 2016. Pooled odd ratios (OR) and respective 95% confidence intervals (CIs) were displayed using the forest plot generator of DistillerSR®. Hazard ratios (HR) and respective 95% CIs were pooled using NCSS® Statistical Software for Data Analysis v11 for meta-analysis of HRs, computed by random effects regression for combining study data.

Cochran's Q test was used to estimate heterogeneity. Random effects are applied to compensate for the potential for between-study heterogeneity in observational studies. Means were rarely reported with an estimate of variability, and consequently, presented as pooled mean with its appropriate standard deviation or the range of means.

Results

Search Results

A total of 2,454 titles were identified through the database search and one manuscript via hand search. Of these, 1,529 were duplicates. Following title and abstract review 66 studies were identified as eligible for full-text review. Finally, 16 studies were considered as relevant to this systematic review as shown in PRISMA flowchart (Figure 1).

Profile of included studies

The characteristics of each included study are shown in Table 1. All included studies were non-interventional. Study populations ranged from 58 – 3,292 HF patients. The combined study population included in the review was 14,354 HF patients and the mean age was 69.0±8.0 years. Patients having HF with reduced ejection fraction (HFrEF) were included in all 16 studies and patients having HF with preserved ejection fraction (HFpEF) in 11 studies [18-28]. The studies reported the use of guideline adherence assessment tools in several different healthcare settings including eight studies performed in ambulatory care [18, 19, 21, 24, 25, 29-31], six studies in primary care [23, 27, 28, 30, 32, 33] and seven studies in hospital inpatient settings [19, 20, 22, 26, 29, 31, 33]. Seven studies [18, 21, 25, 26, 29-31] included a follow-up period of 6-12 months while two studies [19, 20] reported a follow-up period of almost two years. Twelve studies were performed in Europe, six of which were performed in Germany [18, 19, 21, 27, 29, 32]. All studies assessed guideline adherence by reference to European Society of Cardiology

(ESC) guidelines except Popescu *et al.* [20] which used an American quality measure. Fifteen studies were adjudged to be of good - high quality (Table 1). One study was judged to be of poor quality and was not included in the meta-analysis [31].

Tools identified in the systematic review

Four objective tools were identified in this review: i) the GAI [18]; ii) the Composite Heart Failure Performance [20]; iii) the Heart Failure Scale [23] and iv) the Individualized Recommended Evidence-based Reconciliation (IRER) [24].

The GAI [18] is defined as the proportion of eligible HF patients who are prescribed guideline-directed therapy by their physician according to the indications of 2001 European HF guidelines [34]. Thirteen of the 16 studies identified used the GAI [18, 19, 21, 22, 25-33]. This tool has been modified in several ways since its publication and only two studies used the original tool [28, 30]. Modifications to the GAI include the consideration of contraindications to therapy [19, 22, 25, 28, 29, 32, 33], recommended target doses [25, 32], general practitioner rationale [27, 33] and patients' socioeconomic level [22, 33] as eligibility criteria for guideline adherence.

Each of the other guideline adherence tools identified has been reported in a single study. The Composite Heart Failure Performance [20] is calculated as a ratio of the number of HF patients in a given hospital who received guideline-directed treatment divided by the number of HF patients in that hospital who should have received the indicated treatment. Therefore, this tool was developed for application at a hospital population level rather than at a direct patient level. The third tool identified is the Heart Failure Scale [23]. It is calculated as

the percentage of HF patients appropriately receiving the following elements of care: laboratory tests, lipid profile, prescription of a RASi and prescription of a beta-blocker. The fourth tool is the Individualized Recommended Evidence-based Reconciliation (IRER) [24]. This tool consists of software that merges the guidelines of several chronic diseases and includes recommendations on vaccination, lifestyle measures and therapy goals as well as pharmacological therapy. The software generates a list of evidence-based recommendations personalised to each HF patient. This is the most recently published tool and is characterised by its multi-disciplinary approach, however it does not take contraindications to therapy into consideration. All non-GAI studies took into account some clinical aspects of prescribing such as availability of echocardiography results or serum creatinine level as a pre-requisite to RASi prescription. The components of clinical care considered by each tool are described in Supplemental Material Table S1.

No tool identified here has been utilised as a tool to improve or to optimise the quality of prescribing in HF patients. Furthermore, no tool assessed the management of acute HF.

Measured guideline adherence and changes in guideline adherence indices over time

The studies reporting the IRER and the Composite Heart Failure Performance both reported guideline adherence of >90% whereas the Heart Failure Scale reported a relatively low guideline adherence score of 1.6 / 4. Among studies reporting GAI, the mean GAI-3 was 62.9% ± 20.4% (range 14% - 95%) in the time period from 2005 to 2016. These changes reflect the on-going modifications to the GAI and guideline updates. Also, small sample size may adversely affect overall GAI score in certain studies such as Oliveira *et al*. [22].

Guideline adherence tools compared to drug utilisation rates

Four GAI based studies reported DUR and GAI scores for RASi, beta-blockers and MRAs (Supplemental Material Table S2). Two studies [18, 22] showed that GAI scores of pharmacological classes were higher than DUR scores as GAI consider patient's eligibility to therapy as denominator. However, the other two studies [28, 32] showed the opposite result. This paradox was explained by Klimm *et al.* [32], as GAI score should take into account both contraindications and achievement of target dose in order to reflect the guideline's recommendations comprehensively. However, in Bosch *et al.*[28], the higher DURs were justified as HF medications were prescribed to patients in absence of their indications.

Daily target dose prescription

Six studies [25-28, 32, 33] reported the frequency of HF patients receiving >50% of the daily target dose of disease-modifying therapy (Figure 2). Overall, 45.5% of patients were prescribed >50% of target dose of RASi and 33.2% of patients were prescribed >50% of target dose of beta-blocker. The daily dose of MRAs was studied in two populations [26, 33] where >50% daily target dose was prescribed to 95.6% and 100% of patients respectively.

Guideline adherence achieved by cardiologists and general practitioners

Three studies compared general practitioner (GP) and cardiologist prescribing patterns. Stork *et al.*[19] calculated the GAI-3 as 67% for cardiologists and 60% for GPs *(p-value= 0.01)*. Luttick *et al.*[30] calculated the GAI for each type of prescriber at baseline and at one-year follow-up. The GAI rates for GP prescribers were 95% at baseline and 92% at

follow-up and the GAI rates for cardiologists were 94.5% at baseline and 91% at follow-up. However, the difference at both time points was non-significant. Elsewhere, Bosch *et al.* [28] found that the percentage of patients receiving the guideline-directed target dose of ACE-inhibitors was significantly higher when prescribed by a cardiologist than when prescribed by a GP (29.5% vs. 14.3%, *p-value <0.05*). Elsewhere, Visca and colleagues [23] found that single or team-based GP practice has no relationship with the HF composite score.

Achievement of High Guideline Adherence Index

High GAI achievement was calculated in eight GAI studies [18, 19, 21, 25-27, 29, 32]. The mean proportion of patients achieving High GAI was 53.8±12.2% (range 38% [19] to 71% [26, 29]). Before 2010, mean proportion of HF patients achieving High GAI was 42.5% while in the period since 2010, a mean of 63% of patients have achieved High GAI. Clinical associates of High GAI achievement are illustrated in Figure 3.

Clinical outcomes associated with Guideline Adherence Index

The clinical impact of guideline adherence was studied in seven study populations [18, 19, 21, 25, 26, 29, 30]. Two studies [21, 29] reported Cox proportional hazards models estimating the relationship between GAI and one-year mortality. Mortality risk associated with High GAI ranged from 5% to 13% while mortality risk associated with Low GAI ranged from 10% to 21.5% (*Log-rank p-value <0.005 each*). On the other hand, six studies [18, 19, 21, 22, 25, 26] reported mortality rates as mortality percentage in the whole population sample, High GAI and Low GAI cohorts separately as 16.0±8.1%, 7.6±3.0% and 33.9±18.8% respectively. Both approaches of mortality outcome measurement showed a significant mortality benefit of High

GAI levels over Low GAI levels. Adjusted for age and sex, High GAI score was a significant independent predictor of mortality risk reduction in five studies (overall HR = 0.289, 95% CI= 0.061 - 0.516, Figure 4).

All-cause hospital admission was studied in three populations [18, 25, 30] where the overall mean rehospitalisation rate was 9.1±6.1%. In addition, the variation of rehospitalisation rates among the different GAI cohorts was studied in two study populations [18, 29], where the overall mean rehospitalisation rate per 100 patients in the High GAI cohorts was 23.5±20.2% but in the Low GAI cohorts was 24.23±10.6%. Paradoxically, Zugck *et al.*[29] reported that HF hospitalisation rate was significantly higher in the High GAI cohort than in the Low GAI cohort (50% vs. 36%, *p-value= 0.026*) although a clear explanation for this effect was not offered. Finally, in the MAHLER study over a 12-month follow-up period, risk of rehospitalisation was significantly reduced in patients with High GAI compared to those with Low GAI (HR = 0.64, 95% CI 0.41 - 1.00).

Discussion

The current review is the first to assess the evidence regarding standardised quantitative tools for assessment of guideline-led prescribing in HF. It is a rigorous study of guideline adherence measurement and its potential to improve patient outcomes. Four quantitative tools were identified from 16 studies, each a comprehensive approach for assessment of prescription of evidenced-based HF therapies. The reviewed studies encompassed different healthcare settings and different prescriber types. Furthermore, several studies reported the effect of guideline adherence on clinical outcomes.

Of the four tools identified for assessing guideline adherence, the GAI was the most frequently cited, and was used predominately in Europe. The GAI only accounts for patients who are eligible for a particular therapy, according to the guideline indications. This is a more accurate assessment of prescribing than simple drug utilisation rates. Moreover, the GAI has been modified to keep pace with on-going guideline changes. The Heart Failure Composite Score and the Heart Failure Scale each considered just two HF medications – RASi and beta-blockers - as these are the therapies with the strongest evidence-base. However, both of these tools included aspects of laboratory or diagnostic medical tests that are not taken into account by the GAI such as examining echocardiographic evidence or serum creatinine levels before prescribing an ACE inhibitor. The IRER is the most recently described tool and is the only tool reviewed here that was developed for electronic use. This tool merges guideline recommendations for HF and for common HF comorbidities such as chronic obstructive pulmonary disease, dyslipidaemia and atrial fibrillation, in a single list for each patient. However, it does not take into account the patient's eligibility or any contraindication to HF drug therapy.

The GAI was originally developed by Komajda and colleagues [18] in 2005 as a means to quantify prescribing quality for HF patients in Europe. However, this original GAI has some limitations. That is why Stork *et al.* and Klimm *et al.*[19, 32] modified the GAI to include target dose and contraindications to therapy. Bosch *et al.* [28] and Deticek *et al.* [26] considered the issue of HF licenced medications as part of guideline adherence although Deticek's study did not illustrate the method of GAI calculation clearly.

Most recently, Hirt *et al.* [27] and Oertle *et al.* [33] included a qualitative aspect in their GAI studies and showed that GAI is significantly higher when quantitative as well as qualitative patient data are considered. This supports previous data showing that patient and prescriber factors may be important barriers to guideline adherence [15]. These barriers included complexity of treatment in the elderly, patient's multiple comorbidities or low socio-economic status. However, these barriers were different to those barriers identified in the SHAPE study [13]. The latter emphasised the prescriber lack of knowledge and education as significant contributors to guideline non-adherence.

Although the mean overall GAI score was moderate, fluctuation in GAI scores might be influenced by the changing definitions of GAI [18, 32] or due to the wide variation in clinical practice between countries [5, 13]. This moderate GAI score demonstrates that there is great scope for optimising HF prescribing internationally. In the work reported here, guideline adherence by cardiologists was similar to that of GPs. The rates reported for both types of prescriber in this review are considerably greater than those reported in the 2008 NEHI report [35], that showed guidelines adherence of 70% for cardiologists and 47% for GPs in cardiac disease management in the United States. The higher guideline adherence rates reported in

this review may indicate greater dissemination and acceptability of HF guidelines and diminishing barriers to guideline adherence in Europe in the intervening period. The increasing proportion of High GAI rates reported from 2005 to 2016 supports this. However, there is still room for optimising target dose prescribing as the combined levels of target dose achievement in this review were lower than those reported recently by Barywani *et al.* [10]. No study examined the role of the GAI in initiatives to improve guideline adherence or how pharmacists or other members of the healthcare team may implement the GAI.

Optimal use of guideline-directed therapy significantly improves HF care. This review reveals a positive relationship between High GAI and beneficial clinical outcomes albeit in a small number of observational studies. This finding is in line with other studies in the literature which show that the beneficial impact of higher levels of guideline adherence [7, 8].

Conclusion

Several tools have been developed to measure guideline adherence in HF. The GAI and its respective modifications represent a comprehensive and practical approach for assessment of guideline-led prescribing in HF. The GAI offers a reliable quantitative tool when compared to DURs. Future work may focus on using the modified GAI as a tool to improve prescribing quality.

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Table 1. Profile and characteristics of the studies included in the systematic review.

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Komajda, France, Italy, Netherlands, Spain, Germany, United Kingdom 2005 [18]	Prospective, observational, multicentre study in ambulatory care settings.	Clinical impact of guideline adherence on hospitalisation and time to hospitalisation	1,410	68.6	European Society of Cardiology 2001	GAI	(Medications indicated / Total medications prescribed) x100	GAI-3 = 60% GAI-5 = 63%	Good

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Stork, Germany 2008 [19]	Prospective, observational, multicentre study in hospitals and ambulatory care settings.	Determinants of guideline adherence	1,054	72.6	European Society of Cardiology 2001	GAI	Consider contraindications	HFrEF GAI-3 = 67% HFrEF GAI-5 = 75% High HFrEF GAI-5 = 47%	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Klimm, Germany 2008 [32]	Prospective, observational, multicentre study in primary care units.	Assessment of guideline adherence among general practitioners	167	68.2	German guidelines 2005	GAI	Consider contraindications and target dose	GAI-3 = 25%, mGAI-3 = 16% Target dose RASi = 16% Target dose beta blocker = 8% Perfect GAI = 44%	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes	Quality of tool
Popescu, USA 2008 [20]	Retrospective, observational, multicentre study in hospitals	Assess hospital compliance with quality measures	N/A	N/A	Centre for Medicare and Medicaid Services performance measures	Composite Heart Failure Performance	(Number of patients prescribed ACE inhibitor / Number of ACE inhibitor candidates) x 100	Performance rate = 90.9%	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Bosch, Netherlands 2010 [28]	Prospective, observational multicentre study in primary care	Evaluation of heart failure treatment in Dutch primary care	357	75.7	European Society of Cardiology 2005	GAI	None	GAI-3 = 53.3% RASi target dose = 48.8% Beta blocker target dose = 12% RASi + beta blocker + MRA = 10.4%	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Frankenstein, Germany 2010 [21]	Prospective, observational, multicentre study in ambulatory care settings	Assessment of impact of guideline adherence on survival	3,292	60.75	European Society of Cardiology 2005	GAI	Consider contraindications; relative GAI	Crude GAI = 47.9% (1994-2000) Crude GAI = 70.8% (2001-2007) Relative GAI-3 improved from 66% (2000) – 100% (2007)	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes	Quality of tool
Oertle, Switzerland 2010 [33]	Retrospective, observational single-centre study in hospital setting	Understanding the suboptimal utilisation of evidence based medicine in heart failure	348	81.5	European Society of Cardiology 2005	GAI	Corrected for chronic kidney disease and adjusted by general practitioners' rational	GAI-3 = 70%, GAI-5 = 60% Corrected GAI-5c = 80% Adjusted GAI-5a = 90%	Good

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes	Quality of tool
Zugck, Germany 2012 [29]	Retrospective, observational, multicentre study in various medical settings	Evaluation of guideline adherence level and its determinants	2,682	65.5	European Society of Cardiology 2005	GAI	Consider contraindications	Perfect GAI = 71.1% Moderate GAI = 22.4% Poor GAI = 6.5%	Good

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes	Quality of tool
Visca, Italy 2013 [23]	Retrospective, observational, multicentre in primary care units	Assess impact of team practice in family medicine	1,962,137 admissions	54.3	New Zealand guidelines 2009 & other international guidelines	Heart Failure Composite Scale	Scale of four evidence based criteria (Serum creatinine + lipid levels + ACE inhibitor + beta blocker)	Heart Failure Composite Scale = 1.64/4	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Oliveira, Brazil 2013 [22]	Prospective, observational single-centre hospital	Evaluation of physician guideline adherence	53	57.1	Brazilian guidelines 2009	GAI	Consider contraindications	GAI-3 = 40.7%	Good
Poezl, Austria 2014 [25]	Multi-centre in ambulatory care settings	Study of guideline adherence and dose effect	2,824	65.0	European Society of Cardiology 2012	GAI	Consider target dose	GAI = 75.7% Improved target dose based GAI = 64.4%	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Yoo, Korea 2014 [31]	Retrospective, observational, multicentre study, hospital settings	Guideline adherence assessment and its outcomes	1,319	69.0	European Society of Cardiology 2008	GAI	None	GAI-0 = 1.5% GAI-3 = 43.6% Good GAI = 82%	Poor

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Luttik, Netherlands 2014 [30]	Prospective, observational, multicentre study in primary care units	Assessment of guideline adherence in general practice compared to heart failure clinics	189	72.5	European Society of Cardiology 2008	GAI	GAI at two time-points	GP GAI $_{baseline}$ = 95% GP GAI$_{1year}$ = 92% HF Clinic GAI $_{baseline}$ = 94.65% HF Clinic GAI$_{1year}$ = 91.1%	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Ho, Australia 2014 [24]	Retrospective, observational, single centre study, in ambulatory care	Assess guideline adherence in heart failure patients with multiple comorbidities	255	81.0	Australian guidelines 2009 and 2012	Individual Reconciled Evidence-based Recommendations	Reconciled list of evidence-based recommendations individualised specifically for each patient	Full evidence-based prescription = 93.7% Therapeutic goals achieved = 88.7% Lifestyle modifications = 64%	High

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Hirt, Germany 2016 [27]	Three-stage study in primary care units	Assessment of guideline adherence in general practice units	206	76.7	European Society of Cardiology 2012	GAI	Consider contraindications, target dose and prescriber concerns	Contraindication based GAI = 56% Target dose based GAI = 3%	Good

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Deticek, Slovenia 2016 [26]	Prospective, single-centre study in a hospital	Assessment of therapy modifications in inpatients	198	77.0	European Society of Cardiology 2012	GAI	Consider target dose and contraindications	GAI-123 = 90% GAI-3 = 14% mGAI-3 = 7.1% GAI-5 = 2.5%	High

Abbreviations: GAI: Guideline Adherence Index; mGAI: modified Guideline Adherence Index; MRA: mineralocorticoid receptor antagonist; RASi: renin-angiotensin system inhibitor.

Figure 1. Flow diagram of the systematic review search strategy.

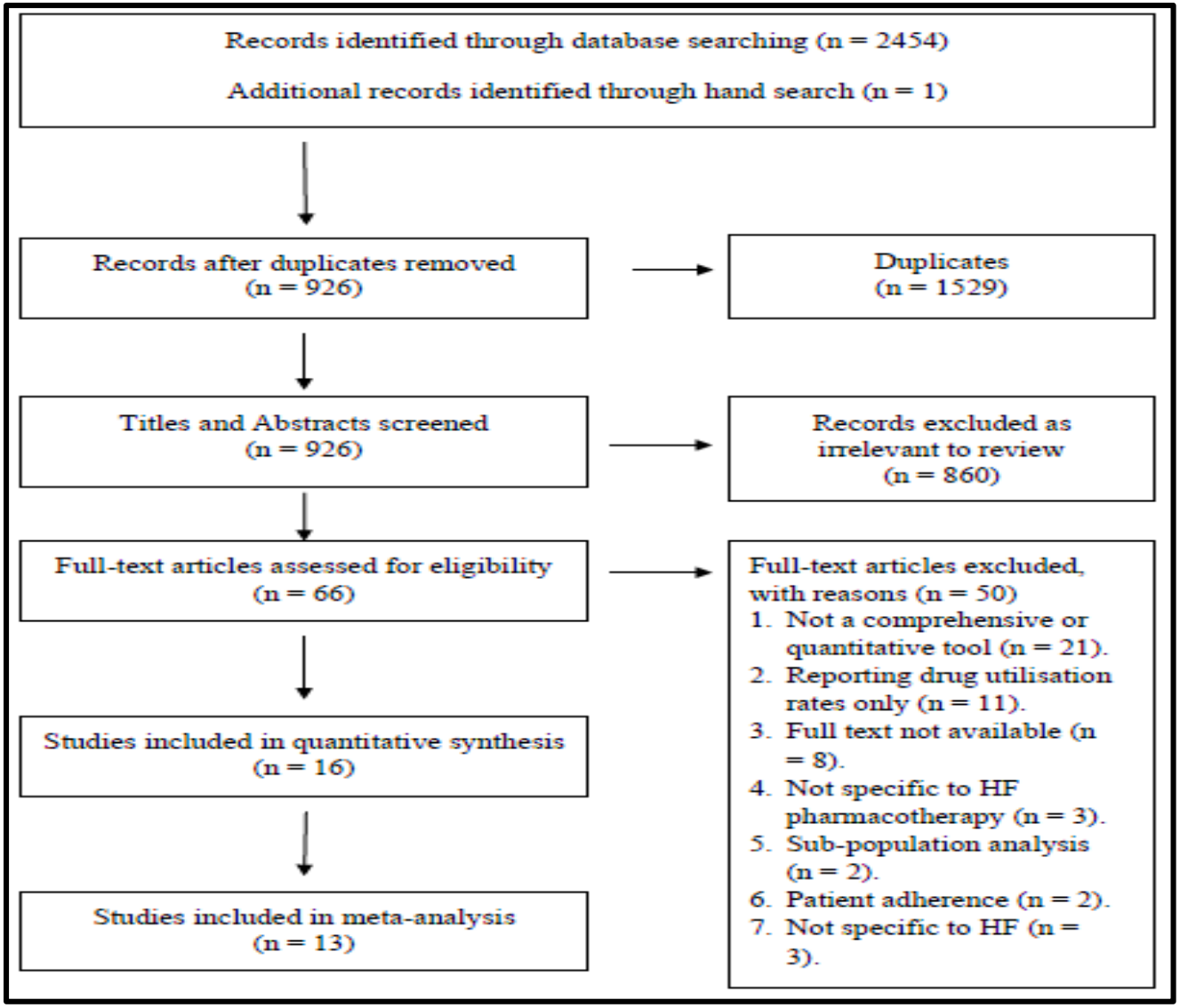


Figure 2. Heart failure patients prescribed >50% of the recommended target dose of (i) beta-blockers and (ii) renin angiotensin system inhibitors.

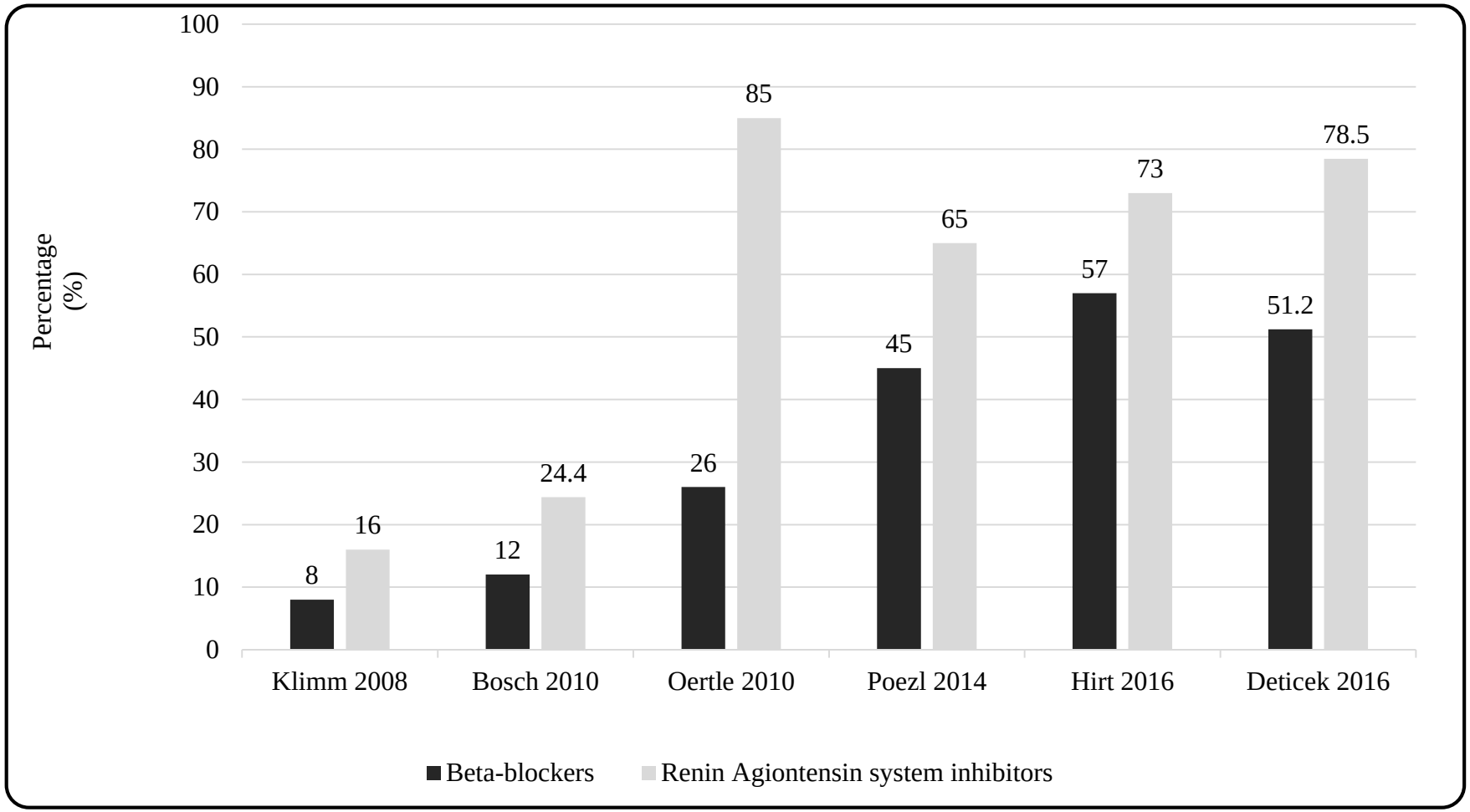


Figure 3.

Clinical associates of High Guideline Adherence Index based on data from two study populations (Bosch[28] and Frankenstein [21]) using multivariate Cox regression analysis. I^2 static = 73.1% p-value <0.001.

Abbreviations: HF: heart failure; LCL: lower confidence level; MDRD: modified diet for renal disease; NYHA: New York Heart Association; OR: odds ratio; UCL: upper confidence level.

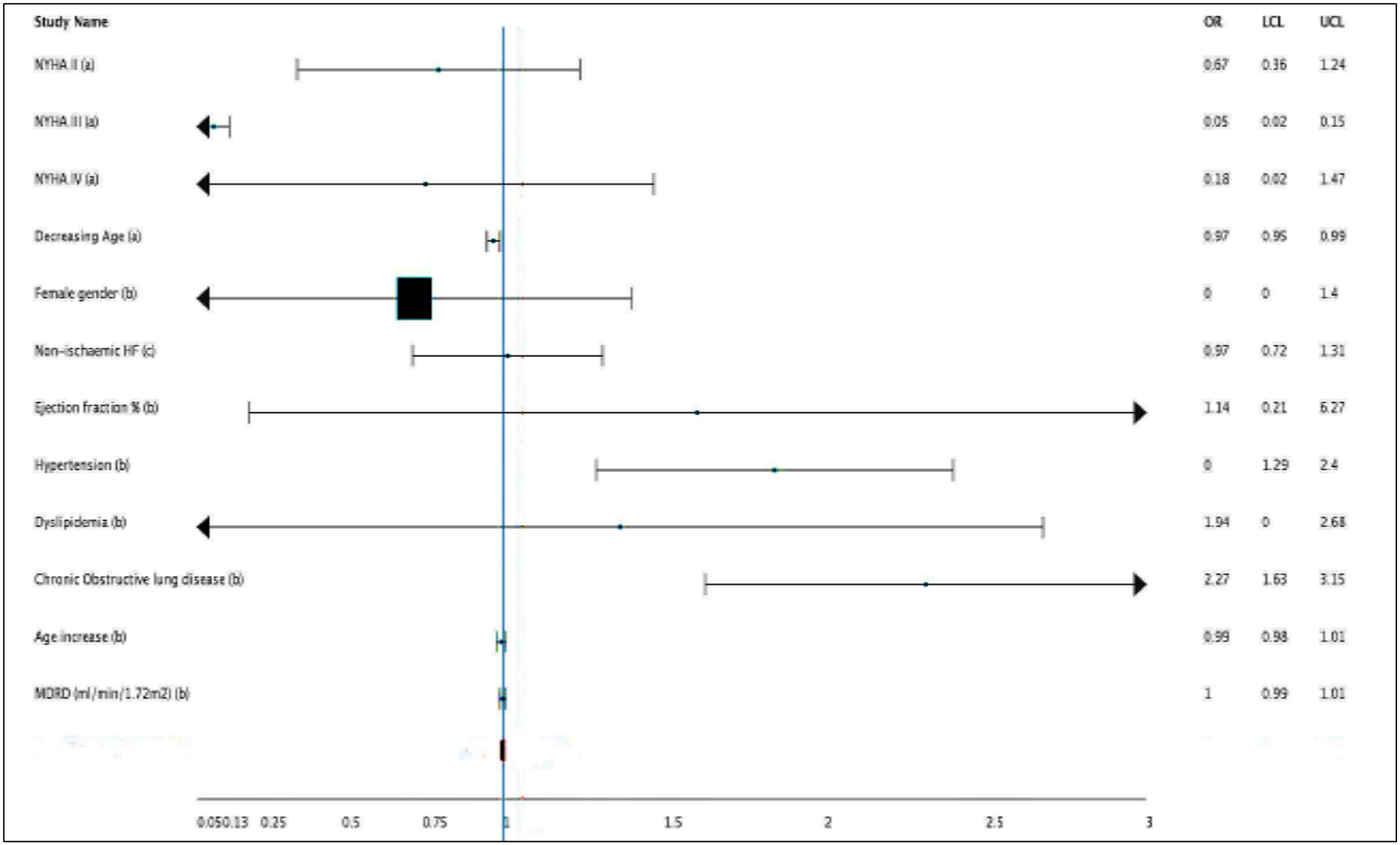
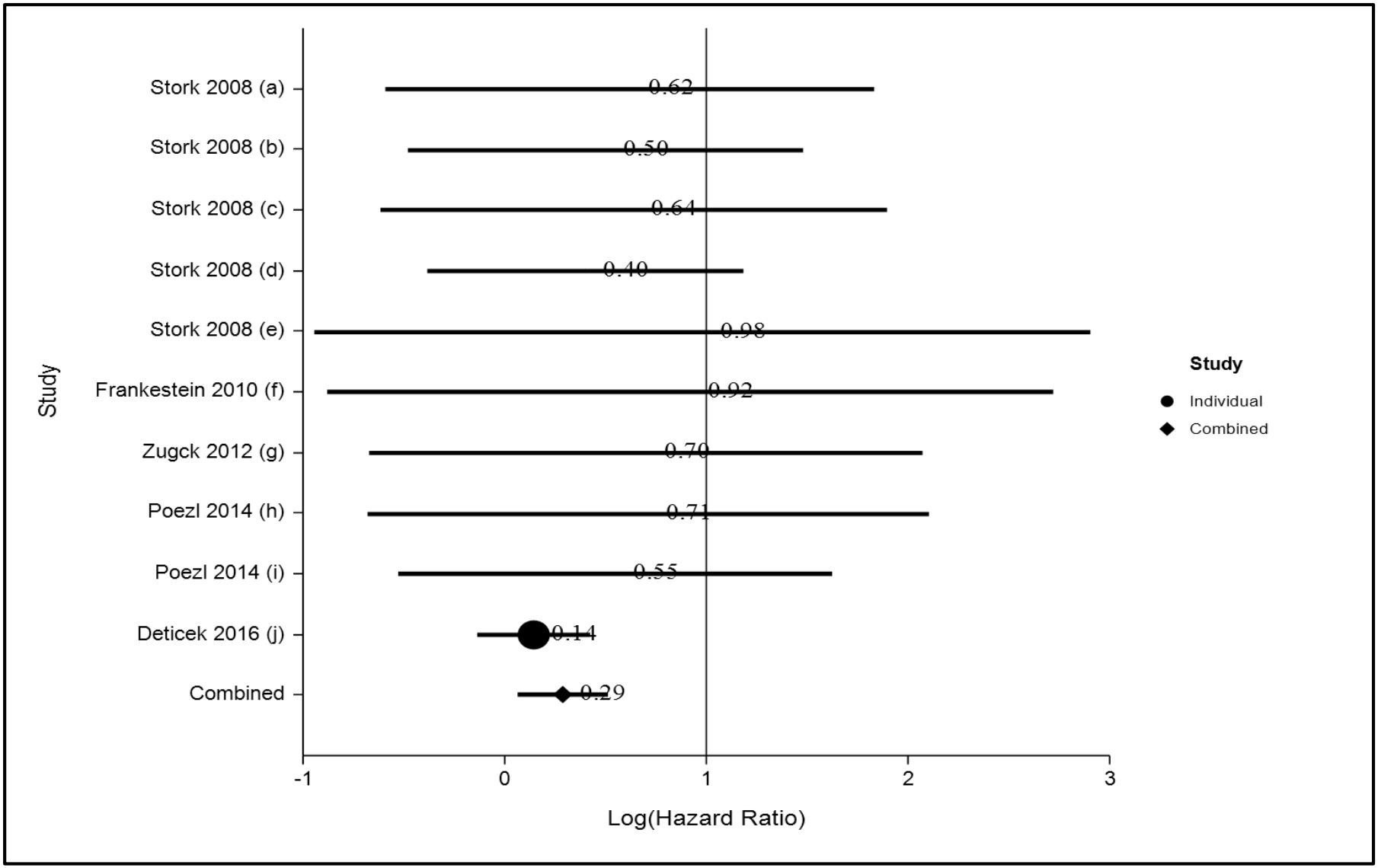

Study Name
OR
LCL
UCL
NYHA II (a)
0.67
0.36
1.24
NYHA III (a)
0.05
0.02
0.15
NYHA IV (a)
0.18
0.02
1.47
Decreasing Age (a)
0.97
0.95
0.99
Female gender (b)
0
0
1.4
Non-ischaemic HF (c)
0.97
0.72
1.31
Ejection fraction % (b)
1.14
0.21
6.27
Hypertension (b)
0
1.29
2.4
Dyslipidemia (b)
1.94
0
2.68
Chronic Obstructive lung disease (b)
2.27
1.63
3.15
Age increase (b)
0.99
0.98
1.01
MDRD (ml/min/1.72m2) (b)
1
0.99
1.01
0.05
0.13
0.25
0.5
0.75
1
1.5
2
2.5
3

Figure 4. Meta-analysis of the association between Guideline Adherence Index and mortality.

Cochran's Q = 3.8; p-value = 0.924. The following Guideline Adherence Index (GAI) parameters were seen to be associated with mortality risk reduction: (a) GAI-3 Medium compared to GAI-3 poor; (b) GAI-3 High compared to GAI-3 low; (c) GAI-5 Medium compared to GAI-5 poor; (d) GAI-5 High compared to GAI-5 low; (e) high dose of ACE inhibitor/angiotensin receptor blocker; (f) GAI per 10% increase; (g) GAI-3; (h) improvement in GAI over one year; (i) improvement in target dose GAI over one year; (j) GAI-123 compared to GAI-0. Results (a) – (e) based on HFrEF cohort, n = 641.

Definitions: GAI-0: No heart failure recommended medication prescribed; GAI-123: prescription of any one of the top three heart failure recommended agents; GAI-3: prescription of all the top three recommended heart failure medications; GAI-5: prescription of all five heart failure recommended medications.


Stork 2008 (a)
Stork 2008 (b)
Stork 2008 (c)
Stork 2008 (d)
Stork 2008 (e)
Frankestein 2010 (f)
Zugck 2012 (g)
Poezl 2014 (h)
Poezl 2014 (i)
Deticek 2016 (j)
Combined
Study
0.62
0.50
0.64
0.40
0.98
0.92
0.70
0.71
0.55
0.14
0.29
-1
0
1
2
3
Log(Hazard Ratio)
Study
Individual
Combined

Supplemetal material

Supplemental Material Table S1:

The components of clinical care considered by each tool.

#	Study by year	Any medical investigation	Any lab tests	Eligibility of prescription	RASi	Beta-blocker	Mineralocorticoid receptor antagonist	Diuretics	Digoxin	Contra-indications	Target Dosing	Heart failure licenced agents	Any other clinical barrier/ GP rationale	Any other patient related factor
Guideline Adherence Index studies				●	●	●	●	●	●	●	●	●	●	●
1	Komajda 2005			●	●	●	●	●	●					
2	Klimm 2008			●	●	●	●			●	●			
3	Stork 2008			●	●	●	●	●	●	●				
4	Bosch 2010			●	●	●	●			●				
5	Frankenstein 2010			●	●	●	●							
6	Oertle 2010			●	●	●	●			●			●	●
7	Zugck 2012			●	●	●	●			●				
8	Oliveira 2013			●	●	●	●	●	●	●				●
9	Luttick 2014			●	●	●	●	●	●					
10	Poelzl 2014			●	●	●	●			●	●			
11	Yoo 2014			●	●	●	●							

#	Study by year	Any medical investigation	Any lab tests	Eligibility of prescription	RASi	Beta-blocker	Mineralocorticoid receptor antagonist	Diuretics	Digoxin	Contra-indications	Target Dosing	Heart failure licenced agents	Any other clinical barrier/ GP rationale	Any other patient related factor
12	Deticek 2016				●	●	●	●	●			●		
13	Hirt 2016			●	●	●	●						●	
Non Guideline Adherence Index studies		●	●	●	●	●	●	●	●	●	●	●	●	
14	Popescu 2008	●		●	●									
15	Visca 2013		●	●	●	●				●				
16	Ho 2014	●			●	●	●	●	●		●	●	●	

Abbreviations: GP: general practitioner; IRER: Individualized Reconciled Evidence-based Recommendations; RASi: renin-angiotensin system inhibitor.

Supplemental Material Table S2

Drug utilisation rates compared to Guideline Adherence Index for principle heart failure medications.

Study	Renin angiotensin systems inhibitors (%)		Beta-blockers (%)		Mineralocorticoid receptor antagonists (%)	
	DUR	GAI	DUR	GAI	DUR	GAI
Komajda 2005	69.0	85.4	53.0	58.0	28.0	36.0
Klimm 2008*	80.0	49.0	75.0	46.0	57.0	-
Bosch 2010	61.3	58.3	54.6	47.0	24.9	31.0
Oliveira 2013	68.8	73.5	54.1	60.4	49.2	57.1
Mean	**69.8**	**66.6**	**59.3**	**52.9**	**39.8**	**41.4**

Abbreviations: DUR: drug utilisation rate; GAI: Guideline Adherence Index.

* Klimm *et al.* used a Modified Guideline Adherence Index adjusted to patient contraindications and target dose.