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Association of loop diuretics use and dose with outcomes in outpatients with heart failure: a systematic review and meta-analysis of observational studies involving 96,959 patients

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Abstract

There is ongoing controversy regarding the association between loop diuretics (LD), especially in high doses, and adverse clinical outcomes in outpatients with heart failure (HF). We performed a systematic review of the evidence for LD in outpatients with HF. We searched MEDLINE, EMBASE, and Cochrane Clinical Trial Collection to identify controlled studies, evaluating the association between LD and morbidity and mortality in patients with HF. The primary endpoint was all-cause mortality and secondary endpoint HF hospitalizations. Quantitative analysis was performed by generating forest plots and pooling adjusted risk estimates across studies using random effects models. Between-study heterogeneity was assessed through Q and I^2 statistics. Twenty-four studies with a total of 96,959 patients were included. No randomized studies were identified. Use of LD was associated with increased all-cause mortality compared with non-use (pooled *adjusted* risk estimates, 1.18; $P = 0.001$) and increased HF hospitalization rates (pooled *adjusted* risk estimates, 1.81; $P < 0.001$). These associations remained significant after excluding studies that included HF patients at discharge from hospital (pooled *adjusted* risk estimates, 1.31 and 1.89, respectively; $P < 0.001$ for both). High-dose LD (median dose 80 mg) were also associated with increased all-cause mortality (pooled *adjusted* risk estimates, 1.99; $P < 0.001$) compared with low-dose LD. Again, this association remained significant after excluding studies that included HF patients at discharge from hospital (pooled *adjusted* risk estimates, 1.33; $P < 0.001$). Existing evidence indicates that LD, especially in high doses, are associated with increased all-cause mortality and HF hospitalization rates. For this reason, prospective, randomized studies are warranted to clarify whether these associations indicate causality or are merely an epiphenomenon due to disease severity. Systematic review registration: PROSPERO database registration number CRD42020153239. Date of registration: 28 April 2020.

Keywords Prognosis · Furosemide · Hospitalization · Mortality · Loop diuretics

Introduction

Loop diuretics (LD) remain the mainstay of treatment for relieving congestion in patients with heart failure (HF), irrespectively of the underlying ejection fraction [1, 2]. Over 80% of HF outpatients are treated with a per os diuretic, a proportion which is consistent both in selected and unselected HF populations [3–6]. However, the quality of data supporting this "standard of care" strategy is sub-optimal, based on expert opinions and a single meta-analysis of a few, small in numbers and out of date randomized studies [7], the clinical relevance of which has been directly challenged [8]. In any case, the paucity of hard evidence from large, randomized trials regarding the proper use of diuretics in HF patients is unequivocal and striking [9]. This lack of data becomes even more remarkable when considering that the use of LD, especially in high doses, has been associated with adverse clinical outcomes in HF patients in multiple cohort studies [10–12].

To our knowledge, the data concerning LD and clinical outcomes in HF patients has not been systematically reviewed. To this end, we undertook a systematic review and meta-analysis of the use and dose of LD in patients with

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HF. We examined randomized and non-randomized data and examined subpopulations with exclusively reduced left ventricular ejection fraction (HFrEF) vs. mixed HF populations and those at stable outpatient status vs. patients at hospital discharge.

Methods

The present study was conducted according to the PRISMA statement (Table A1-Appendix) [13]. The review protocol has been registered in PROSPERO: International Prospective Register of Systematic Reviews (number: CRD42020153239) [14].

Identification and selection of studies

MEDLINE, EMBASE, clinicaltrials.gov, and Cochrane Clinical Trial Collection were searched on October 15, 2019, with a combinatorial approach (Boolean operator "AND") of three broader search terms. The broader search terms were derived using the Boolean operator "OR" between synonyms for "chronic heart failure," "outcomes," and "diuretics." Detailed descriptions of the terms used for MEDLINE and EMBASE searches are outlined in Appendix Table A2. The search was restricted to the period from January 1, 1990, onwards, out of concern for a high risk of imprecision in the clinical diagnosis of HF and the different pharmacologic background (and therefore high possibility of clinical irrelevance) of studies prior to 1990. Only articles written in English were eligible, while there was no restriction regarding publication status. The reference lists of previous reviews and a recent position paper of the European Society of Cardiology relevant to our topic were hand-screened for studies [9, 15, 16], whereas references of the included articles were screened for additional studies. If needed, authors were contacted to request unpublished original papers or further details not available on the official version.

Study eligibility criteria included (a) comparison of loop diuretics (furosemide, torasemide, bumetanide, azosemide) with placebo/control or/and comparison of high doses of loop diuretics (HDLD) with low doses of loop diuretics (LDLD); (b) adult patients diagnosed with HF; (c) follow-up ≥ 6 months, as the administration of LD for a shorter period was considered unlikely to significantly impact outcomes; and (d) report of the outcomes of interest, i.e., all-cause mortality and/or HF hospitalization. HF definition included patients with HF symptoms irrespectively of left ventricular ejection fraction (LVEF). We excluded studies if they included patients with acute HF or compared one LD with another LD or/and another active comparator. However, HF patients at time of hospital discharge were included. Ethical approval was not required, as no patients were recruited.

The search was independently performed by two reviewers (CJK and MB). Mendeley reference manager was used to remove duplicates. All titles and abstracts were screened individually by all authors, in order to select those that met the inclusion criteria. Differences in assessment of eligibility between reviewers were resolved through discussion and consensus.

Risk of bias

Risk of bias (RoB) within studies was assessed using the Cochrane Risk Of Bias In Non-Randomized Studies–of Interventions (ROBINS-I) tool. The assessment was performed at the study level and regarded components recommended by the Cochrane Collaboration for non-randomized studies, namely confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result [17]. For each component, trials were categorized as low, moderate, serious, critical, or as having no information on risk of bias. Two reviewers (CJK and MB) performed their personal assessment and any disagreements were discussed until consensus was reached.

Risk of bias across studies was evaluated by assessing meta-bias. Meta-bias was evaluated by drawing funnel plots of the included studies for the different study outcomes. A rule of thumb of ten studies per study outcome was used as a cut-off to draw funnel plots.

Data extraction

A systematic approach was used to extract the relevant variables from the selected studies. The variables for which data were sought are shown in detail in Table A3 (Appendix) and regarded study identity and design, patient population, intervention, and outcomes. All authors extracted study characteristics and data input was cross-validated between reviewer databases.

Qualitative and statistical analysis

Data were combined in a systematic review, forest plots, and, if appropriate, in a meta-analysis. We set two studies as the minimum number for quantitative synthesis of data in a meta-analysis for each study parameter. Because heterogeneity between studies was expected, we pooled adjusted risk estimates across studies using random effects models with inverse variance weighting as recommended in the Cochrane handbook to summarize the associations between LD use (and dose) on mortality and hospitalizations [18]. For studies evaluating endpoints at multiple time points, short-term outcomes (6 months to 2 years) were used when possible for the pooling of the results. Heterogeneity was assessed by the Q statistic;

however, due to its limited power to rule out heterogeneity, a P value threshold of 0.10 was used. A quantitative analysis of the impact of heterogeneity using the I^2 statistic was also performed. I^2 values $>50\%$ were considered highly heterogeneous.

Three subgroup analyses to explore heterogeneity had been pre-specified (randomized vs. non-randomized studies, studies only with HFrEF [left ventricular ejection fraction $\leq 45\%$] vs. mixed HF patients and studies examining patients at hospital discharge vs. stable outpatients).

All P values were two-tailed with statistical significance set at 0.05 (if not otherwise specified) and confidence intervals (CI) computed at 95% level. All analyses were performed with the use of Stata 15 Software (StataCorp LLC, TX, USA).

Results

Identified and eligible studies

The number of identified and screened studies is indicated in Fig. 1. Our initial search identified a total 3995 studies from 1990 onwards; after removal of duplicates and screening of titles, abstracts, and full-texts, 24 studies were included in the qualitative synthesis (Table 1).

Characteristics of included studies

No randomized controlled trials of the use of or dose of LD in patients with HF were identified. The studies enrolled 96,959 patients who were followed for 6 up to a mean of 70 months. The number of patients analyzed ranged from 173 up to 26,218.

Risk of bias within studies

All included non-randomized studies were assessed as presenting moderate to serious risk of bias, driven primarily by confounding, missing data and selection of the reported result. On the other hand, selection of participants, classification of interventions, deviations from intended interventions, and measurement of outcomes were not identified as major sources of risk of bias among the selected studies.

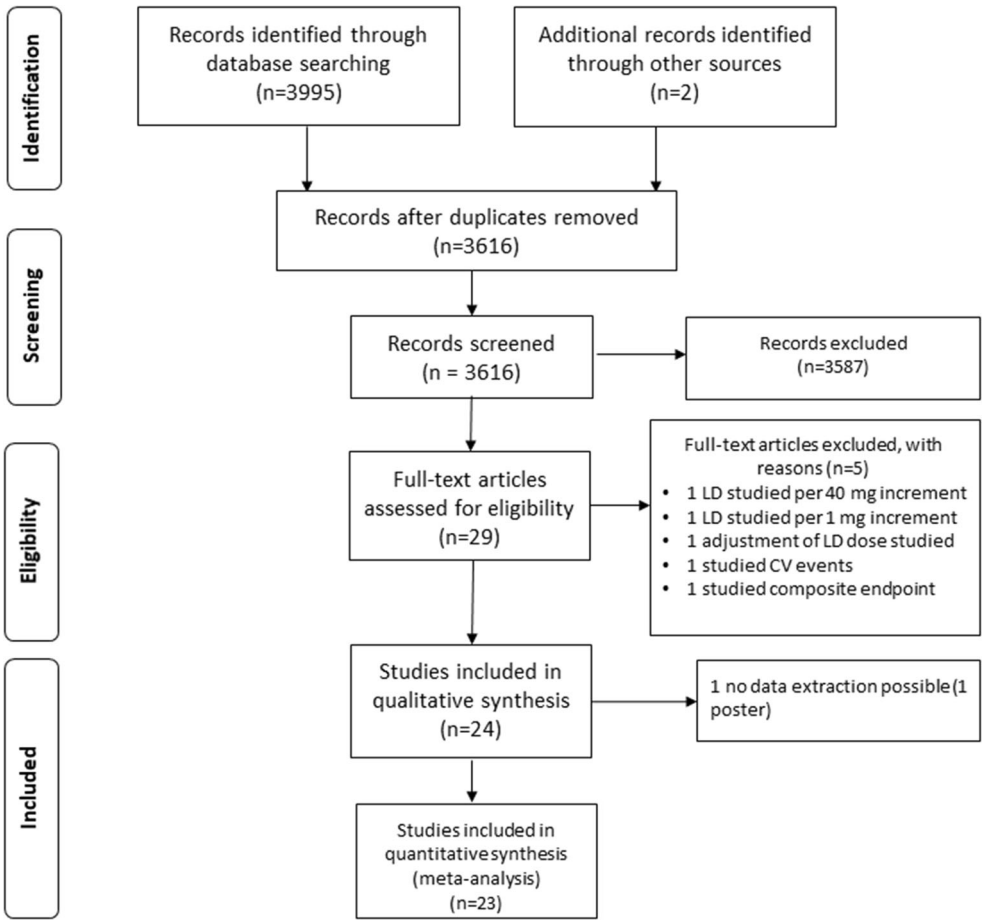

Fig. 1 PRISMA flow chart of study identification and selection

Table 1 Characteristics of included studies

Author (year)	Patients	LVEF (%)	Daily furosemide dose (mg)	Follow-up (months or otherwise specified)	LD vs. no LD	HDLD vs. LDLD	Outcomes
Neuberg (2002) [19]	1153	21	Median 80	Median 14	–	x	TM, SCD, PFD
Domanski (2003) [20]	6797	27	NR	Mean 39	x	–	TM, CVM, HFM and/or HFH
Eshaghian (2006) [11]	1354	24	Median 80	24	–	x	TM, SCD, PFD
Ahmed (2006) [21]	2782	34	NR	Median 40	x	–	TM, HFH
Domanski (2006) [22]	6567	28	NR	Mean 37	x	–	TM, CVM, SCD, HFM, HFH, HFH or HFM
Mielniczuk (2008) [23]	183	38	LD median, 40; HD median, 160	12	–	x	Composite of HFH, HTx, MCS, or death. WRF
Abdel-Qadir (2010) [12]	2999	Missing in > 60%	LD mean, 35; HD mean, 160	12,751 pt-years	–	x	TM
Testani (2011) [24]	2456	23	HD group ≥ 160	Median 24	–	x	TM
Hamaguchi (2012) [25]	2305	42	NR	Mean 26	x	–	TM, CM, HFH, TM or HFH
Dini (2013) [26]	813	31	Median 25	Median 44	–	x	TM
Vidula (2013) [27]	1333	27	LD, 0.017–0.494/kg BW HD, 1.278–16.484/kg BW	Median 9.9	–	X	TM, composite of TM or HFH
Kapelios (2015) [10]	173	27	Mean 107	Mean 70	–	x	TM, HTx, or MCS. WRF, hypokalemia
Damman (2016) [28]	3318	31	LD median, 40; MD median, 80; HD median, 125	Median 33	x	x	CVM or HFH, TM, HFH, change in GFR
Miura (2016) [29]	4134	57	Median 40	Median 36	x	–	Composite of TM, HFH, AMI, or stroke
Pellicori (2016) [30]	979	Median 40–45	LD, 10–40; MD, 41–80; HD, > 80	Median 31	x	x	Composite of TM or HFH
Sargento (2016) [31]	266	28	Mean 57	36	x	x	TM
Galochkin (2017) [32]	265	44% had LVEF < 40%	NR	6	–	x	TM
Costa (2017) [33]	313	43% had LVEF < 45%	LD mean ≤ 40, HD mean > 80	24	–	x	TM
Laszczyska (2017) [34]	560	Median 26	LD, 0–59; MD, 60–119; HD, 120–159; VHD, ≥ 160	Median 23	–	x	TM
Gonzalez-Loyola (2018) [35]	13,334	NR	NR	Mean 27	x	–	TM
Kapelios (2018) [36]	8130	37	Median 40	12	x	x	Composite of TM or HFH, WRF
Okabe (2018) [37]	215	41	LD mean < 40, HD mean ≥ 40	Median 21	–	x	TM, CVM
Paren (2018) [38]	26,218	56% had LVEF<40%	NR	Median 34	x	–	TM
Frohlich (2019) [39]	10,312	34	Median 40	Median 66	x	–	TM

AMI acute myocardial infarction, *CM* cardiac mortality, *CVM* cardiovascular mortality, *GFR* glomerular filtration rate, *HD* high dose, *HFH* heart failure hospitalization, *HFM* heart failure mortality, *HTx* heart transplantation, *LD* low dose, *LVEF* left ventricular ejection fraction, *MCS* mechanical circulatory support, *MD* medium dose, *NR* not reported, *PFD* pump failure death, *SCD* sudden cardiac death, *TM* total mortality, *VHD* very high dose, *WRF* worsening renal function

Risk of bias across studies

Funnel plots were drawn for assessment of meta-bias in regard to all-cause mortality among studies examining LD vs. no LD (Fig. 2a) and high-dose LD vs. low-dose LD (Fig. 2b). Importantly, assessing meta-bias through funnel plots for HF hospitalizations was not feasible as the rule of thumb of ten studies was not fulfilled for this outcome. Funnel plots for both groups of studies (yes vs. no and high- vs. low dose) look asymmetrical as there appear to be more studies missing on the left-hand side. The source of risk of bias across studies can only be speculated and could be attributed to publication bias, substantial heterogeneity, or even chance.

Results of individual studies and synthesis of results

All-cause mortality

All-cause mortality was frequently investigated and reported among studies. Ten studies reported adjusted HRs for the association between all-cause mortality and use of LD (vs. no use), whereas ten was also the number of studies that provided adjusted HRs for the association between all-cause mortality and high doses (vs. low doses) of LD.

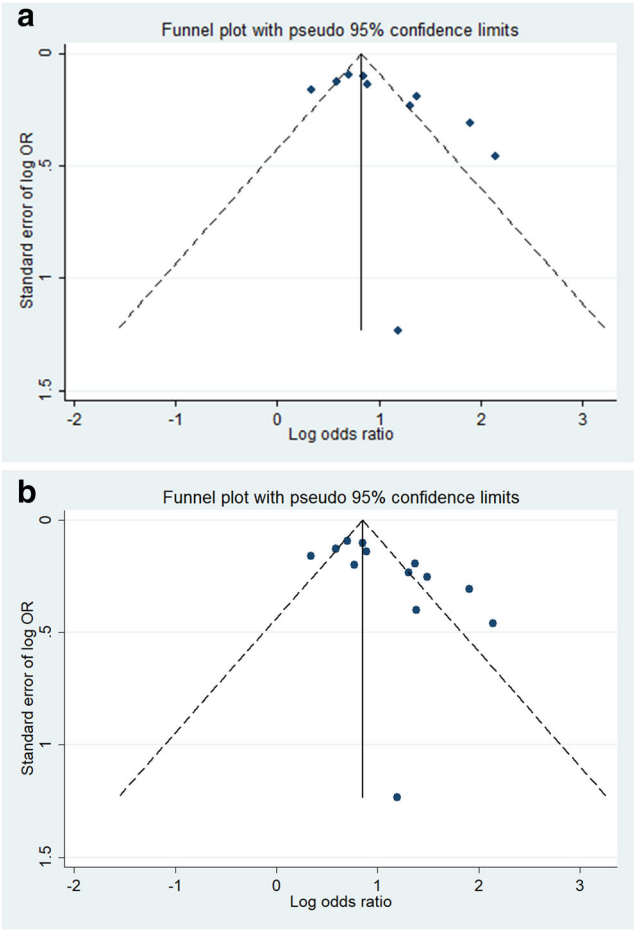

Fig. 2 Funnel plots of studies assessing association of all-cause mortality with **a** use vs. no use of LD and **b** high vs. low doses of LD

LD use (vs. no use) was associated with increased all-cause mortality (pooled *adjusted* risk estimates, 1.18; 95% CI 1.16–1.20, $P = 0.001$ [Fig. 3a]), as were high doses of LD (pooled *adjusted* risk estimates, 1.99; 95% CI 1.86–2.13, $P < 0.001$) compared with low doses of LD (Fig. 3b).

In additional subgroup analyses for all-cause mortality, LD use (vs. no use) was associated with increased all-cause mortality both among studies which included only patients with HFrEF ($N = 4$) (pooled *adjusted* risk estimates, 1.33; 95% CI 1.22–1.45, $P < 0.001$ [Fig. 4a) and among studies which included mixed HF patients ($N = 6$) (pooled *adjusted* risk estimates, 1.17; 95% CI 1.15–1.19, $P < 0.001$ [Fig. 4b]). Similarly, high doses of LD (vs. low doses) were associated with increased all-cause mortality in both studies with exclusively HFrEF patients ($N = 6$) (pooled *adjusted* risk estimates, 1.30; 95% CI 1.16–1.45, $P < 0.001$ [Fig. 4c]) and among studies which included mixed HF patients ($N = 4$) (pooled *adjusted* risk estimates, 2.52; 95% CI 2.32–2.74, $P < 0.001$ [Fig. 4d]).

In the second subgroup analysis, LD use was associated with increased all-cause mortality among studies which included only patients at hospital discharge ($N = 2$) (pooled *adjusted* risk estimates, 1.16; 95% CI 1.14–1.18, $P < 0.001$ [Fig. 5a]) and among studies which exclusively included HF outpatients ($N = 8$) (pooled *adjusted* risk estimates, 1.31; 95% CI 1.25–1.38, $P < 0.001$ [Fig. 5b]). Similarly, high doses of LD were significantly associated with increased all-cause mortality in both studies with patients at discharge ($N = 4$) (pooled *adjusted* risk estimates, 2.88; 95% CI 2.63–3.16, $P < 0.001$ [Fig. 5c]) and among studies which included only HF outpatients ($N = 6$) (pooled *adjusted* risk estimates, 1.33; 95% CI 1.21–1.46, $P < 0.001$ [Fig. 5d]).

The third pre-specified subgroup analysis (randomized vs. non-randomized studies) could not be performed as no randomized studies were identified.

Heart failure hospitalizations

HF hospitalizations were assessed and reported in less than 50% of the included studies. Five studies reported adjusted HRs for association between HF hospitalizations and use of LD (vs. no use), whereas three studies provided adjusted HRs for association between HF hospitalizations and high doses (vs. low doses) of LD.

LD use was associated with increased risk for HF hospitalizations (pooled *adjusted* risk estimates, 1.81; 95% CI 1.60–2.05, $P < 0.001$ [Fig. 6a]). High doses of LD were also associated with increased risk for HF hospitalizations (pooled *adjusted* risk estimates, 1.58; 95% CI 1.44–1.73, $P < 0.001$]) compared with low doses of LD (Fig. 6b).

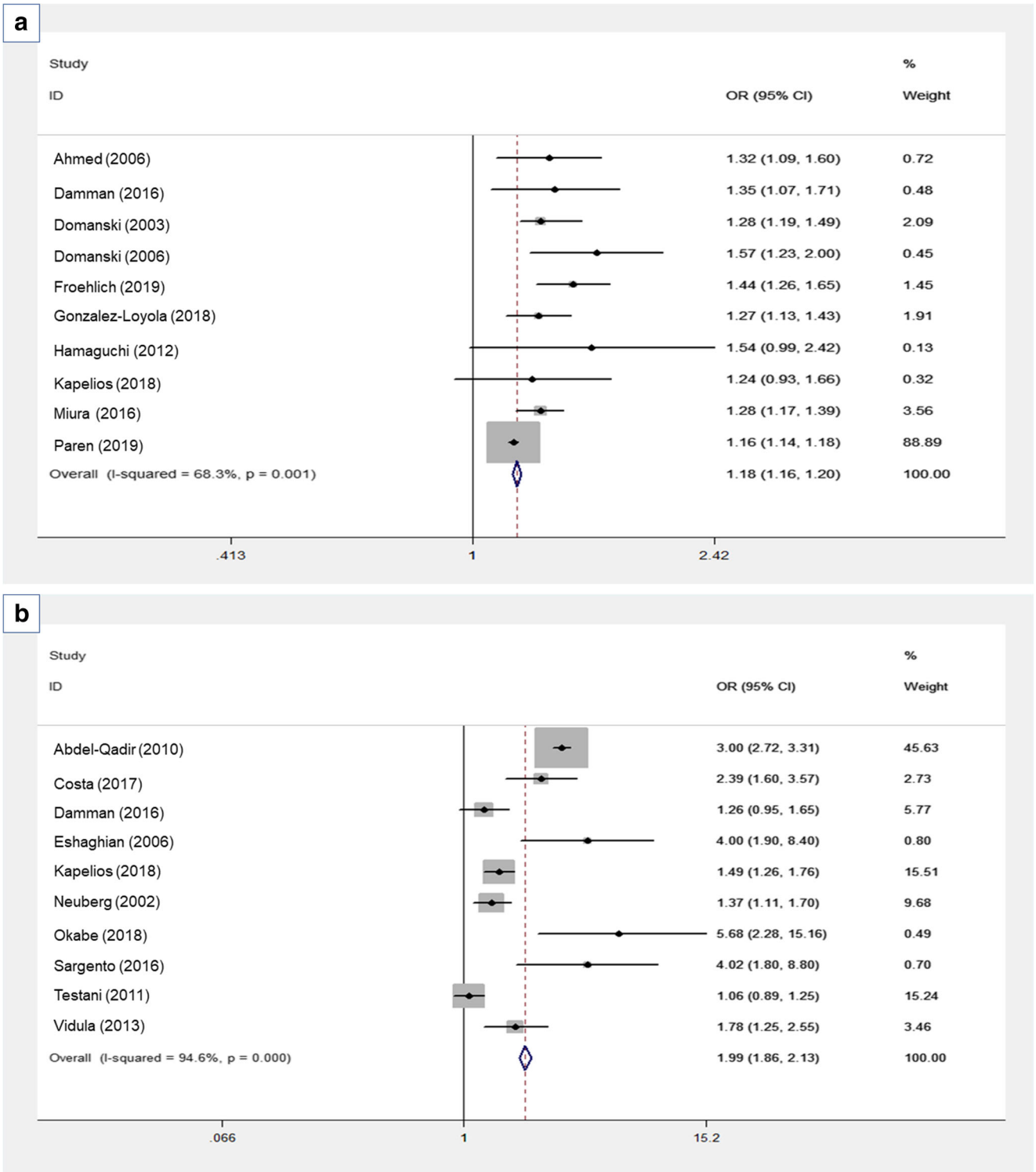

Fig. 3 Pooled adjusted risk estimates of all-cause mortality for patients **a** receiving vs. not receiving LD and **b** receiving high vs. low doses of LD

In additional subgroup analyses for HF hospitalizations, LD use (vs. no use) was associated with increased HF hospitalizations among studies which included only HFrEF patients ($N = 4$) (pooled *adjusted* risk estimates, 1.89; 95% CI 1.65–2.16, $P < 0.001$ [Fig. 7a]). Similarly, high doses of LD (vs. low doses) were associated with increased risk for HF hospitalizations in studies with exclusively HF outpatients ($N = 2$) (pooled *adjusted* risk estimates, 1.59; 95% CI 1.44–1.74, $P < 0.001$ [Fig. 7b]). Pooling of HRs for studies with patients including mixed LVEFs was not feasible for either outcome ($N = 1$ for each).

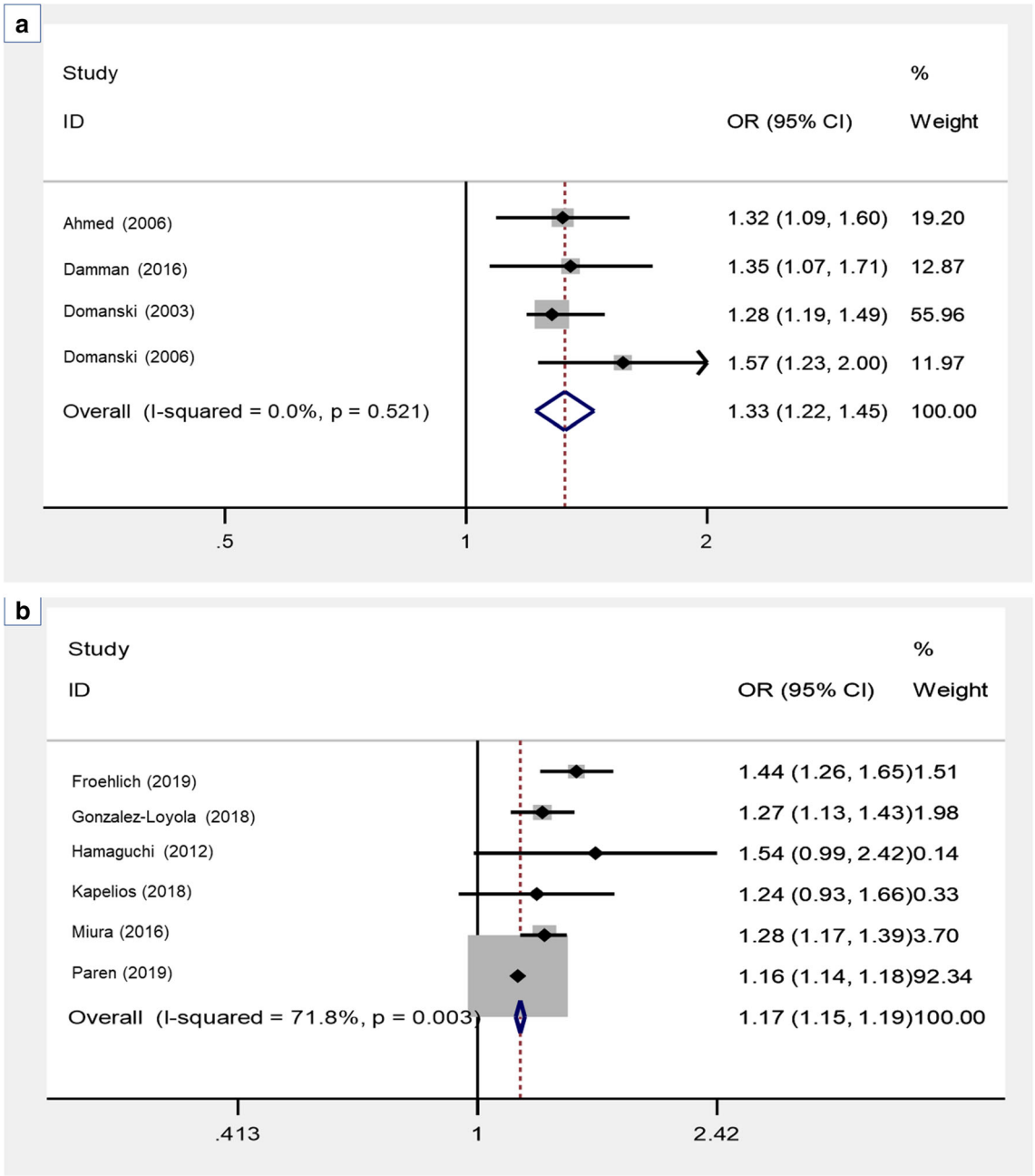

Fig. 4 Pooled adjusted risk estimates of all-cause mortality for patients receiving vs. not receiving LD among studies including patients with **a** HFrEF only and **b** mixed left ventricular ejection fractions. Pooled adjusted risk estimates of all-cause mortality for patients receiving high vs. low doses of LD among studies including patients with **c** HFrEF only and **d** mixed left ventricular ejection fractions

In the second subgroup analysis, LD use was associated with increased HF hospitalizations among studies which included only HF outpatients ($N = 4$) (pooled *adjusted* risk estimates, 1.89; 95% CI 1.65–2.16, $P < 0.001$ [Fig. 7c]), whereas pooling of HRs for studies with patients at hospital discharge was not feasible ($N = 1$). Similarly, high doses of LD were significantly associated with increased risk for HF hospitalizations in studies with outpatients ($N = 2$) (pooled *adjusted* risk estimates, 1.74; 95% CI 1.53–1.97, $P < 0.001$ [Fig. 7d]), whereas pooling of HRs for studies with patients at hospital discharge was again not feasible ($N = 1$).

The third pre-specified subgroup analysis (randomized vs. non-randomized studies) could not be performed as no randomized studies were identified.

Discussion

The main findings of this meta-analysis on the associations between LD use and dose with hard clinical outcomes in patients with HF are (a) no contemporary,

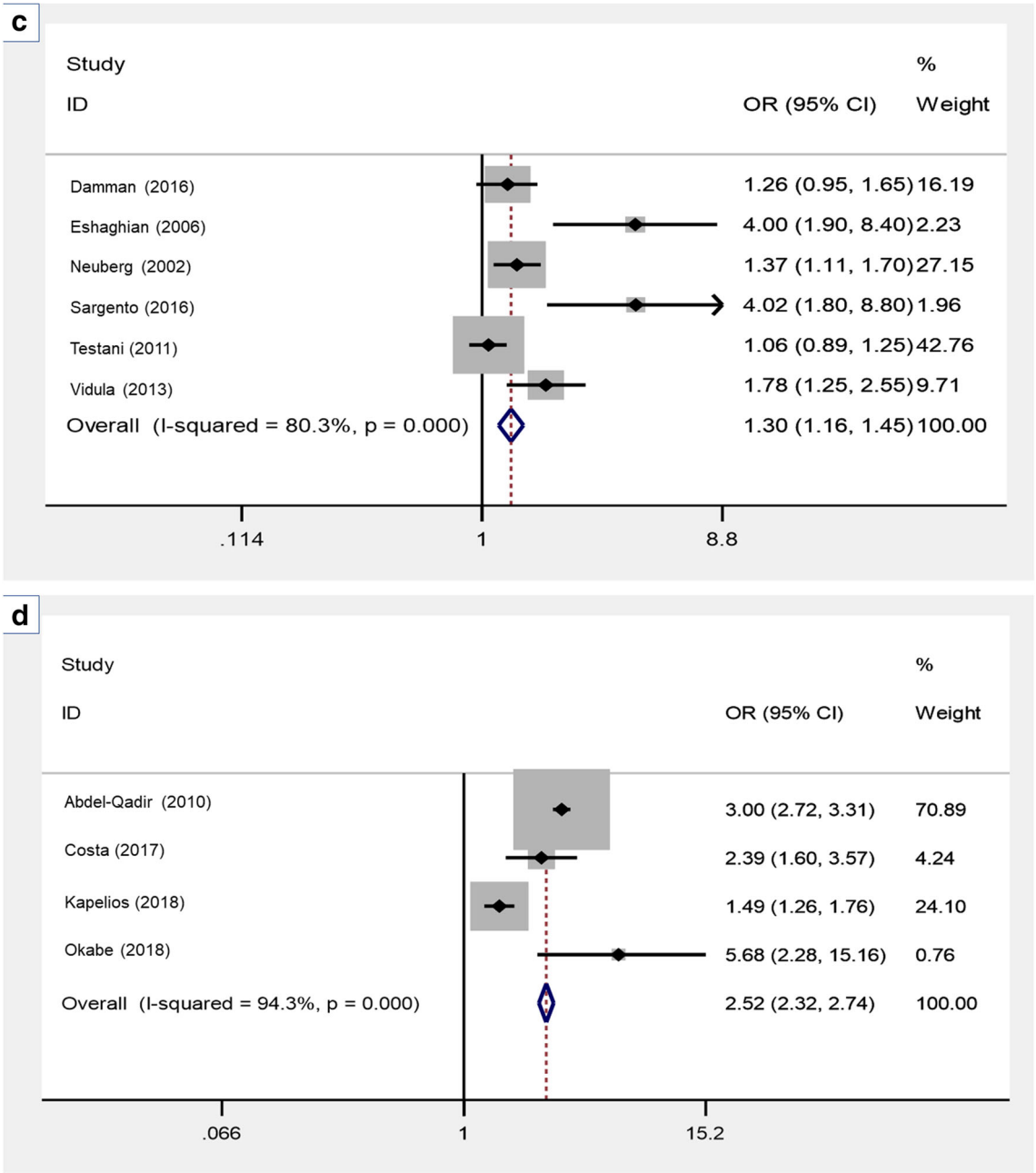

Fig. 4 (continued)

clinically relevant randomized studies exist; (b) LD use (vs. non-use) and high dose LD (vs. low dose) are significantly associated with increased risk for all-cause mortality and HF hospitalization; (c) these associations are strong and significant both among studies including exclusively patients with HFrEF and studies with mixed HF populations; and (d) these associations are strong and significant in both studies including HF outpatients and HF patients at hospital discharge.

Although our study adheres to PRISMA reporting, it included studies with significant diversity and patient populations with a wide range of HF severity. Notably, all 24 studies were observational; the few randomized controlled trials on the topic have been either LD dose decrease or withdrawal studies and were thus excluded from the analysis [39–41]. Nonetheless, our systematic review provides the best, to date, available evidence to suggest that receipt of LD (vs. non-use) and receipt of high-dose LD (vs. low-dose) is significantly associated with increased risk of death and HF hospitalization in patients with chronic HF, irrespectively of ejection fraction and timing of dose investigation (hospital discharge or "stable" outpatient state).

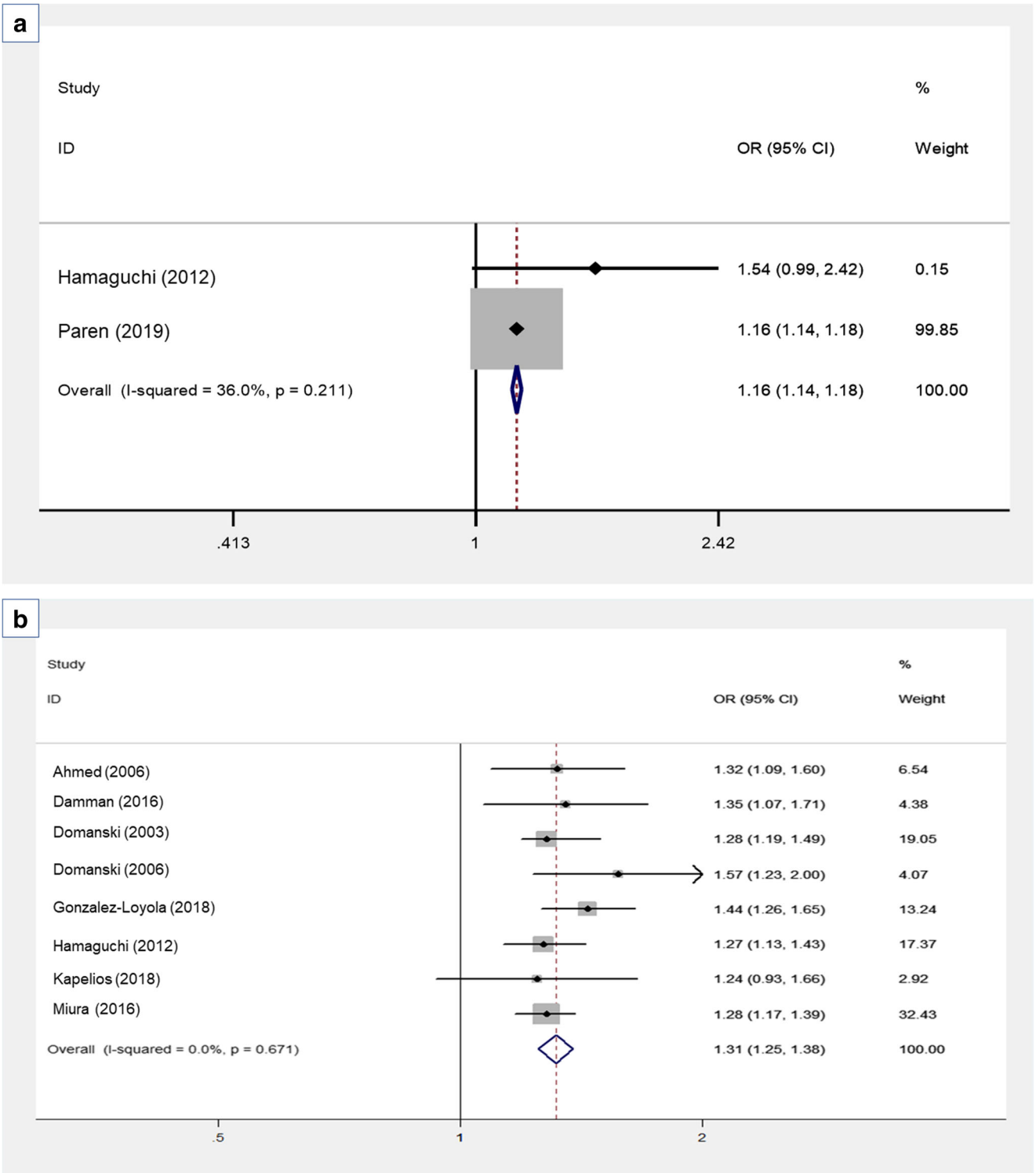

Fig. 5 Pooled adjusted risk estimates of all-cause mortality for patients receiving vs. not receiving LD among studies including **a** patients at hospital discharge and **b** only outpatients. Pooled adjusted risk estimates of all-cause mortality for patients receiving high vs. low doses of LD among studies including **c** patients at hospital discharge and **d** only outpatients

Our study provides evidence to support that LD use, especially in higher doses, is associated with worse clinical outcomes. This of course may be simply a risk marker of greater HF severity among patients who were receiving higher LD doses, but uniquely, our meta-analysis utilized hazard ratios after adjustment for variables that may have affected both LD doses and outcomes. Even after adjustment for these potential

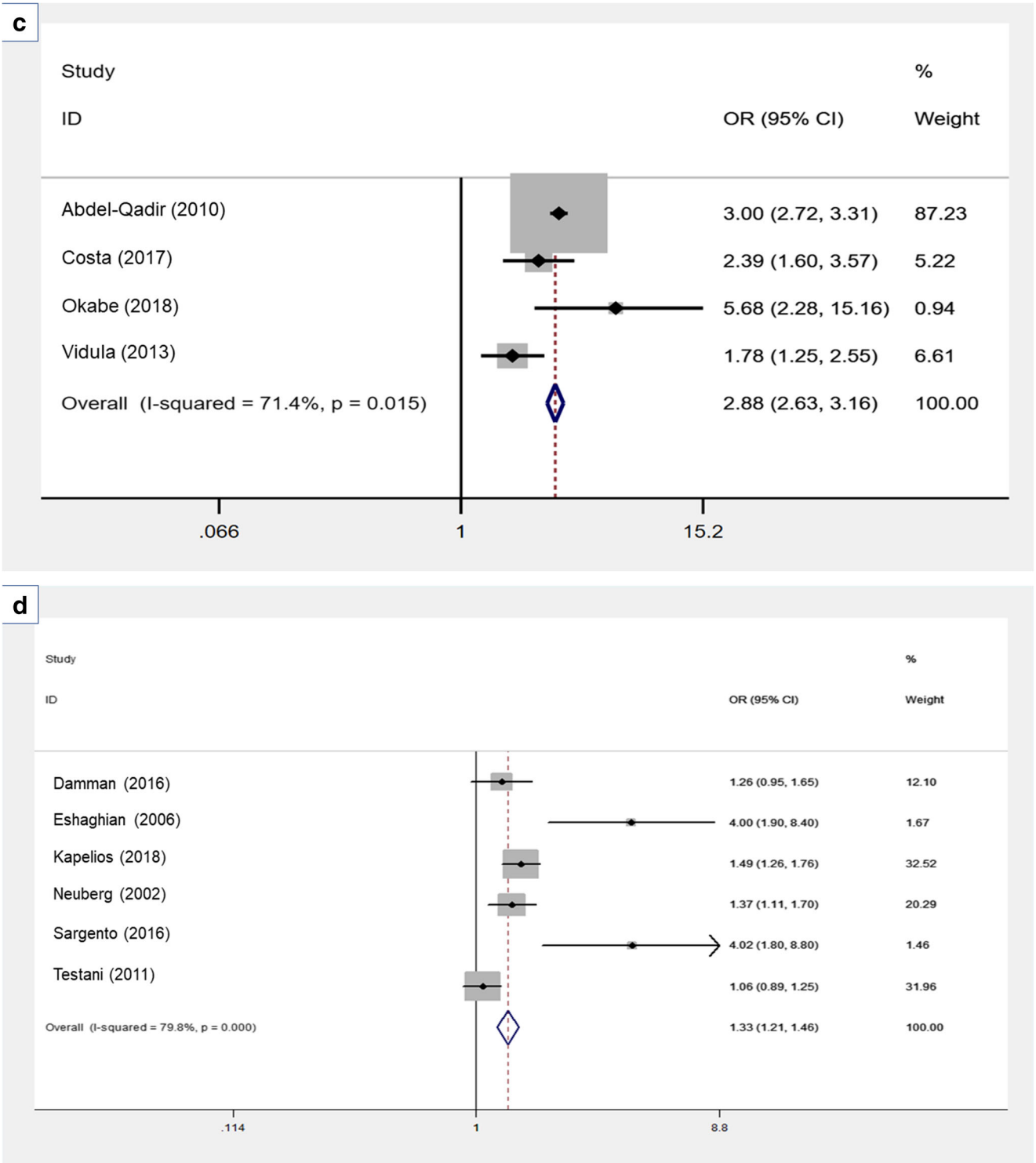

Fig. 5 (continued)

confounders, the risk associated with LD use remained approximately 20% higher for all-cause death and approximately 80% increased for HF hospitalizations. On the other hand, high LD dose also presented with a twofold higher risk for all-cause mortality. This magnitude of risk excess after extensive adjustment suggests that it is likely, although not proven, that LD use, especially in higher doses, might not only represent markers of HF severity but also true risk factors for worse outcomes. In their study, Mielniczuk et al. [23]

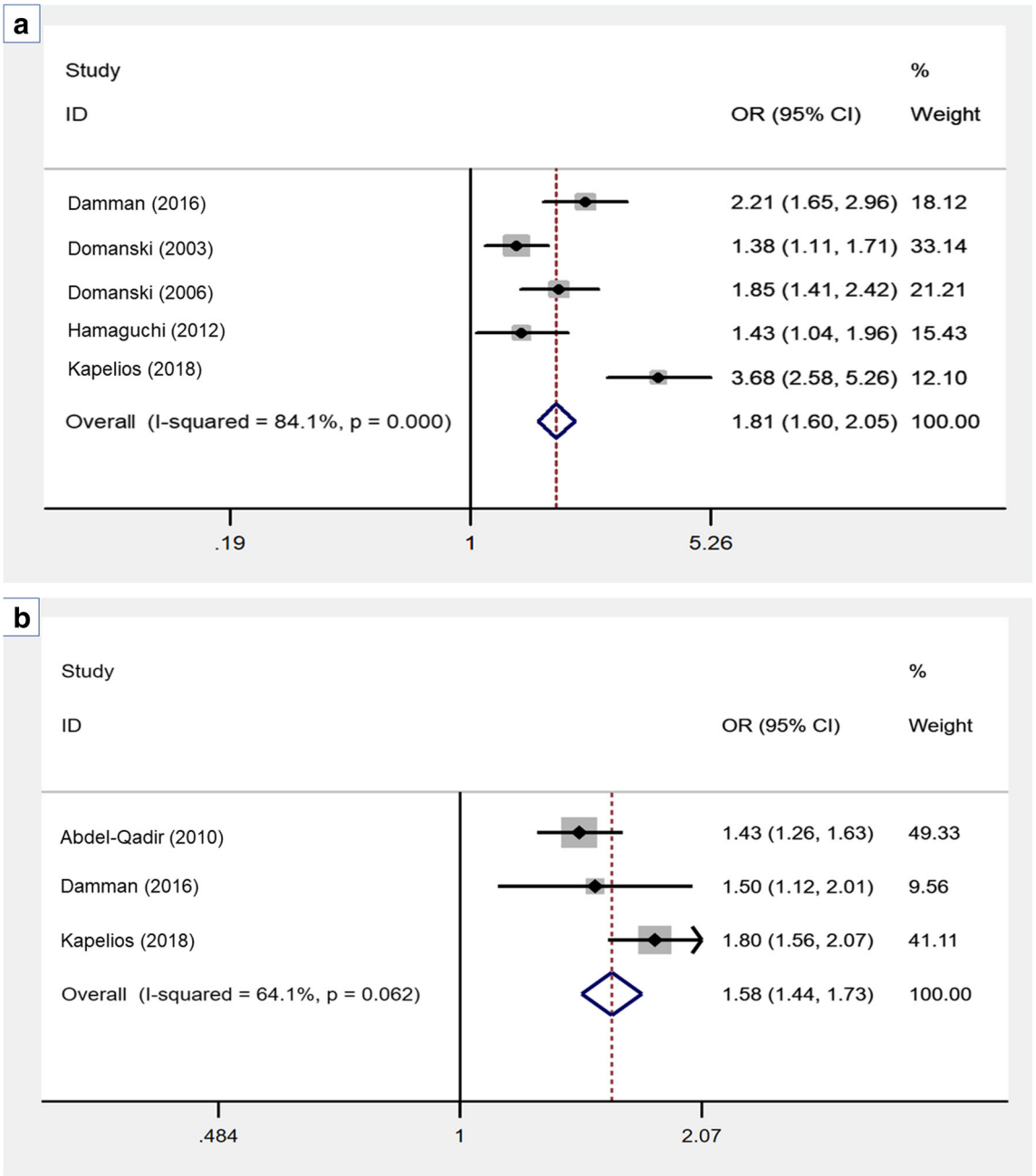

Fig. 6 Pooled adjusted risk estimates of HF hospitalization for patients **a** receiving vs. not receiving LD and **b** receiving high vs. low doses of LD

observed that the association between LD and adverse outcomes was rendered insignificant after adjustment for clinical stability, implying that higher doses of LD were a proxy for clinical instability and were not responsible on their own for the excessive mortality; however, in another analysis from the European Long-Term HF registry among > 8000 HF outpatients, it was demonstrated that associations between LD dose and outcomes were independent of clinical stability and other factors of disease severity [36]. Several mechanisms have been proposed as putative explanations for the unfavorable associations between LD and the clinical outcomes of HF patients. LD cause depletion of the effective blood volume and through this stimulate the sympathetic nervous and renin-angiotensin-aldosterone systems, contributing to further HF progression and dismal outcomes [42, 43]. The association of high-dose LD with increased mortality in patients with elevated but not normal blood urea nitrogen further suggests that neurohormonal activation may mediate these dismal effects [24]. Others have implicated electrolyte depletion and induction of fatal arrhythmias as a main contributor to the

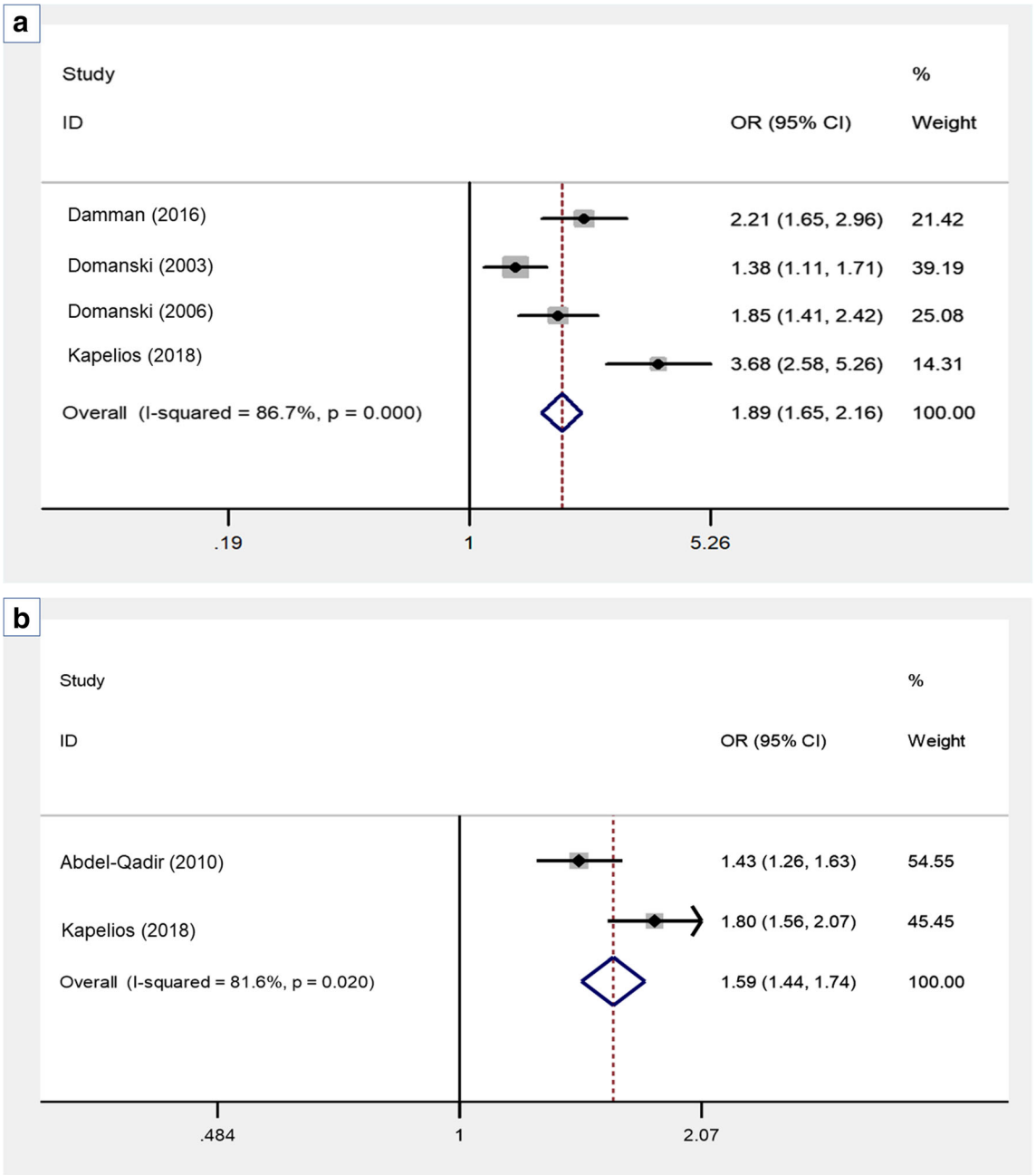

Fig. 7 Pooled adjusted risk estimates of HF hospitalization for **a** patients receiving vs. not receiving LD and **b** receiving high vs. low doses of LD among studies including patients with HFrEF only. Pooled adjusted risk estimates of HF hospitalization for **c** outpatients receiving vs. not receiving LD and **d** outpatients receiving high vs. low doses of LD

negative effects of LD [44]. Moreover, high doses of LD have been associated with an increased incidence of renal dysfunction in HF patients [45], a well-established predictor of morbidity and mortality in patients hospitalized for HF decompensation [45]. Furthermore, inappropriately high doses of LD might hamper up-titration of guideline-directed medical therapy and may result through this mechanism in suboptimal outcomes [46].

Limitations

Our study has several important limitations. First, heterogeneity in the criteria employed to diagnose HF and HFrEF and in the design of studies represent major limitations, as they may have resulted in heterogeneous patient populations. Furthermore, study outcomes were not consistently reported in all included studies. All these limitations may in part be responsible for significant heterogeneity observed among the

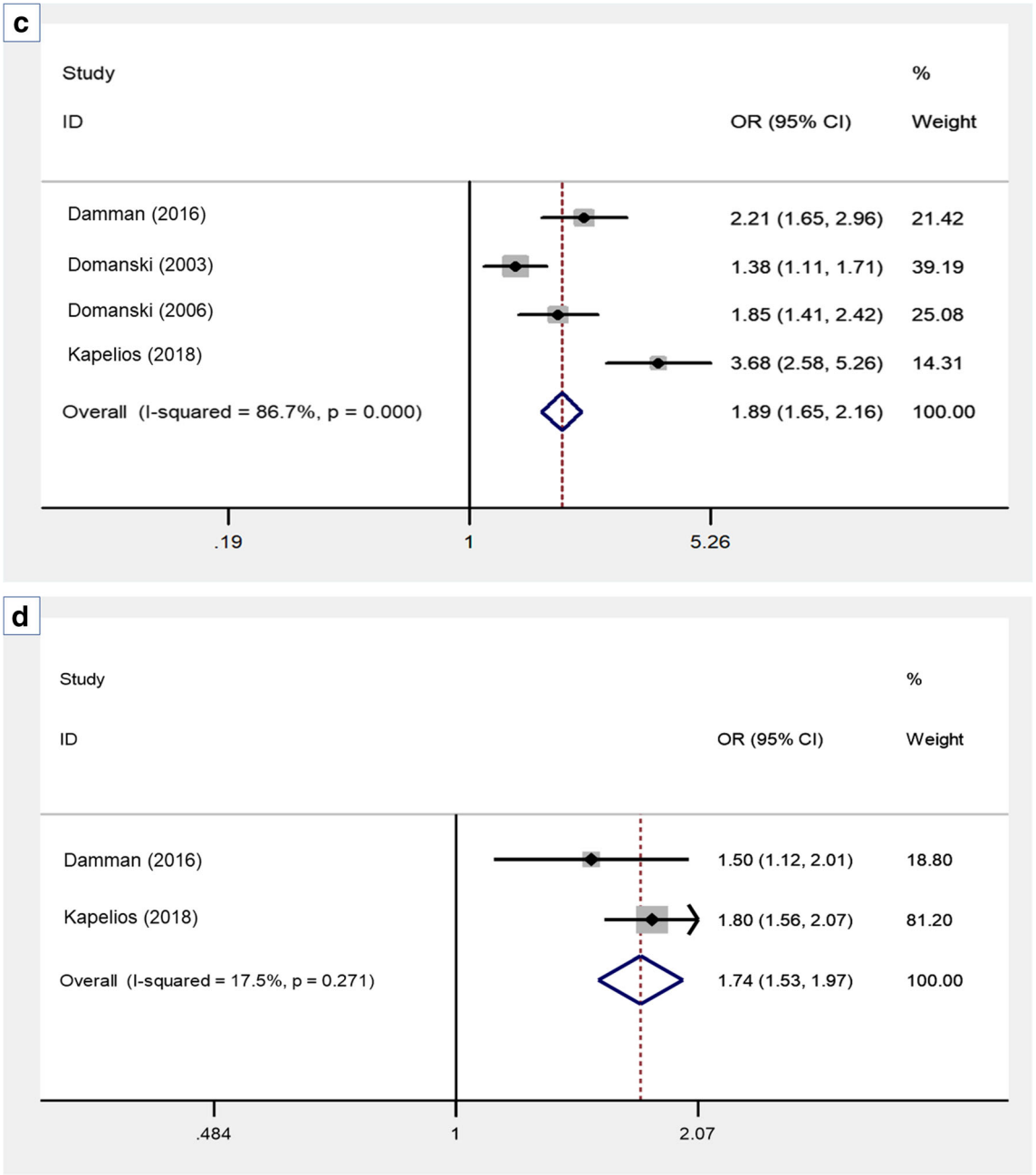

Fig. 7 (continued)

pooled analyses for some outcomes. Moreover, this meta-analysis was not performed on a patient level but collected aggregate data from studies of different cohorts. This fact precluded performance of subgroup analysis in a specific subpopulation.

Despite these caveats, this meta-analysis may have significant therapeutic implications. In view of the aggregate dismal associations demonstrated, LD should be used at the lowest possible dose and should be adjusted to individual needs. The feasibility, clinical parameters which can guide, and potential beneficial effects of such a strategy have been recently recognized [46, 47].

Conclusions

Existing evidence indicates that LD, especially in high doses, are associated with increased all-cause mortality in patients with HF. The use of LD is also associated with higher rates of HF hospitalizations. Although this study represents the

most comprehensive, to date, review of associations of LD use and dose with hard clinical outcomes in patients with HF, large prospective studies are warranted to provide definitive answers.

Data availability Not provided.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Consent to participate Not applicable.

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