REVIEW

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Brain-Type Natriuretic Peptide and Amino-Terminal Pro–Brain-Type Natriuretic Peptide Discharge Thresholds for Acute Decompensated Heart Failure

A Systematic Review

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Background: Acute decompensated heart failure (ADHF) requiring hospitalization is associated with high postdischarge mortality and readmission rates.

Purpose: To examine the association between achieving predischarge natriuretic peptide (NP) thresholds and mortality and readmission rates in adults hospitalized for ADHF.

Data Sources: Multiple databases from 1947 to October 2016 (English-language studies only).

Study Selection: Trials and observational studies that compared mortality and readmission outcomes between patients with ADHF achieving a specific predischarge NP goal and those not achieving the goal.

Data Extraction: Two investigators independently extracted study characteristics and assessed study risk of bias. One author graded the overall strength of evidence, with review by a second author.

Data Synthesis: One randomized trial, 3 quasi-experimental studies, and 40 observational studies were identified. The most commonly used thresholds were a brain-type NP (BNP) level of 250 pg/mL or less or an amino-terminal pro–brain-type NP (NT-proBNP) decrease of at least 30%. Achievement of absolute BNP thresholds reduced postdischarge all-cause mortality (7 of 8 studies) and the composite outcome of mortality and readmission (12 of 14 studies). Achievement of percentage-change BNP thresholds reduced the composite outcome (5 of 6 studies), and achievement of percentage-change NT-proBNP thresholds reduced all-cause and cardiovascular mortality (2 of 4 studies) and the composite outcome (9 of 9 studies). All findings were low-strength. The randomized trial, assessed as having high risk of bias, suggested that a predischarge decrease in NT-proBNP level was associated with lower risk for the composite outcome. Two quasi-experimental studies and 5 observational studies had low risk of bias. Low-risk-of-bias studies had outcome estimates similar in magnitude and direction to estimates from high-risk-of-bias studies.

Limitation: Most studies failed to adjust for critical confounders and had inadequate definition or assessment of exposures and outcomes.

Conclusion: Low-strength evidence suggests an association between achieving NP predischarge thresholds and reduced ADHF mortality and readmission.

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For author affiliations, see end of text.
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Nearly 1 million patients are hospitalized each year with acute decompensated heart failure (ADHF), costing the U.S. health care system more than $16 billion annually (1, 2). Guidelines recommend inpatient treatment with intravenous diuretics guided by frequent clinical reassessment and measurements of net urine output and body weight (3). However, more than 50% of patients hospitalized for ADHF are readmitted within 6 months with similar symptoms (4).

Many factors contribute to the high rate of heart failure readmission, including the potential for incomplete diuresis during hospitalization (3–5). Physical examination findings, such as jugular venous pressure, have intrinsically high interobserver variability (6). Even seemingly objective data, such as net urine output and daily weight measurements, are prone to inaccuracy and inconsistency (3, 5). Physicians using only these methods to make decisions about patient discharge are thus at risk for stopping inpatient treatment early, inadvertently contributing to the increased rates of decompensation, readmission, and mortality.

Natriuretic peptide (NP) testing has the potential to add valuable data to a physician's assessment of patient readiness for discharge. Guiding outpatient treatment using brain-type NP (BNP) and amino-terminal pro–brain-type NP (NT-proBNP) levels has demonstrated effectiveness in meta-analyses (7, 8). However, no corresponding meta-analysis has been done with regard to inpatient ADHF treatment. We performed a systematic review to examine the effect of using NP thresholds as a discharge criterion on readmission and mortality rates in patients hospitalized for ADHF.

See also:

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Web-Only
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METHODS

We developed a protocol a priori for this systematic review (**Supplement**, available at Annals.org).

Data Sources and Searches

We first developed an "evidence inventory" (9, 10) of methods commonly studied for making discharge decisions in patients presenting to the hospital with ADHF. Our search strategy included English-language studies published from 1947 to 9 October 2016 that examined the association between a goal-driven method for assessing the success of decongestion in ADHF and patient-centered outcomes. Studies were identified in MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. We also screened the reference lists of included articles and articles that cited the included studies. Database search strategies were developed with librarians and combined structured language and keywords representing 5 search domains: heart failure, acuteness, use of diuretics, various approaches for assessing the effectiveness of diuretic therapy, and study type (for example, randomized, controlled trials; nonrandomized, controlled trials; cohort studies; and case–control studies). Database searches excluded abstract-only publications. An example search strategy is provided in **Appendix Table 1** (available at Annals.org). Because most studies used NP levels to guide discharge decisions, we focused this review on those articles. **Figure 1** shows the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram.

Study Selection

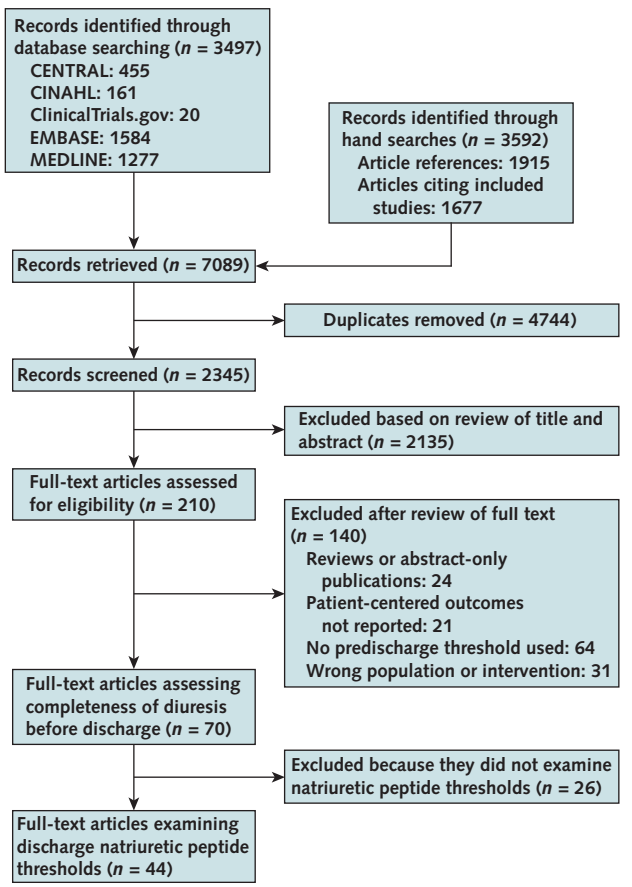
Studies were included if they reported data on patients aged 18 years or older who were hospitalized for ADHF and treated with diuretics in the acute setting. We included the following study types, regardless of follow-up duration and sample size, as available: randomized, controlled trials; nonrandomized, controlled trials; cohort studies; case–control studies; and quasi-experimental studies. Acute exacerbations of chronic heart failure and new heart failure presenting as acute decompensation were included, regardless of the inpatient care setting (for example, general medicine ward, heart failure service, or intensive care unit). To be included, studies had to compare patients achieving a specific predischarge goal versus those not achieving the goal. Studies exclusively examining ADHF secondary to acute coronary syndrome or treatment with ultrafiltration rather than diuretics were excluded. The following outcomes were required to be reported: all-cause or cardiovascular mortality after hospital discharge, readmissions after hospital discharge, or a composite of these measures.

One reviewer (C.N.M.) screened titles and abstracts for inclusion in the full-text review, and 2 reviewers (C.N.M. and M.M.) independently examined all full texts for inclusion. Disagreements were resolved by consensus or by a third reviewer (C.A.U.) as necessary.

Data Extraction and Quality Assessment

Study characteristics, including the NP thresholds used, outcomes data, and analytic methods, were extracted independently by 2 reviewers (C.N.M. and M.M.) using a standardized data abstraction sheet. Disagreements were resolved by consensus or by a third reviewer if necessary.

Figure 1. Flow diagram for identification of studies that assessed completeness of diuresis for patients hospitalized for acute decompensated heart failure.



CENTRAL = Cochrane Central Register of Controlled Trials.

Two investigators independently used the Cochrane risk-of-bias tool to assess the quality of randomized trials (11) and the Newcastle-Ottawa Scale to assess the quality of cohort and case–control studies (12). Disagreements were resolved by consensus or by a third reviewer if necessary. The Newcastle-Ottawa Scale assesses study quality in 3 domains: selection (4 stars possible), comparability (2 stars possible), and outcome/exposure (3 stars possible). The **Appendix** (available at Annals.org) provides a detailed explanation of these domains. When assessing comparability, we required adjustment for left ventricular ejection fraction (LVEF) (1 star possible) and at least 1 measure of disease severity on admission (NP level or New York Heart Association [NYHA] class; 1 additional star possible) because of the effect these variables have on the attainability of low NP thresholds before discharge (13). Studies receiving all 9 stars were defined as having low risk of bias, and all others were at high risk of bias. We assessed risk of bias separately for each outcome in

studies reporting more than 1 relevant clinical outcome.

Data Synthesis and Analysis

Because of significant clinical heterogeneity between studies, a meta-analysis was not performed. Sensitivity analyses examining study-level estimates were performed based on the following factors if at least 2 studies were available for each exposure–outcome pair: risk of bias, duration of follow-up, study design (retrospective vs. prospective), care setting (critical care admission vs. ward admission), LVEF of the study population (reduced vs. preserved), studies prospectively using NP levels to make discharge decisions, studies in which admission NP levels were reported and statistically equivalent for both groups, and adjustment for critical confounders (14, 15) of NP levels (age, sex, admission NP level, admission NYHA class, chronic kidney disease, body mass index [BMI], LVEF, and medication use). Forest plots without meta-estimates were constructed with Review Manager 5.3.5 (The Cochrane Collaboration). We defined statistical significance as a *P* value less than 0.05. Data are reported as means and SDs unless otherwise noted. One investigator assessed the overall strength of evidence for each comparison and outcome using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (16), with a second investigator reviewing all evidence grades. Disagreements were resolved by consensus or by a third reviewer if necessary.

Role of the Funding Source

This study received no external funding.

RESULTS

Our evidence inventory included 70 full-text articles addressing 10 distinct methods for evaluating readiness for discharge for patients admitted for ADHF. Appendix Figure 1 (available at Annals.org) shows an evidence map of the identified articles. Forty-four full-text articles examining NP discharge thresholds were identified for inclusion in this review: 1 randomized, controlled trial (17); 3 quasi-experimental studies (18–20); 38 cohort studies (21–58); and 2 case–con-trol studies (59, 60). Thirty-one studies used BNP thresholds, with 27 examining an absolute threshold and 9 examining a threshold based on percentage reduction. Thirteen studies used NT-proBNP thresholds, with 9 examining an absolute threshold and 9 examining a threshold based on percentage reduction. Sixteen studies examined mortality, 5 examined readmissions, and 33 examined a composite of these outcomes. One study reported outcomes at 30 days, 20 studies reported outcomes at 6 months, 7 studies reported outcomes at 1 year, and 9 studies reported outcomes at longer intervals up to 4 years.

Selected characteristics and risk-of-bias assessments of the included studies are shown in Appendix Table 2 (available at Annals.org). Hazard ratios (HRs) for the association between achievement of BNP or NT-proBNP discharge thresholds and mortality, readmission rates, and the composite outcome are presented in Figures 2 and 3, respectively. Studies most often examined men (weighted mean, 53%), European patients (70% of studies), patients admitted to a general medicine unit (75% of studies), and older patients (66% with a mean or median patient age ≥70 years). Most were published in the past 10 years (77%). Few studies (16%) examined patients cared for by heart failure specialists, and 84% of studies included both patients with preserved LVEF and those with reduced LVEF. The methods used for ascertaining our clinical outcomes of interest were the same within each study examined, leading to a single risk-of-bias rating for each study. The mean reported 6-month all-cause mortality and readmission rates, weighted by study size, were 15.3% and 30.3%, respectively. The mean 1-year all-cause mortality and readmission rates were 32.1% and 64.0%, respectively.

Seven studies had low risk of bias. Similar to the general body of evidence, these studies were more likely to examine men (weighted mean, 56%) and European patients (85%), and 85% included both patients with preserved LVEF and those with reduced LVEF. However, studies with low risk of bias were less likely to examine patients admitted to general medicine units (43%) and more likely to have a mean or median patient age older than 70 years (85%). The randomized trial (17) and the quasi-experimental studies (18–20) were also similar to the general body of evidence. Two had low risk of bias (18, 19).

Overall, 14 of 16 studies reported a statistically significant reduction in the risk for death, 3 of 5 reported a statistically significant reduction in readmissions, and 31 of 33 reported a statistically significant reduction in the composite outcome.

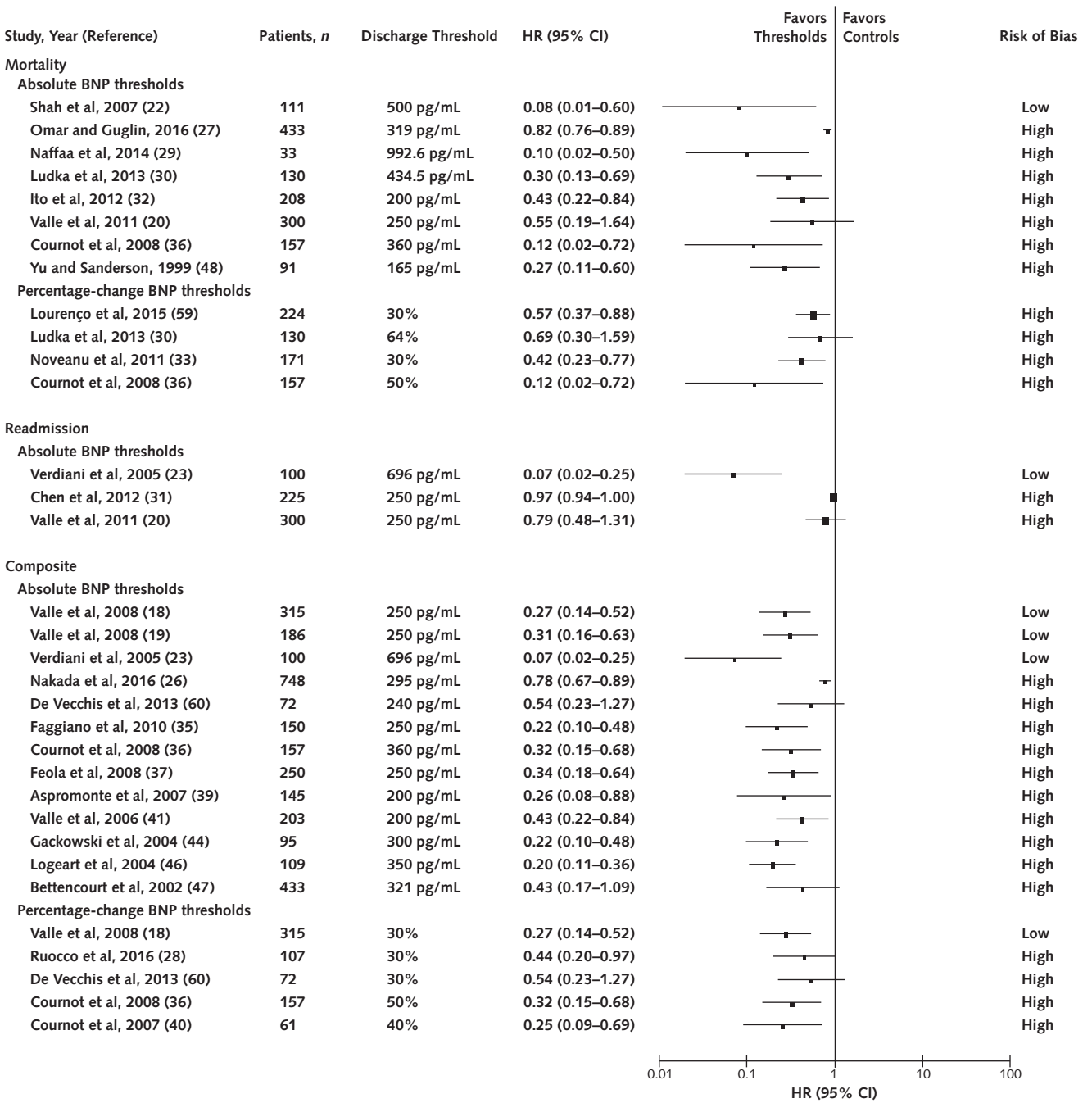
Most studies were deemed to have high risk of bias for failing to meet criteria in the domains of comparability and definition of the outcome or exposure. Studies with high risk of bias frequently did not adjust for the small set of critical confounders specified as necessary in our comparability rating (LVEF and admission NP level or NYHA class). Other important confounders, such as age, sex, BMI, chronic kidney disease, and medications, were inconsistently considered. Studies with high risk of bias relied on self-reported outcomes (20 of 36 studies) and had important loss to follow-up (7 of 36 studies).

Factors contributing to the clinical heterogeneity of studies included the number and type of confounders included in model adjustments, the follow-up durations used, the type and level of discharge threshold studied, the method used for judging patient readiness for discharge, and the admission NP levels for included patients.

Absolute BNP Thresholds

Twenty-seven studies, including 3 quasi-experimental studies (18–20), examined the association between achievement of an absolute BNP threshold and mortality, readmission, or a composite of the two. Five studies (18–22) had low risk of bias.

Figure 2. Risk for outcomes associated with achievement of a BNP discharge threshold, by threshold type.



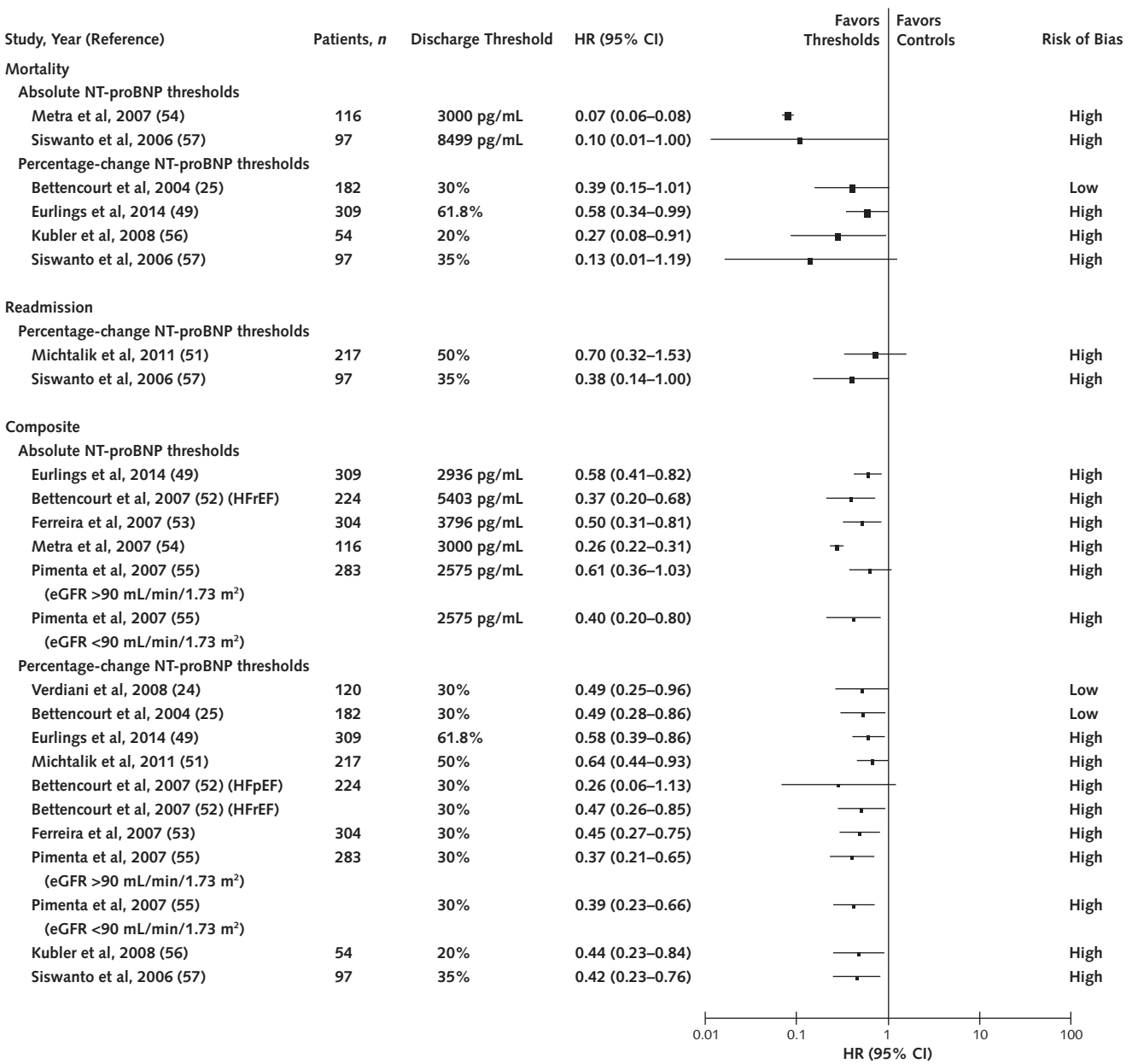
Studies are presented in reverse chronological order within each risk-of-bias subgroup. Box size is proportional to the inverse square of the risk estimates. Low risk of bias was defined as a score of 9 out of 9 stars on the Newcastle-Ottawa Scale. All other studies were categorized as having high risk of bias. BNP = brain-type natriuretic peptide; HR = hazard ratio.

Three quasi-experimental studies by Valle and colleagues (18–20) examined consecutive admissions before and after a new hospital policy mandated the use of a BNP discharge criterion: either a BNP level of 250 pg/mL or less or a decrease greater than 30% from admission, when predefined clinical stability criteria were fulfilled. These studies used an algorithmic approach to increase diuresis, vasodilator use, and blood pressure control for patients who had a BNP level above the set thresholds. The 2 studies (18, 19) with low risk of bias reported statistically significant reductions in the composite measure (HRs, 0.27 and 0.31). The other study (20), assessed as having high risk of bias, reported a statistically nonsignificant reduction in mortality (HR, 0.55 [95% CI, 0.19 to 1.64]) and readmission (HR, 0.79 [CI, 0.48 to 1.31]).

The most commonly used threshold was a BNP level of 250 pg/mL or less (18–21, 31, 35, 37, 42). Fifteen of 27 studies examined absolute thresholds at or below this level (for example, 250, 240, or 230 pg/mL). Twenty of 27 studies determined thresholds empirically (such as by using receiver-operating characteristic curves), and the rest derived them from the literature.

Achievement of an absolute BNP threshold before discharge was associated with statistically significantly reduced rates of mortality in 7 of 8 studies (HR range, 0.08 to 0.82), readmission in 2 of 3 studies (HR range, 0.07 to 0.97), and the composite outcome in 11 of 13 studies (HR range, 0.07 to 0.79) reporting HRs. The largest estimated risk reduction was reported by a study with low risk of bias for all 3 outcomes. In addition, 5 studies (18, 38, 42, 43, 45) reported log-rank statistics consistent with a reduction in the composite measure (log-rank $P < 0.05$). One study (34) reported an odds ratio (OR) for the composite outcome for a BNP level less than 300 pg/mL (OR, 0.32 [CI, 0.18 to 0.56]).

Figure 3. Risk for outcomes associated with achievement of an NT-proBNP discharge threshold, by threshold type.



Studies are presented in reverse chronological order within each risk-of-bias subgroup. Box size is proportional to the inverse square of the risk estimates. Low risk of bias was defined as a score of 9 out of 9 stars on the Newcastle-Ottawa Scale. All other studies were categorized as having high risk of bias. eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; NT-proBNP = amino-terminal pro–brain-type natriuretic peptide.

Percentage-Change BNP Thresholds

Nine studies examined thresholds for percentage change in BNP level from admission to discharge. One study had low risk of bias (18). Two studies used BNP thresholds to prospectively make discharge decisions (18, 60). Two studies matched patients by admission BNP level (40, 59). The most commonly used threshold was a change in BNP level of at least 30% between admission and discharge (18, 28, 33, 59, 60). Five of 9 thresholds examined were 30% or less. Four of 9 thresholds were derived empirically.

Achievement of a percentage-change BNP threshold was associated with reduced rates of mortality in 3 of 4 studies (HR range, 0.12 to 0.69) and the composite outcome in 4 of 5 studies (HR range, 0.25 to 0.54) reporting HRs. The HR from the single study with low risk of bias was similar to that of the other studies. One study (34) reported an OR for the composite outcome for a BNP decrease greater than 46% (OR, 0.17 [CI, 0.09 to 0.29]).

Absolute NT-proBNP Thresholds

Nine studies examined absolute NT-proBNP thresholds, including 1 randomized trial (17). No studies in this subgroup had low risk of bias.

The study by Carubelli and colleagues (17) was a single-center, nonblinded trial of 271 patients who were randomly assigned to either discharge when clinically stable (n = 134 [49%]) or discharge based on an NT-proBNP level when clinically stable (n = 137 [51%]). Patients in the NT-proBNP group were discharged immediately if their NT-proBNP level was less than 3000 pg/mL (n = 74 [27%]) or after "medical intensification" if their NT-proBNP level was greater than 3000 pg/mL (n = 63 [23%]). The method of intensification, its duration, and its goal were not specified and varied among patients; for example, only 24% in the intensification group received further intravenous diuretics. The number of patients who reached an NT-proBNP level less than 3000 pg/mL after medical intensification was not reported, and it was unclear how and when the decision to discharge these patients was made. Ultimately, the medication doses given and the NT-proBNP values at discharge were similar between groups (2047 pg/mL [interquartile range, 1048 to 4285 pg/mL] vs. 2156 pg/mL [interquartile range, 1113 to 4794 pg/mL] in the control and NT-proBNP groups, respectively; P = 0.55). The intervention was not associated with a statistically significant reduction in a composite outcome of cardiovascular death or rehospitalization at 6 months (HR, 1.08 [CI, 0.74 to 1.59]). However, multivariate analysis of the entire study cohort showed that a decrease in NT-proBNP level of nearly 800 pg/mL from randomization to discharge was associated with a significant decrease in the composite outcome (HR, 0.90 [CI, 0.84 to 0.96]).

Although this study successfully randomly assigned patients on the basis of age, sex, chronic kidney disease, BMI, and LVEF, it did not report admission NT-proBNP levels and did not estimate the percentage change in NT-proBNP level since admission. More than 57% of patients already had an NT-proBNP level less than 3000 pg/mL at discharge, and only 23% underwent medical intensification, limiting our ability to assess the efficacy of this intervention. Using the Cochrane tool, we found that the following aspects of the trial were associated with a high risk of bias: insufficient random-sequence generation and allocation concealment methods, lack of physician blinding, poorly designed intervention procedure, and lack of consideration for admission NT-proBNP levels.

The most commonly used threshold for all studies examining NT-proBNP was 3000 pg/mL or less (17, 54). Six of 9 studies examined absolute NT-proBNP thresholds that were 3000 pg/mL or less. Eight of 9 thresholds were derived empirically.

For the nonrandomized studies, achievement of a predischarge absolute NT-proBNP threshold reduced mortality in 2 of 2 studies (HRs, 0.07 and 0.10) and the composite measure in 5 of 5 studies (HR range, 0.26 to 0.61). Two studies (50, 58) reported log-rank statistics consistent with a significant reduction in mortality and the composite measure, respectively (log-rank $P <$ 0.05).

Percentage-Change NT-proBNP Thresholds

Nine studies examined thresholds for percentage change in NT-proBNP level from admission to discharge. Two studies had low risk of bias (24, 25).

The most commonly reported threshold was a decrease in NT-proBNP level of at least 30% from admission to discharge (24, 25, 52, 53, 55). Six of 9 percentage-change thresholds examined (67%) were 30% or less. Four of 9 thresholds were derived empirically.

Achievement of a percentage-change NT-proBNP threshold before discharge was associated with reduced risk for death in 2 of 4 studies (HR range, 0.13 to 0.58), readmission in 1 of 2 studies (HRs, 0.38 and 0.70), and the composite measure in 9 of 9 studies (HR range, 0.26 to 0.64). The HRs reported by the 2 studies with low risk of bias were similar to the other HRs for mortality and the composite outcome.

Sensitivity Analysis

Studies with low risk of bias had relative estimates similar to or more extreme than estimates from studies with high risk of bias (**Figures 2** and **3**). Relative estimates reported for short-term outcomes (such as 30-day follow-up) were generally more extreme than those reported for longer follow-up (such as 1 year) (**Appendix Figures 2** and **3**, available at Annals.org). Finally, studies that addressed a larger number of important confounders generally reported more extreme estimates than other studies (**Appendix Figures 4** and **5**, available at Annals.org). No other differences in findings were evident in our subgroup analyses compared with our overall findings, including analyses examining study design (**Appendix Figures 6** and **7**), care setting (**Appendix Figure 8**), LVEF (**Appendix Figure 9**), or prospective decision making (**Appendix Figure 10**; all available at Annals.org). Insufficient evidence was avail-

able to perform sensitivity analysis on the basis of matched NP levels at admission.

Strength of Evidence

The overall strength of evidence for each intervention and outcome is summarized in the Table. Because of the clinical heterogeneity of the available literature and the small number of studies with low risk of bias, the evidence supporting an association between achievement of a predischarge NP threshold and decreased rates of mortality and readmission was rated as low-strength for all comparisons.

DISCUSSION

Our systematic review identified a large number of observational studies examining the association between achievement of predischarge NP thresholds and rates of all-cause and cardiovascular mortality and readmission for patients hospitalized for ADHF. The included studies examined heart failure populations from several continents with a nearly even proportion of men and women and included patients with reduced and preserved ejection fractions. Both general medicine and intensive care unit admissions were represented.

Table. Evidence Summary and GRADE Evidence Assessment

Study Type, by Intervention and Outcome	Participants, *n*	Studies, *n*	Range of Relative Estimates (95% CI)	Factors That Weaken the Strength of Evidence	Factors That Increase the Strength of Evidence	Strength of Evidence
Absolute BNP threshold						
Mortality				None	None	Low
NCT	300	1	HR: 0.55 (0.19–1.64)			
Cohort	730	7	HR: 0.08 (0.01–0.60) to 0.82 (0.76–0.89)			
Readmission				None	None	Low
NCT	300	1	HR: 0.79 (0.48–1.31)			
Cohort	325	2	HR: 0.07 (0.02–0.25) to 0.97 (0.94–1.00)			
Composite				None	None	Low
NCT	501	2	HR: 0.27 (0.14–0.52) to 0.31 (0.16–0.53)			
Cohort	2637	11	HR: 0.07 (0.02–0.25) to 0.79 (0.67–0.89) OR: 0.32 (0.18–0.56)			
Case–control	72	1	HR: 0.54 (0.23–1.27)			
Percentage-change BNP threshold						
Mortality				None	None	Low
Cohort	458	3	HR: 0.12 (0.02–0.72) to 0.69 (0.30–1.59)			
Case–control	224	1	HR: 0.57 (0.37–0.88)			
Composite				None	None	Low
NCT	315	1	HR: 0.27 (0.14–0.52)			
Cohort	572	4	HR: 0.25 (0.09–0.69) to 0.44 (0.20–0.97) OR: 0.17 (0.09–0.29)			
Case–control	72	1	HR: 0.54 (0.23–1.27)			
Absolute NT-proBNP threshold						
Mortality				None	None	Low
Cohort	213	2	HR: 0.07 (0.06–0.08) to 0.10 (0.01–1.00)			
Composite				Study limitations, imprecision	None	Low
RCT	271	1	HR: 1.08 (0.74–1.59)			
Cohort	1236	5	HR: 0.26 (0.22–0.31) to 0.61 (0.36–1.03)			
Percentage-change NT-proBNP threshold						
Mortality				None	None	Low
Cohort	642	4	HR: 0.13 (0.01–1.19) to 0.58 (0.34–0.99)			
Readmission				None	None	Low
Cohort	314	2	HR: 0.38 (0.14–1.00) to 0.70 (0.32–1.53)			
Composite				None	None	Low
Cohort	1790	9	HR: 0.26 (0.06–1.13) to 0.64 (0.44–0.93)			

BNP = brain-type natriuretic peptide; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HR = hazard ratio; NCT = nonrandomized, controlled trial; NT-proBNP = amino-terminal pro–brain-type natriuretic peptide; OR = odds ratio; RCT = randomized, controlled trial.

The available evidence, which consisted mostly of studies with high risk of bias, was clinically heterogeneous in terms of confounders considered, follow-up durations used, discharge thresholds studied, methods used for judging patient readiness for discharge, and admission NP levels for included patients. However, studies consistently showed a statistically significant reduction in all-cause and cardiovascular mortality and readmission when predischarge thresholds were achieved. The association was further supported when we examined studies with low risk of bias and those adjusting for large numbers of critical confounders.

A well-designed and well-executed randomized, controlled trial with a clear intervention algorithm is needed to prove the clinical benefits of targeting NP thresholds before discharge of patients hospitalized for ADHF. Comparison of studies with low and high risk of bias reveals several factors that should influence the design of such trials.

First, several studies used carefully standardized methods for hospital interventions and discharge. Two quasi-experimental studies with low risk of bias (18, 19) used a flexible combination of absolute and relative BNP discharge thresholds with a standardized algorithmic intervention protocol. In contrast, a trial with high risk of bias (17) that did not standardize the intervention treatment had a control group of patients with discharge NT-proBNP levels and medication use similar to the intervention group. A clear algorithmic approach to diuresis and the use of NP thresholds would help avoid undertreatment of patients and help achieve between-group differences in decongestion and short-term clinical outcomes.

Second, BNP and NT-proBNP levels likely comprise both dynamic ("wet," affected by volume status) and static ("dry") components. Some patients with high NP levels after treatment have advanced heart failure with an intrinsic risk for readmission and mortality not due to underdiuresis (21, 22). Large trial sizes, adequate randomization, and adjustment for remaining differences in admission NP levels and common confounders of NP levels (age, sex, renal function, and BMI [14]) are therefore essential to maintain a trial's validity. A lack of achievement of discharge thresholds could also be used to identify patients at high risk for poor outcomes after discharge, prompting more intensive outpatient follow-up care to reduce adverse outcomes (7, 8) or informing further adjustment of related quality measures.

Similarly, careful attention must be paid to the type and level of the threshold studied. The evidence best supports using either a BNP threshold of less than 250 pg/mL or a decrease in NT-proBNP level of at least 30% between admission and discharge after clinical stability has been achieved. These thresholds were empirically derived and have demonstrated an association with decreased mortality and readmission. However, as discussed by Stienen and colleagues (13), low absolute thresholds, such as a BNP level less than 250 pg/mL, are sometimes difficult to attain. In their analysis, moderate thresholds were more easily achieved and retained clinically meaningful effect sizes for clinical outcomes of interest, especially for patients with extremely elevated NP levels at admission. For patients with more advanced disease who cannot reach a low absolute threshold (such as a BNP level ≤250 pg/mL), a decrease of at least 30% from admission to discharge may be a more feasible target (19, 23, 24). Whether discharge NP thresholds can benefit all patients with ADHF or only those not yet at an advanced heart failure stage needs further study.

Finally, our sensitivity analyses also emphasize the effect of follow-up duration on our outcomes of interest. As expected, the effect of using NP thresholds as discharge criteria wanes as longer follow-ups (61) are examined. New randomized, controlled trials should utilize 30-day, 90-day, and 1-year outcomes to identify and quantify the durability of effects over time.

Our systematic review builds on a 2014 review (15) that suggested that discharge BNP and NT-proBNP levels were independent of admission values for predicting patient outcomes. Our review incorporated many articles not included in the previous review, performed sensitivity analyses, appraised and graded the strength of evidence for interventions and outcomes, and provides recommendations for threshold choices and the design of future randomized trials. Through its use of an evidence inventory, this review is also the first to identify a paucity of trials assessing common methods for evaluating the success of diuresis for patients admitted with ADHF, which is surprising given the great patient burden and costs associated with such admissions.

Our review has important limitations, primarily related to the quality of the available literature. Most available studies are cohort or case–control studies with heterogeneity of the exposures and outcomes they examined and the analytic methods they used. The single available randomized trial has important limitations and high risk of bias. Because the studies were not amenable to meta-analysis, we were unable to examine publication bias using funnel plots. However, there is a potential for publication bias, which might be expected to bias our results away from the null.

In conclusion, our systematic review suggests a potential role for BNP and NT-proBNP levels beyond prognosis to help providers assess the quality of inpatient care for patients admitted for ADHF and to improve patient outcomes after discharge. Low-strength evidence supports an association between predischarge BNP and NT-proBNP thresholds and decreased rates of mortality and readmission. The quality of the current body of literature is inadequate to fully assess whether discharge thresholds can be prospectively used to improve clinical outcomes. Future, carefully designed randomized, controlled trials must use clear algorithmic methods to guide diuresis, consider important confounders of NP levels, test achievable predischarge thresholds (perhaps multiple ones), and analyze data for both short- and long-term follow-up to address this important clinical question.

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Reproducible Research Statement: *Study protocol:* See the Supplement. *Statistical code:* See the Methods section of the text. *Data set:* See the Appendix. Further requests can be sent to the authors (e-mail, mcquadec@upmc.edu).

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References

1. **Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; Writing Group Members.** Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation. 2016;133:e38-360. [PMID: 26673558] doi:10.1161/CIR.0000000000000350

2. **Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al; American Heart Association Advocacy Coordinating Committee.** Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6:606-19. [PMID: 23616602] doi:10.1161/HHF.0b013e318291329a

3. **Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al; Heart Failure Society of America.** HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16:e1-194. [PMID: 20610207] doi:10.1016/j.cardfail.2010.04.004

4. **Desai AS, Stevenson LW.** Rehospitalization for heart failure: predict or prevent? Circulation. 2012;126:501-6. [PMID: 22825412] doi:10.1161/CIRCULATIONAHA.112.125435

5. **Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP, et al; NHLBI Heart Failure Network Steering Committee and Investigators.** Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail. 2013;6:240-5. [PMID: 23250981] doi:10.1161/CIRCHEARTFAILURE.112.969246

6. **Cook DJ, Simel DL.** The rational clinical examination. Does this patient have abnormal central venous pressure? JAMA. 1996;275:630-4. [PMID: 8594245]

7. **Troughton RW, Frampton CM, Brunner-La Rocca HP, Pfisterer M, Eurlings LW, Erntell H, et al.** Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J. 2014;35:1559-67. [PMID: 24603309] doi:10.1093/eurheartj/ehu090

8. **Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, et al.** Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. PLoS One. 2013;8:e58287. [PMID: 23472172] doi:10.1371/journal.pone.0058287

9. **Mitchell MD, Williams K, Kuntz G, Umscheid CA.** When the decision is what to decide: using evidence inventory reports to focus health technology assessments. Int J Technol Assess Health Care. 2011;27:127-32. [PMID: 21450127] doi:10.1017/S0266462311000031

10. **Hartling L, Guise JM, Kato E, Anderson J, Belinson S, Berliner E, et al.** A taxonomy of rapid reviews links report types and methods to specific decision-making contexts. J Clin Epidemiol. 2015;68:1451-62. [PMID: 26278023] doi:10.1016/j.jclinepi.2015.05.036

11. **The Cochrane Collaboration.** The Cochrane Collaboration's tool for assessing risk of bias. Cochrane Handbook for Reviews of Interventions. 2008. Accessed at http://handbook.cochrane.org/chapter_8/8_5_the_cochrane_collaborations_tool_for_assessing_risk_of_bias.htm on 16 September 2016.

12. **Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al.** The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2014.

13. **Stienen S, Salah K, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, et al.** Challenging the two concepts in determining the appropriate pre-discharge *N*-terminal pro-brain natriuretic peptide treatment target in acute decompensated heart failure patients: absolute or relative discharge levels? Eur J Heart Fail. 2015;17:936-44. [PMID: 26222618] doi:10.1002/ejhf.320

14. **Balion C, Santaguida PL, Hill S, Worster A, McQueen M, Oremus M, et al.** Testing for BNP and NT-proBNP in the diagnosis and prognosis of heart failure. Evid Rep Technol Assess (Full Rep). 2006:1-147. [PMID: 17764210]

15. **Santaguida PL, Don-Wauchope AC, Oremus M, McKelvie R, Ali U, Hill SA, et al.** BNP and NT-proBNP as prognostic markers in persons with acute decompensated heart failure: a systematic review. Heart Fail Rev. 2014;19:453-70. [PMID: 25062653] doi:10.1007/s10741-014-9442-y

16. **Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al; GRADE Working Group.** GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.BMJ.2008;336:924-6.[PMID:18436948]doi:10.1136/bmj.39489.470347.AD

17. **Carubelli V, Lombardi C, Lazzarini V, Bonadei I, Castrini AI, Gorga E, et al.** *N*-terminal pro-B-type natriuretic peptide-guided therapy in patients hospitalized for acute heart failure. J Cardiovasc Med (Hagerstown). 2016;17:828-39. [PMID: 27322401] doi:10.2459/JCM.0000000000000419

18. **Valle R, Aspromonte N, Carbonieri E, D'Eri A, Feola M, Giovinazzo P, et al.** Fall in readmission rate for heart failure after implementation of B-type natriuretic peptide testing for discharge decision: a retrospective study. Int J Cardiol. 2008;126:400-6. [PMID: 17804095]

19. **Valle R, Aspromonte N, Giovinazzo P, Carbonieri E, Chiatto M, di Tano G, et al.** B-type natriuretic peptide-guided treatment for predicting outcome in patients hospitalized in sub-intensive care unit with acute heart failure. J Card Fail. 2008;14:219-24. [PMID: 18381185] doi:10.1016/j.cardfail.2007.10.009

20. **Valle R, Aspromonte N, Milani L, Peacock FW, Maisel AS, Santini M, et al.** Optimizing fluid management in patients with acute decompensated heart failure (ADHF): the emerging role of combined measurement of body hydration status and brain natriuretic peptide (BNP) levels. Heart Fail Rev. 2011;16:519-29. [PMID: 21604179] doi:10.1007/s10741-011-9244-4

21. **Feola M, Lombardo E, Testa M, Avogadri E, Piccolo S, Vado A.** Prognostic factors of mid-term clinical outcome in congestive heart failure patients discharged after acute decompensation. Arch Med

Sci. 2012;8:462-70. [PMID: 22852001] doi:10.5114/aoms.2012.29401
22. **Shah MR, Hasselblad V, Tasissa G, Christenson RH, Binanay C, O'Connor CM, et al.** Rapid assay brain natriuretic peptide and troponin I in patients hospitalized with decompensated heart failure (from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness Trial). Am J Cardiol. 2007;100:1427-33. [PMID: 17950802]
23. **Verdiani V, Nozzoli C, Bacci F, Cecchin A, Rutili MS, Paladini S, et al.** Pre-discharge B-type natriuretic peptide predicts early recurrence of decompensated heart failure in patients admitted to a general medical unit. Eur J Heart Fail. 2005;7:566-71. [PMID: 15921796]
24. **Verdiani V, Ognibene A, Rutili MS, Lombardo C, Bacci F, Terreni A, et al.** NT-ProBNP reduction percentage during hospital stay predicts long-term mortality and readmission in heart failure patients. J Cardiovasc Med (Hagerstown). 2008;9:694-9. [PMID: 18545069] doi:10.2459/JCM.0b013e3282f447ae
25. **Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A.** *N*-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation. 2004;110:2168-74. [PMID: 15451800]
26. **Nakada Y, Kawakami R, Nakano T, Takitsume A, Nakagawa H, Ueda T, et al.** Sex differences in clinical characteristics and long-term outcome in acute decompensated heart failure patients with preserved and reduced ejection fraction. Am J Physiol Heart Circ Physiol. 2016;310:H813-20. [PMID: 26747499] doi:10.1152/ajpheart.00602.2015
27. **Omar HR, Guglin M.** Discharge BNP is a stronger predictor of 6-month mortality in acute heart failure compared with baseline BNP and admission-to-discharge percentage BNP reduction. Int J Cardiol. 2016;221:1116-22. [PMID: 27467969] doi:10.1016/j.ijcard.2016.07.117
28. **Ruocco G, Pellegrini M, De Gori C, Franci B, Nuti R, Palazzuoli A.** The prognostic combined role of B-type natriuretic peptide, blood urea nitrogen and congestion signs persistence in patients with acute heart failure. J Cardiovasc Med (Hagerstown). 2016;17:818-27. [PMID: 26702597] doi:10.2459/JCM.0000000000000350
29. **Naffaa M, Makhoul BF, Tobia A, Jarous M, Kaplan M, Aronson D, et al.** Brain natriuretic peptide at discharge as a predictor of 6-month mortality in acute decompensated heart failure. Am J Emerg Med. 2014;32:44-9. [PMID: 24210886] doi:10.1016/j.ajem.2013.10.002
30. **Ludka O, Stipal R, Senkyrikova M, Musil V, Trna J, Zbynek P, et al.** The importance of admission and discharge BNP assessment in patients hospitalized for acutely decompensated chronic systolic heart failure. Cor Vasa. 2013;55:1286-92.
31. **Chen CY, Yoshida A, Asakura M, Hasegawa T, Takahama H, Amaki M, et al.** Serum blood urea nitrogen and plasma brain natriuretic peptide and low diastolic blood pressure predict cardiovascular morbidity and mortality following discharge in acute decompensated heart failure patients. Circ J. 2012;76:2372-9. [PMID: 22785557]
32. **Ito K, Kawai M, Nakane T, Narui R, Hioki M, Tanigawa S, et al.** Serial measurements associated with an amelioration of acute heart failure: an analysis of repeated quantification of plasma BNP levels. Eur Heart J Acute Cardiovasc Care. 2012;1:240-7. [PMID: 24062913] doi:10.1177/2048872612458580
33. **Noveanu M, Breidthardt T, Potocki M, Reichlin T, Twerenbold R, Uthoff H, et al.** Direct comparison of serial B-type natriuretic peptide and NT-proBNP levels for prediction of short- and long-term outcome in acute decompensated heart failure. Crit Care. 2011;15:R1. [PMID: 21208408] doi:10.1186/cc9398
34. **Di Somma S, Magrini L, Pittoni V, Marino R, Mastrantuono A, Ferri E, et al.** In-hospital percentage BNP reduction is highly predictive for adverse events in patients admitted for acute heart failure: the Italian RED Study. Crit Care. 2010;14:R116. [PMID: 20550660] doi:10.1186/cc9067
35. **Faggiano P, Valle R, Aspromonte N, D'Aloia A, Di Tano G, Barro S, et al.** How often we need to measure brain natriuretic peptide (BNP) blood levels in patients admitted to the hospital for acute severe heart failure? Role of serial measurements to improve short-term prognostic stratification. Int J Cardiol. 2010;140:88-94. [PMID: 19321212] doi:10.1016/j.ijcard.2008.11.020
36. **Cournot M, Mourre F, Castel F, Ferrières J, Destrac S.** Optimization of the use of B-type natriuretic peptide levels for risk stratification at discharge in elderly patients with decompensated heart failure. Am Heart J. 2008;155:986-91. [PMID: 18513508] doi:10.1016/j.ahj.2008.01.011
37. **Feola M, Aspromonte N, Milani L, Bobbio M, Bardellotto S, Barro S, et al.** Plasma brain natriuretic peptide predicts short-term clinical outcome in heart failure patients with restrictive filling pattern. J Card Fail. 2008;14:420-5. [PMID: 18514935] doi:10.1016/j.cardfail.2008.01.013
38. **Seo Y, Ishizu T, Kawano S, Watanabe S, Ishimitsu T, Aonuma K.** Combined approach with Doppler echocardiography and B-type natriuretic peptide to stratify prognosis of patients with decompensated systolic heart failure. J Cardiol. 2008;52:224-31. [PMID: 19027600] doi:10.1016/j.jjcc.2008.07.008
39. **Aspromonte N, Feola M, Milli M, Scardovi AB, Coletta C, Carbonieri E, et al.** Prognostic role of B-type natriuretic peptide in patients with diabetes and acute decompensated heart failure. Diabet Med. 2007;24:124-30. [PMID: 17257273]
40. **Cournot M, Leprince P, Destrac S, Ferrières J.** Usefulness of in-hospital change in B-type natriuretic peptide levels in predicting long-term outcome in elderly patients admitted for decompensated heart failure. Am J Geriatr Cardiol. 2007;16:8-14. [PMID: 17215637]
41. **Valle R, Prevaldi C, D'Eri A, Fontebasso A, Giovinazzo P, Noventa F, et al.** B-type natriuretic peptide predicts postdischarge prognosis in elderly patients admitted due to cardiogenic pulmonary edema. Am J Geriatr Cardiol. 2006;15:202-7. [PMID: 16849885]
42. **Dokainish H, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, et al.** Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. J Am Coll Cardiol. 2005;45:1223-6. [PMID: 15837253]
43. **Hamada Y, Tanaka N, Murata K, Takaki A, Wada Y, Oyama R, et al.** Significance of predischarge BNP on one-year outcome in decompensated heart failure—comparative study with echo-Doppler indexes. J Card Fail. 2005;11:43-9. [PMID: 15704063]
44. **Gackowski A, Isnard R, Golmard JL, Pousset F, Carayon A, Montalescot G, et al.** Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. Eur Heart J. 2004;25:1788-96. [PMID: 15474693]
45. **Koitabashi T, Inomata T, Niwano S, Nishii M, Takeuchi I, Nakano H, et al.** Distinguishable optimal levels of plasma B-type natriuretic peptide in heart failure management based on complicated atrial fibrillation. Int Heart J. 2005;46:453-64. [PMID: 16043941]
46. **Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, et al.** Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol. 2004;43:635-41. [PMID: 14975475]
47. **Bettencourt P, Ferreira S, Azevedo A, Ferreira A.** Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcome after hospital discharge in patients with heart failure. Am J Med. 2002;113:215-9. [PMID: 12208380]
48. **Yu CM, Sanderson JE.** Plasma brain natriuretic peptide—an independent predictor of cardiovascular mortality in acute heart failure. Eur J Heart Fail. 1999;1:59-65. [PMID: 10937981]
49. **Eurlings LW, Sanders-van Wijk S, van Kraaij DJ, van Kimmenade R, Meeder JG, Kamp O, et al.** Risk stratification with the use of serial *N*-terminal pro-B-type natriuretic peptide measurements during admission and early after discharge in heart failure patients: post hoc analysis of the PRIMA study. J Card Fail. 2014;20:881-90. [PMID: 25175696] doi:10.1016/j.cardfail.2014.08.014
50. **Ho SJ, Feng AN, Lee LN, Chen JW, Lin SJ.** Predictive value of predischarge spectral tissue Doppler echocardiography and *N*-terminal pro-B-type natriuretic peptide in patients hospitalized with acute heart failure. Echocardiography. 2011;28:303-10. [PMID: 21395667] doi:10.1111/j.1540-8175.2010.01322.x

51. **Michtalik HJ, Yeh HC, Campbell CY, Haq N, Park H, Clarke W, et al.** Acute changes in *N*-terminal pro-B-type natriuretic peptide during hospitalization and risk of readmission and mortality in patients with heart failure. Am J Cardiol. 2011;107:1191-5. [PMID: 21296322] doi:10.1016/j.amjcard.2010.12.018

52. **Bettencourt P, Azevedo A, Fonseca L, Araújo JP, Ferreira S, Almeida R, et al.** Prognosis of decompensated heart failure patients with preserved systolic function is predicted by NT-proBNP variations during hospitalization. Int J Cardiol. 2007;117:75-9. [PMID: 16843555]

53. **Ferreira S, Almeida R, Guerrero H, Lourenço-Ferreira S, Fonseca L, Rocha R, et al.** Prognosis of decompensated heart failure: role of NT-proBNP. Rev Port Cardiol. 2007;26:535-45. [PMID: 17691279]

54. **Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, et al.** The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. Eur J Heart Fail. 2007;9:776-86. [PMID: 17573240]

55. **Pimenta JM, Almeida R, Araújo JP, Azevedo A, Friões F, Rocha-Gonçalves F, et al.** Amino terminal B-type natriuretic peptide, renal function, and prognosis in acute heart failure: a hospital cohort study. J Card Fail. 2007;13:275-80. [PMID: 17517347]

56. **Kubler P, Jankowska EA, Majda J, Reczuch K, Banasiak W, Ponikowski P.** Lack of decrease in plasma *N*-terminal pro-brain natriuretic peptide identifies acute heart failure patients with very poor outcome. Int J Cardiol. 2008;129:373-8. [PMID: 18054808]

57. **Siswanto BB, Sunanto, Munawar M, Kusmana D, Hanafiah A, Waspadji S, et al.** Predictor of mortality and rehospitalization of acute decompensated heart failure at six months follow-up. Crit Care Shock. 2006;9:61-7.

58. **O'Brien RJ, Squire IB, Demme B, Davies JE, Ng LL.** Predischarge, but not admission, levels of NT-proBNP predict adverse prognosis following acute LVF. Eur J Heart Fail. 2003;5:499-506. [PMID: 12921811]

59. **Lourenço P, Ribeiro A, Pintalhão M, Silva S, Bettencourt P.** Predictors of six-month mortality in BNP-matched acute heart failure patients. Am J Cardiol. 2015;116:744-8. [PMID: 26115901] doi:10.1016/j.amjcard.2015.05.046

60. **De Vecchis R, Esposito C, Di Biase G, Ariano C.** B-type natriuretic peptide. Guided vs. conventional care in outpatients with chronic heart failure: a retrospective study. Minerva Cardioangiol. 2013;61:437-49. [PMID: 23846010]

61. **Jencks SF, Williams MV, Coleman EA.** Rehospitalizations among patients in the Medicare Fee-for-Service program. N Engl J Med. 2009;360:1418-28. [PMID: 19339721] doi:10.1056/NEJMsa0803563

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Appendix: Newcastle-Ottawa Scale Domains

The Newcastle-Ottawa Scale assesses risk of bias in 3 domains. The "selection" domain awards 1 star each for meeting the following criteria: 1) the "exposed cohort" is representative of individuals in the greater community, 2) the nonexposed cohort is drawn from the same community as the exposed cohort, 3) the ascertainment of the "exposure" is obtained from either a secure record or a structured interview, and 4) the study adequately demonstrates that the outcome of interest was not present at the start of the study. Studies were judged to not be representative of individuals in the greater community if they used selective inclusion criteria (for example, only patients aged >70 years or only patients with diabetes).

The "comparability" domain awards 1 star for controlling for the most important confounding factor and 1 additional star for controlling for the second most important confounding factor. We required adjustment for LVEF (1 star possible) and at least 1 measure of disease severity on admission (NP level or NYHA class; 1 additional star possible).

The "outcome" domain awards 1 star each for meeting the following criteria: 1) outcomes are assessed by an independent blinded assessment or by record linkage, 2) follow-up was long enough for the outcomes of interest to occur, and 3) the participants who were lost to follow-up were unlikely to introduce bias.

Web-Only References

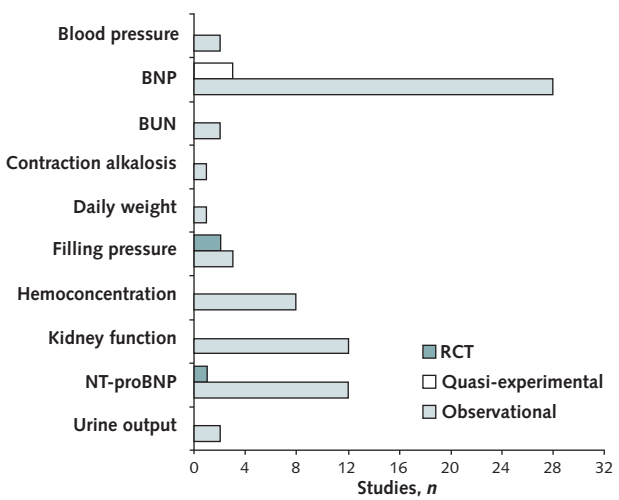
62. **The Cochrane Collaboration.** Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version. Cochrane Handbook for Reviews of Interventions. 2008. Accessed at http://handbook.cochrane.org/chapter_6 on 1 September 2015.
63. **Relevo R, Balshem H.** Finding evidence for comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64:1168-77. [PMID: 21684115] doi:10.1016/j.jclinepi.2010.11.022

Appendix Table 1. Search Strategies in Ovid MEDLINE

Set Number	Concept	Search Statement
1	Heart failure	heart failure.mp. or exp Heart Failure/or Ventricular Dysfunction/or Ventricular Dysfunction, Left/or exp Pulmonary Edema/or (pulmonary adj2 (congestion OR edema)).mp. or dyspn*.mp.
2	Acute	exp Hospitalization/or hospitaliz*.mp. or (acute* adj1 (decompensat* or exacerbat*)).mp. or (patient* adj3 admitted).mp or (acute* adj2 heart failure).mp. or (decompensat* adj2 heart failure).mp.
3	Diuretics	exp Diuretics/or diure*.mp. or (acetazolamide or amiloride or bumetanide or chlorothiazide or eplerenone or furosemide or hydrochlorothiazide or B-type natriuretic peptide or mannitol or metolazone or spironolactone or torsemide or tolvaptan).mp.
4	Cochrane RCT filter maximizing sensitivity (62)	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or group.ab.) not (exp animals/not humans.sh.)
5	Observational studies filter (63)	epidemiologic studies/or exp case control studies/or exp cohort studies/or case control.tw. or (cohort adj (study or studies)).tw. or cohort analy$.tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or longitudinal.tw. or retrospective.tw. or cross sectional.tw. or cross-sectional studies/or post hoc analysis.tw.
6	Combine filters (RCT and observational studies)	4 or 5
7	Intervention filter	daily weigh*.mp. or weight.mp. or (urin* adj2 output).mp. or (input adj2 output).mp. or hematocrit$.mp. or hemoglobin$.mp. or hemoconcentration.mp. or haemoconcentration.mp. or creatinine.mp. or worsening renal function.mp. or worsening kidney function.mp. or acute kidney injury.mp. or acute renal failure.mp. or BNP.mp. or B type natriuretic peptide or Brain type natriuretic peptide.mp. or bicarbonate.mp. or contraction alkalosis.mp. or hyponatremia.mp. or serum sodium.mp. or CVP.mp. or central venous pressure.mp. or PCWP.mp. or PAWP.mp. or PAOP.mp. or PWP.mp. or (pulmonary adj2 wedge pressure).mp. or wedge pressure.mp. or hematocrit/or hemoglobins/or creatinine/or acute kidney injury/or Natriuretic Peptide, Brain/or bicarbonates/or hyponatremia/or Sodium/bl or Central Venous Pressure/or Pulmonary Wedge Pressure/
8	Combine sets	1 and 2 and 3 and 6 and 7
9	English	Limit 8 to english language

RCT = randomized, controlled trial.

Appendix Figure 1. Evidence map of study interventions.



We initially created an "evidence inventory" of all data-driven methods for assessing the readiness of patients with acute decompensated heart failure for discharge. From this pool of 70 studies, we included in our review only the 44 studies examining BNP or NT-proBNP thresholds. Several studies used multiple intervention types (e.g., BNP, kidney function, and blood pressure). BNP = brain-type natriuretic peptide; BUN = blood urea nitrogen; NT-proBNP = amino-terminal pro–brain-type natriuretic peptide; RCT = randomized, controlled trial.

Appendix Table 2. Selected Characteristics of the Included Studies*

Study, Year (Reference)	Intervention	Threshold	Design	Location	Patients, *n*	Outcomes	Median Follow-up†	Mean Age (SD), *y*‡	Men, %	Population	LVEF	Mean BNP Level on Admission (SD), *pg/mL*‡	Adjustment Variables	Newcastle-Ottawa Scale Ratings		
														Selection (Maximum: 4)	Comparability (Maximum: 2)	Outcome (Maximum: 3)
RCTs																
Carubelli et al, 2016 (17)	NT-proBNP	3000 pg/mL	RCT	Italy	271	Composite	182 d	69 (10)	70	General ward	All	NA	Age, CKD, BMI, medications, BUN, Hb, HF etiology, SBP, QRS duration	NR	NR	NR
Nonrandomized studies																
Low risk of bias																
Valle et al, 2008 (18)	BNP	Combined 250 pg/mL or 30% decrease	QES	Italy	315	Composite	6 mo	77 (9)	47	HF unit	All	Intervention: 764 (699) Control: NA	Age, sex, admission NYHA class, CKD, LVEF, medications, Afib, mitral stenosis	4	2	3
Valle et al, 2008 (19)	BNP	250 pg/mL	QES	Italy	186	Composite	6 mo	77 (10)	50	HF unit	All	Intervention: 439 (299) Control: 1037 (630)	Age, sex, admission BNP, admission NYHA class, CKD, LVEF, medications, Afib, restrictive filling pattern	4	2	3
Feola et al, 2012 (21)	BNP	250 pg/mL	PC	Italy	237	Composite‖	14 mo	71 (10)	65	HF unit	All	593 (717)	Age, sex, admission BNP, admission NYHA class, CKD, LVEF, medications, Afib, DM, Hb	4	2	3
Shah et al, 2007 (22)	BNP	500 pg/mL	RC	United States	111	All-cause mortality	6 mo	Median, 57 (IQR, 50–68)	74	Intensive care unit	<30%	Median, 783 (IQR, 329–1565)	Age, sex, admission BNP, LVEF, BUN, SBP, sodium, 6-min walk test	4	2	3
Verdiani et al, 2005 (23)	BNP	696 pg/mL	RC	Italy	100	Readmission, composite	30 d	78 (10)	71	General ward	All	Median, 739 (IQR, 355–1333)	Age, admission NYHA class, CKD, LVEF, COPD, depression, sodium	4	2	3
Verdiani et al, 2008 (24)	NT-proBNP	30% decrease	PC	Italy	120	Composite	358 d	78 (9)	57	General ward	All	10 912 (12 239)	Age, admission NYHA class, CKD, LVEF, COPD, depression, sodium	4	2	3
Bettencourt et al, 2004 (25)	NT-proBNP	30% decrease	RC	Portugal	182	All-cause mortality, composite	6 mo	73 (11)	47	General ward	All	14 463 (24 859)	Age, sex, admission NYHA class, CKD, LVEF, medications, Afib, BUN, DBP, DM, SBP, HR, sodium, physical examination	4	2	3
High risk of bias																
Valle et al, 2011 (20)	BNP	250 pg/mL	QES	Italy	300	All-cause mortality, readmission	6 mo	77 (10)	55	HF unit	All	Intervention: 495 (372) Control: 1285 (1061)	Not applicable; univariate analysis only	4	0	2
Nakada et al, 2016 (26)	BNP	295 pg/mL	RC	Japan	748	Composite	18.5 mo	70 (12)	58	General ward	All	Median, 1043 (IQR, 616–1817)	Age, CKD, BMI, LVEF, medications, Afib, DM, Hb, HTN, SBP, sodium	4	1	3
Omar and Guglin, 2016 (27)	BNP	319 pg/mL	RC	United States	433	All-cause mortality	6 mo	56 (14)	73	Intensive care unit	<30%	1009 (NA)	Age, CKD, right atrial pressure, SBP	4	0	3
Lourenço et al, 2015 (59)	BNP	30% decrease	RCC	Portugal	224	All-cause mortality	6 mo	Median, 80 (IQR, 73–85)	43	General ward	<50%	Median, 2510 (IQR, 1326–3238)§	Age, sex, CKD, congestion score, DM, HL, HTN, smoking	2	0	3
Ruocco et al, 2016 (28)	BNP	30% decrease	RC	Italy	107	Composite	6 mo	81 (6)	43	General ward	All	1014 (767)	Admission NYHA class, LVEF, Afib, BUN, Hb, HF etiology, HTN, SBP	4	2	2
Naffaa et al, 2014 (29)	BNP	992.6 pg/mL	PC	Israel	33	All-cause mortality	6 mo	80 (12)	33	General ward	All	NA	Age, sex, CKD, Afib, albumin, HF etiology, smoking	4	0	2
De Vecchis et al, 2013 (60)	BNP	Combined 240 pg/mL or 30% decrease	PCC	Italy	72	Composite	4 mo	76 (3)	61	General ward	>30%	622 (167)	Age, sex, LVEF, time since HF diagnosis	2	1	3

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Appendix Table 2–Continued

Study, Year (Reference)	Intervention	Threshold	Design	Location	Patients, *n*	Outcomes	Median Follow-up†	Mean Age (SD), *y*‡	Men, %	Population	LVEF	Mean BNP Level on Admission (SD), *pg/mL*‡	Adjustment Variables	Newcastle-Ottawa Scale Ratings		
														Selection (Maximum: 4)	Comparability (Maximum: 2)	Outcome (Maximum: 3)
Ludka et al, 2013 (30)	BNP	434.5 pg/mL; 64% decrease	PC	Czech Republic	130	All-cause mortality	3 y	70 (9)	77	General ward	<45%	Median, 1101 (IQR, 290–3996)	Not applicable; univariate analysis only	4	0	3
Chen et al, 2012 (31)	BNP	250 pg/mL	RC	Japan	225	Readmission	3 y	67 (15)	59	General ward	All	NA	Age, sex, CKD, medications, DBP, DM, HL, HTN, SBP	4	0	3
Ito et al, 2012 (32)	BNP	200 pg/mL	PC	Japan	208	All-cause mortality	4 y	70 (15)	71	General ward	All	NA	Age, sex, CKD, BMI, LVEF	4	1	2
Noveanu et al, 2011 (33)	BNP	30% decrease	PC	Switzerland	171	All-cause mortality	1 y	Median, 80 (IQR, 73–85)	60	General ward	All	Median, 1315 (IQR, 759–2349)	Age, admission BNP and NT-proBNP, admission NYHA class, CKD, troponins	4	1	2
Di Somma et al, 2010 (34)	BNP	300 pg/mL; 46% decrease	PC	Italy	247	Composite‖	6 mo	76 (12)	48	General ward	All	Median, 822 (IQR, 412–1390)	Adjustment performed but variables not described	4	0	2
Faggiano et al, 2010 (35)	BNP	250 pg/mL	PC	Italy	150	Composite	6 mo	69 (12)	67	HF unit	All	Intervention: 720 (353) Control: 1148 (699)	Age, admission BNP, admission NYHA class, CKD, LVEF, restrictive filling pattern	3	2	2
Cournot et al, 2008 (36)	BNP	Combined 360 pg/dL or 50% decrease	PC	France	157	All-cause mortality, composite	7 mo	83 (6)	51	General ward	All	Median, 1057 (IQR, 639–1764)	Age, sex, admission NYHA class, CKD, LVEF, LOS	4	2	2
Feola et al, 2008 (37)	BNP	250 pg/mL	PC	Italy	250	Composite	6 mo	73 (12)	66	General ward	All	NA	Age, admission BNP, admission NYHA class, CKD, LVEF, Afib, HF etiology	3	2	3
Seo et al, 2008 (38)	BNP	254.5 pg/mL	PC	Japan	73	Composite‖	3 y	55 (15)	76	General ward	All	NA	Echo parameters (except LVEF)	4	0	1
Aspromonte et al, 2007 (39)	BNP	200 pg/mL	RC	Italy	145	Composite	6 mo	72 (9)	60	General ward	All	NA	Age, admission BNP, admission NYHA class, CKD, LVEF, Afib, HF etiology, restrictive filling pattern	3	2	3
Cournot et al, 2007 (40)	BNP	40% decrease	PC	France	61	Composite	7 mo	83 (6)	50	General ward	All	Intervention: median, 1146 (IQR, 570–1708) Control: median, 1095 (IQR, 587–1903)§	Age, sex, admission BNP, CKD, CAD, LOS, pulmonary HTN	3	1	2
Valle et al, 2006 (41)	BNP	200 pg/mL	RC	Italy	203	Composite	6 mo	80 (7)	47	HF unit	All	NA	Age, admission BNP, admission NYHA class, CKD, LOS, mitral stenosis	4	1	2
Dokainish et al, 2005 (42)	BNP	250 pg/mL	PC	Houston, Texas	116	Composite‖	18 mo	59 (13)	49	General ward	All	NA	Age, LVEF, DM, HF etiology, HTN, other echo parameters, smoking	4	0	2
Hamada et al, 2005 (43)	BNP	230 pg/mL	PC	Japan	52	Composite‖	1 y	64 (12)	63	General ward	<40%	724 (561)	Not applicable; univariate analysis only	4	0	2
Gackowski et al, 2004 (44)	BNP	300 pg/mL	PC	France	95	Composite	60 d	67 (16)	66	Intensive care unit	All	346 (177)	Admission BNP, LVEF, medications, HF etiology	4	2	2
Koitabashi et al, 2005 (45)	BNP	125 pg/mL	RC	Japan	187	Composite‖	33 mo (medial)	63 (14)	62	General ward	All	712 (515)	Not applicable; univariate analysis only	4	0	3
Logeart et al, 2004 (46)	BNP	350 pg/mL	PC	France	109	Composite	6 mo	70 (14)	68	HF unit	All	941 (526)	Age, sex, CKD, LVEF, medications, Afib, DM, HF etiology	4	1	1
Bettencourt et al, 2002 (47)	BNP	321 pg/mL	PC	Portugal	50	Composite	6 mo	71 (14)	44	General ward	All	549 (488)	Not applicable; univariate analysis only	4	0	3
Yu and Sanderson, 1999 (48)	BNP	165 pg/mL	PC	Wales	91	All-cause mortality	1 y	61 (2)	70	General ward	<50%	NA	Age, sex, admission NYHA class, LVEF	4	2	2
Eurlings et al, 2014 (49)	NT-proBNP	2936 pg/mL; 61.8% decrease	RC	The Netherlands	309	All-cause mortality, composite	1 y	72 (12)	57	General ward	All	Median, 7897 (IQR, 4345–14 030)	Age, CKD, HF etiology, MAP	4	1	2

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***Appendix Table 2*–Continued**

Study, Year (Reference)	Intervention	Threshold	Design	Location	Patients, *n*	Outcomes	Median Follow-up†	Mean Age (SD), *y*‡	Men, %	Population	LVEF	Mean BNP Level on Admission (SD), *pg/mL*‡	Adjustment Variables	Newcastle-Ottawa Scale Ratings		
														Selection (Maximum: 4)	Comparability (Maximum: 2)	Outcome (Maximum: 3)
Ho et al, 2011 (50)	NT-proBNP	1875 pg/mL	PC	Taiwan	87	Composite	191 d	73 (14)	79	General ward	All	3997 (4877)	Echo parameters (except LVEF)	4	0	3
Michtalik et al, 2011 (51)	NT-proBNP	50% decrease	PC	Baltimore, Maryland	217	Readmission, composite	1 y	65 (15)	50	General ward	All	Intervention: median, 5599 (IQR, 2217–9556) Control: median, 6087 (IQR, 1394–11 868)	Age, sex, admission NT-proBNP, CKD, LVEF, DM, LOS	4	2	2
Bettencourt et al, 2007 (52)	NT-proBNP	5403 pg/mL; 30% decrease	PC	Portugal	224	Composite	6 mo	72 (11)	48	General ward	All	Median, 6792 (IQR, 2131–13 594)	Age, sex, CKD, medications, Afib, DM, Hb, HF etiology, sodium	4	0	1
Ferreira et al, 2007 (53)	NT-proBNP	3796 pg/mL; 30% decrease	RC	Portugal	304	Composite	6 mo	73 (12)	46	General ward	All	7006 (NA)	Admission NYHA class, CKD, LVEF, medications, Hb	4	2	1
Metra et al, 2007 (54)	NT-proBNP	3000 pg/mL	PC	Italy	116	All-cause mortality, composite	247 d	66 (12)	92	General ward	All	Median, 4421 (IQR, 1621–8536)	Age, sex, admission NYHA class, PCWP, BMI, LVEF, medications, HR, Hb, SBP, sodium	4	2	2
Pimenta et al, 2007 (55)	NT-proBNP	2575 pg/mL; 30% decrease	RC	Portugal	283	Composite	6 mo	Median, 73 (IQR, 61–80)	70	General ward	All	Median, 7512 (IQR, 3431–16 416)	Age, sex, admission NYHA class, LVEF, Hb, SBP, sodium	4	2	1
Kubler et al, 2008 (56)	NT-proBNP	20% decrease	RC	Poland	54	Cardiovascular mortality, composite	1 y	62 (14)	83	General ward	<45%	Intervention: 6604 (12 532) Control: 8052 (7872)	Age, sex, admission NYHA class, CKD, LVEF, medications, DM, HF etiology, HR, SBP, pulmonary edema	4	2	2
Siswanto et al, 2006 (57)	NT-proBNP	8499 pg/mL; 35% decrease	PC	Indonesia	97	All-cause mortality, readmission, composite	6 mo	55 (10)	75	General ward	All	Median, 6113 (IQR, 2127–16 108)	Age, sex, admission NT-proBNP, admission NYHA class, BMI, medications, DM, HL, HTN, SBP	4	1	2
O'Brien et al, 2003 (58)	NT-proBNP	1944 fmol/mol	PC	England	96	All-cause mortality	1 y	Median, 74 (IQR, 46–93)	56	Intensive care unit	All	Median, 5395 (IQR, 14–29 368)	Age, CKD, DM, history of MI, HTN, Killip class	4	1	2

Afib = atrial fibrillation; BMI = body mass index; BNP = brain-type natriuretic peptide; BUN = blood urea nitrogen; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; DM = diabetes mellitus; echo = echocardiographic; Hb = hemoglobin; HF = heart failure; HL = hyperlipidemia; HR = heart rate; HTN = hypertension; IQR = interquartile range; LOS = length of stay; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MI = myocardial infarction; NA = not available; NR = not relevant; NT-proBNP = amino-terminal pro–brain-type natriuretic peptide; NYHA = New York Heart Association; PC = prospective cohort study; PCC = prospective case–control study; PCWP = pulmonary capillary wedge pressure; QES = quasi-experimental study; RC = retrospective cohort study; RCC = retrospective case–control study; RCT = randomized, controlled trial; SBP = systolic blood pressure.

* A total Newcastle-Ottawa Scale rating of 9 stars indicated low risk of bias; all other studies were classified as high risk of bias.

† Except for 30 d, 6 mo, and 1 y.

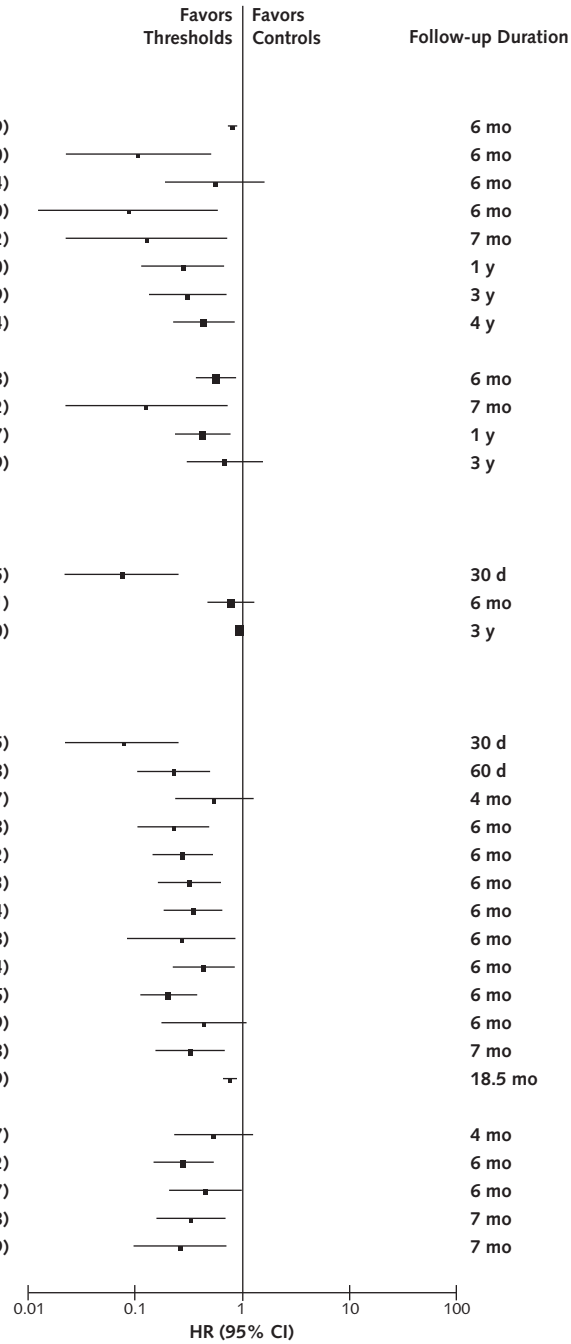
‡ Unless otherwise indicated.

§ Participants were matched according to admission BNP level.

‖ Hazard ratio not reported.

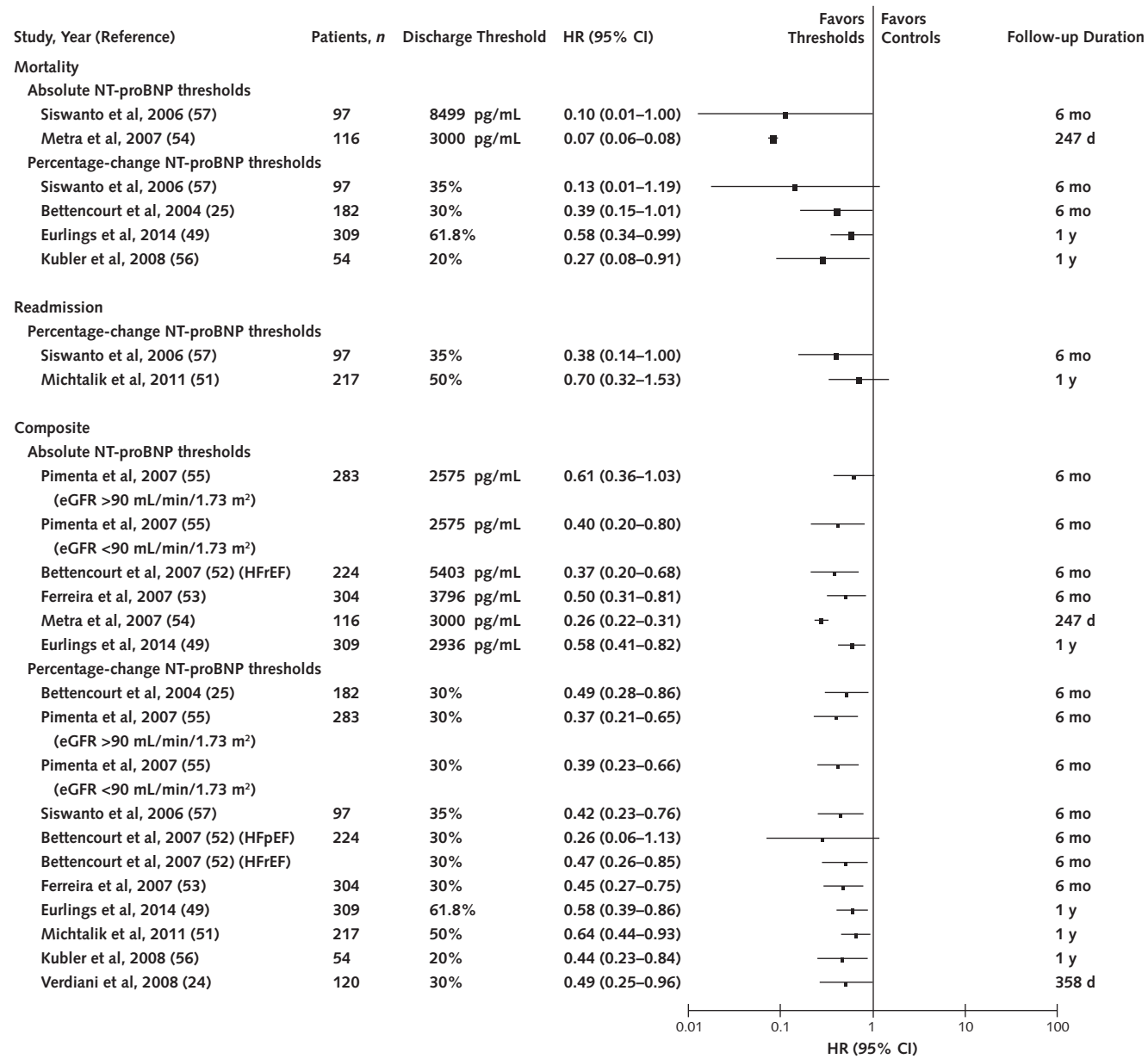
Appendix Figure 2. Risk for outcomes associated with achievement of a BNP discharge threshold, by follow-up duration.

Study, Year (Reference)	Patients, *n*	Discharge Threshold	HR (95% CI)	Follow-up Duration
Mortality				
Absolute BNP thresholds				
Omar and Guglin, 2016 (27)	433	319 pg/mL	0.82 (0.76–0.89)	6 mo
Naffaa et al, 2014 (29)	33	992.6 pg/mL	0.10 (0.02–0.50)	6 mo
Valle et al, 2011 (20)	300	250 pg/mL	0.55 (0.19–1.64)	6 mo
Shah et al, 2007 (22)	111	500 pg/mL	0.08 (0.01–0.60)	6 mo
Cournot et al, 2008 (36)	157	360 pg/mL	0.12 (0.02–0.72)	7 mo
Yu and Sanderson, 1999 (48)	91	165 pg/mL	0.27 (0.11–0.60)	1 y
Ludka et al, 2013 (30)	130	434.5 pg/mL	0.30 (0.13–0.69)	3 y
Ito et al, 2012 (32)	208	200 pg/mL	0.43 (0.22–0.84)	4 y
Percentage-change BNP thresholds				
Lourenço et al, 2015 (59)	224	30%	0.57 (0.37–0.88)	6 mo
Cournot et al, 2008 (36)	157	50%	0.12 (0.02–0.72)	7 mo
Noveanu et al, 2011 (33)	171	30%	0.42 (0.23–0.77)	1 y
Ludka et al, 2013 (30)	130	64%	0.69 (0.30–1.59)	3 y
Readmission				
Absolute BNP thresholds				
Verdiani et al, 2005 (23)	100	696 pg/mL	0.07 (0.02–0.25)	30 d
Valle et al, 2011 (20)	300	250 pg/mL	0.79 (0.48–1.31)	6 mo
Chen et al, 2012 (31)	225	250 pg/mL	0.97 (0.94–1.00)	3 y
Composite				
Absolute BNP thresholds				
Verdiani et al, 2005 (23)	100	696 pg/mL	0.07 (0.02–0.25)	30 d
Gackowski et al, 2004 (44)	95	300 pg/mL	0.22 (0.10–0.48)	60 d
De Vecchis et al, 2013 (60)	72	240 pg/mL	0.54 (0.23–1.27)	4 mo
Faggiano et al, 2010 (35)	150	250 pg/mL	0.22 (0.10–0.48)	6 mo
Valle et al, 2008 (18)	315	250 pg/mL	0.27 (0.14–0.52)	6 mo
Valle et al, 2008 (19)	186	250 pg/mL	0.31 (0.16–0.63)	6 mo
Feola et al, 2008 (37)	250	250 pg/mL	0.34 (0.18–0.64)	6 mo
Aspromonte et al, 2007 (39)	145	200 pg/mL	0.26 (0.08–0.88)	6 mo
Valle et al, 2006 (41)	203	200 pg/mL	0.43 (0.22–0.84)	6 mo
Logeart et al, 2004 (46)	109	350 pg/mL	0.20 (0.11–0.36)	6 mo
Bettencourt et al, 2002 (47)	433	321 pg/mL	0.43 (0.17–1.09)	6 mo
Cournot et al, 2008 (36)	157	360 pg/mL	0.32 (0.15–0.68)	7 mo
Nakada et al, 2016 (26)	748	295 pg/mL	0.78 (0.67–0.89)	18.5 mo
Percentage-change BNP thresholds				
De Vecchis et al, 2013 (60)	72	30%	0.54 (0.23–1.27)	4 mo
Valle et al, 2008 (18)	315	30%	0.27 (0.14–0.52)	6 mo
Ruocco et al, 2016 (28)	107	30%	0.44 (0.20–0.97)	6 mo
Cournot et al, 2008 (36)	157	50%	0.32 (0.15–0.68)	7 mo
Cournot et al, 2007 (40)	61	40%	0.25 (0.09–0.69)	7 mo



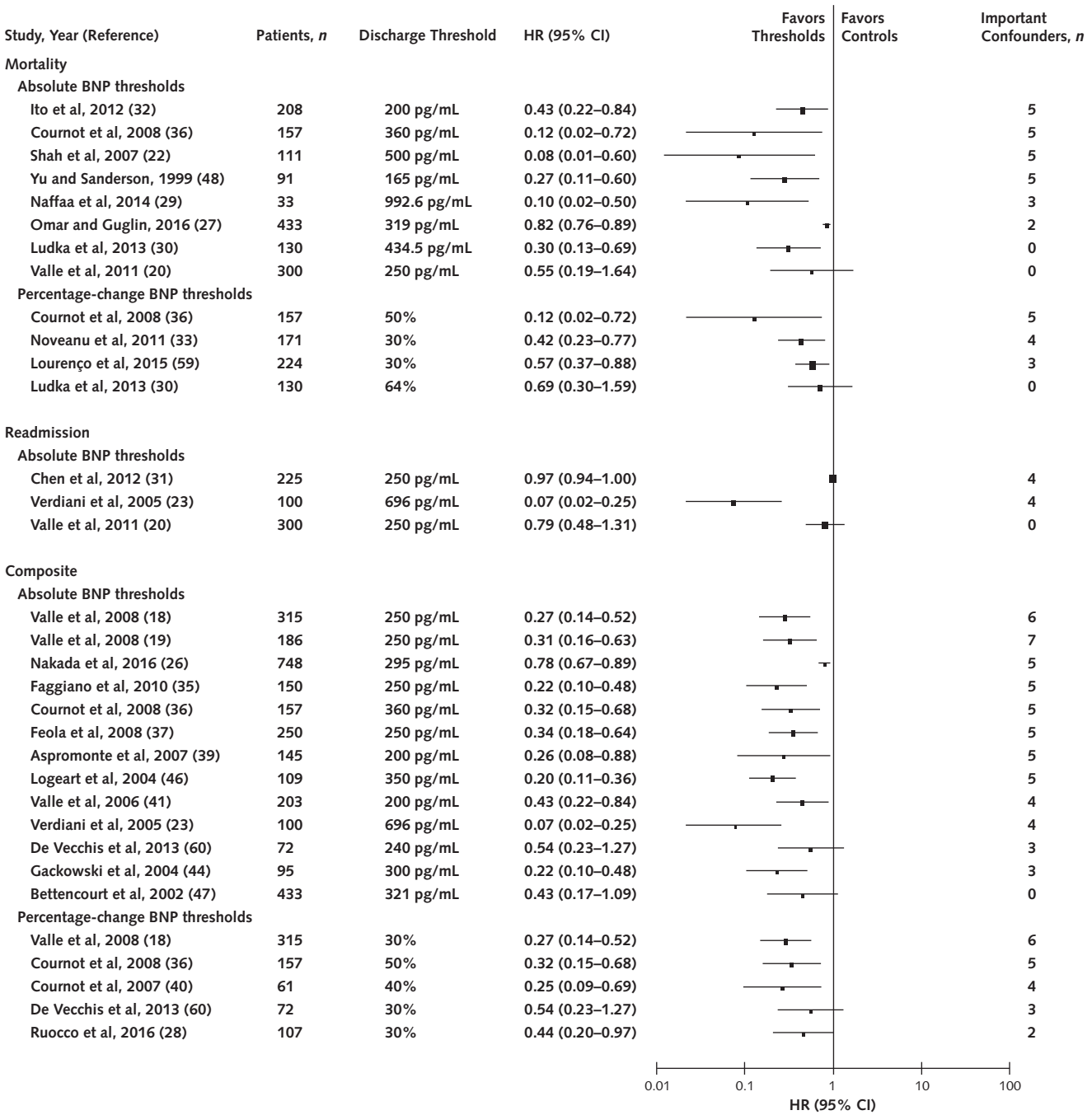
BNP = brain-type natriuretic peptide; HR = hazard ratio.

Appendix Figure 3. Risk for outcomes associated with achievement of an NT-proBNP discharge threshold, by follow-up duration.



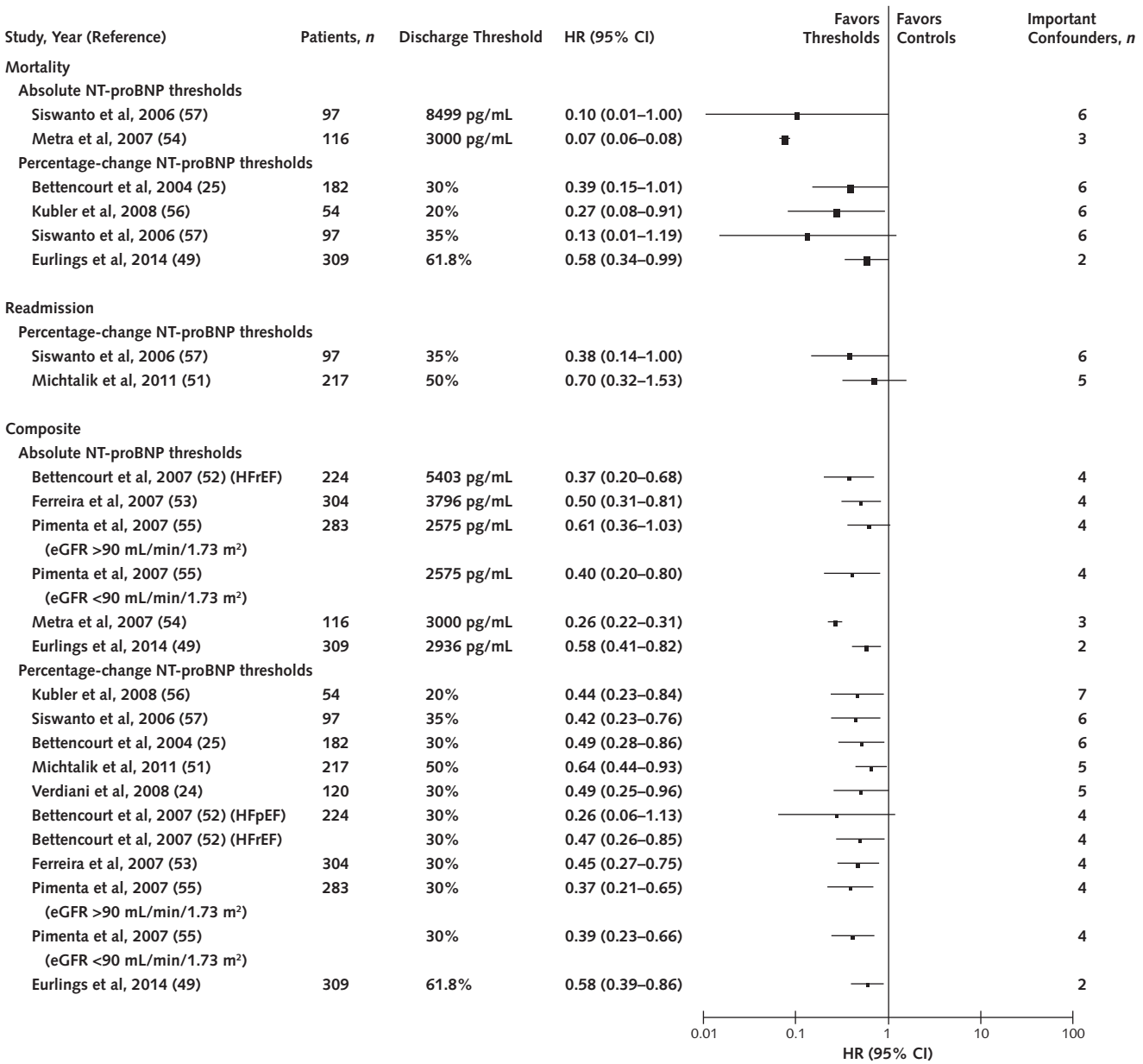
eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; NT-proBNP = amino-terminal pro–brain-type natriuretic peptide.

Appendix Figure 4. Risk for outcomes associated with achievement of a BNP discharge threshold, by the number of important confounders addressed by multivariate analysis.



BNP = brain-type natriuretic peptide; HR = hazard ratio.

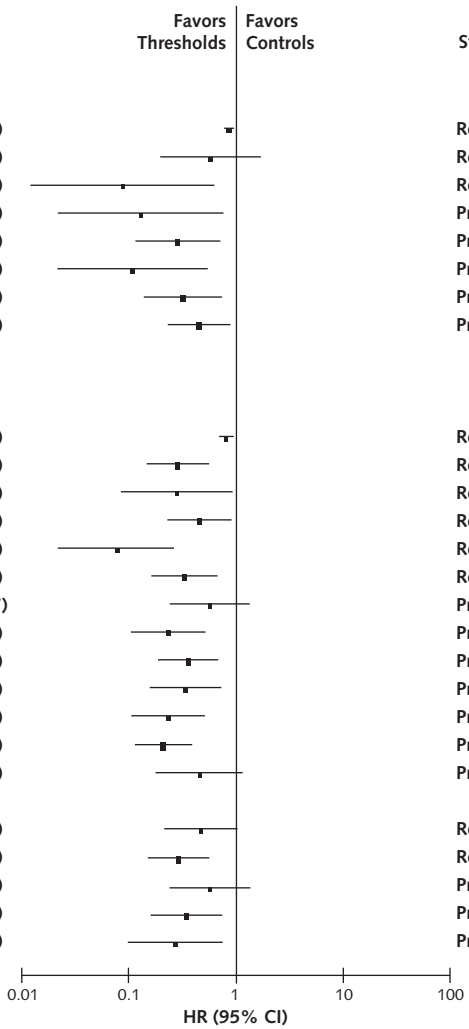
Appendix Figure 5. Risk for outcomes associated with achievement of an NT-proBNP discharge threshold, by the number of important confounders addressed by multivariate analysis.



eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; NT-proBNP = amino-terminal pro–brain-type natriuretic peptide.

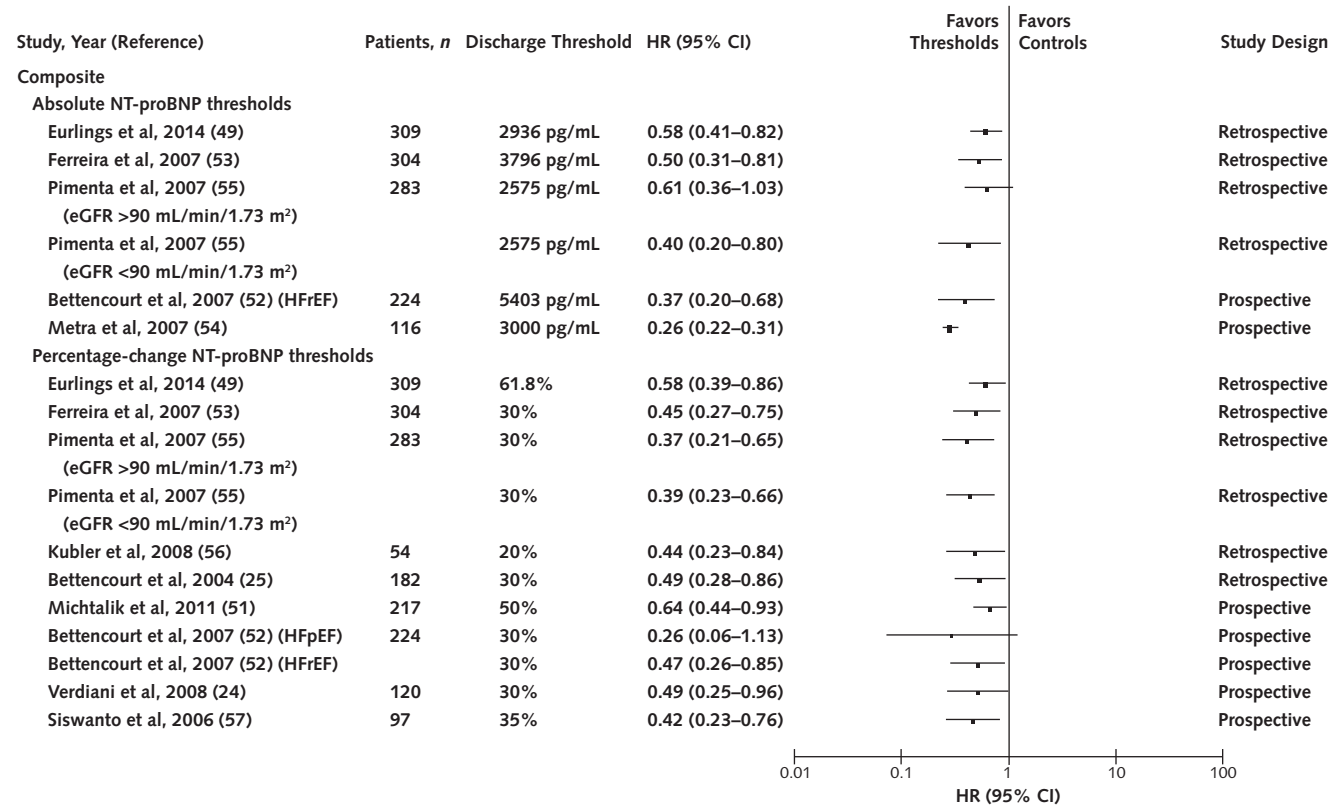
Appendix Figure 6. Risk for outcomes associated with achievement of a BNP discharge threshold, by study design.

Study, Year (Reference)	Patients, *n*	Discharge Threshold	HR (95% CI)	Study Design
Mortality				
Absolute BNP thresholds				
Omar and Guglin, 2016 (27)	433	319 pg/mL	0.82 (0.76–0.89)	Retrospective
Valle et al, 2011 (20)	300	250 pg/mL	0.55 (0.19–1.64)	Retrospective
Shah et al, 2007 (22)	111	500 pg/mL	0.08 (0.01–0.60)	Retrospective
Cournot et al, 2008 (36)	157	360 pg/mL	0.12 (0.02–0.72)	Prospective
Yu and Sanderson, 1999 (48)	91	165 pg/mL	0.27 (0.11–0.60)	Prospective
Naffaa et al, 2014 (29)	33	992.6 pg/mL	0.10 (0.02–0.50)	Prospective
Ludka et al, 2013 (30)	130	434.5 pg/mL	0.30 (0.13–0.69)	Prospective
Ito et al, 2012 (32)	208	200 pg/mL	0.43 (0.22–0.84)	Prospective
Composite				
Absolute BNP thresholds				
Nakada et al, 2016 (26)	748	295 pg/mL	0.78 (0.67–0.89)	Retrospective
Valle et al, 2008 (18)	315	250 pg/mL	0.27 (0.14–0.52)	Retrospective
Aspromonte et al, 2007 (39)	145	200 pg/mL	0.26 (0.08–0.88)	Retrospective
Valle et al, 2006 (41)	203	200 pg/mL	0.43 (0.22–0.84)	Retrospective
Verdiani et al, 2005 (23)	100	696 pg/mL	0.07 (0.02–0.25)	Retrospective
Valle et al, 2008 (19)	186	250 pg/mL	0.31 (0.16–0.63)	Retrospective
De Vecchis et al, 2013 (60)	72	240 pg/mL	0.54 (0.23–1 .27)	Prospective
Faggiano et al, 2010 (35)	150	250 pg/mL	0.22 (0.10–0.48)	Prospective
Feola et al, 2008 (37)	250	250 pg/mL	0.34 (0.18–0.64)	Prospective
Cournot et al, 2008 (36)	157	360 pg/mL	0.32 (0.15–0.68)	Prospective
Gackowski et al, 2004 (44)	95	300 pg/mL	0.22 (0.10–0.48)	Prospective
Logeart et al, 2004 (46)	109	350 pg/mL	0.20 (0.11–0.36)	Prospective
Bettencourt et al, 2002 (47)	433	321 pg/mL	0.43 (0.17–1.09)	Prospective
Percentage-change BNP thresholds				
Ruocco et al, 2016 (28)	107	30%	0.44 (0.20–0.97)	Retrospective
Valle et al, 2008 (18)	315	30%	0.27 (0.14–0.52)	Retrospective
De Vecchis et al, 2013 (60)	72	30%	0.54 (0.23–1.27)	Prospective
Cournot et al, 2008 (36)	157	50%	0.32 (0.15–0.68)	Prospective
Cournot et al, 2007 (40)	61	40%	0.25 (0.09–0.69)	Prospective



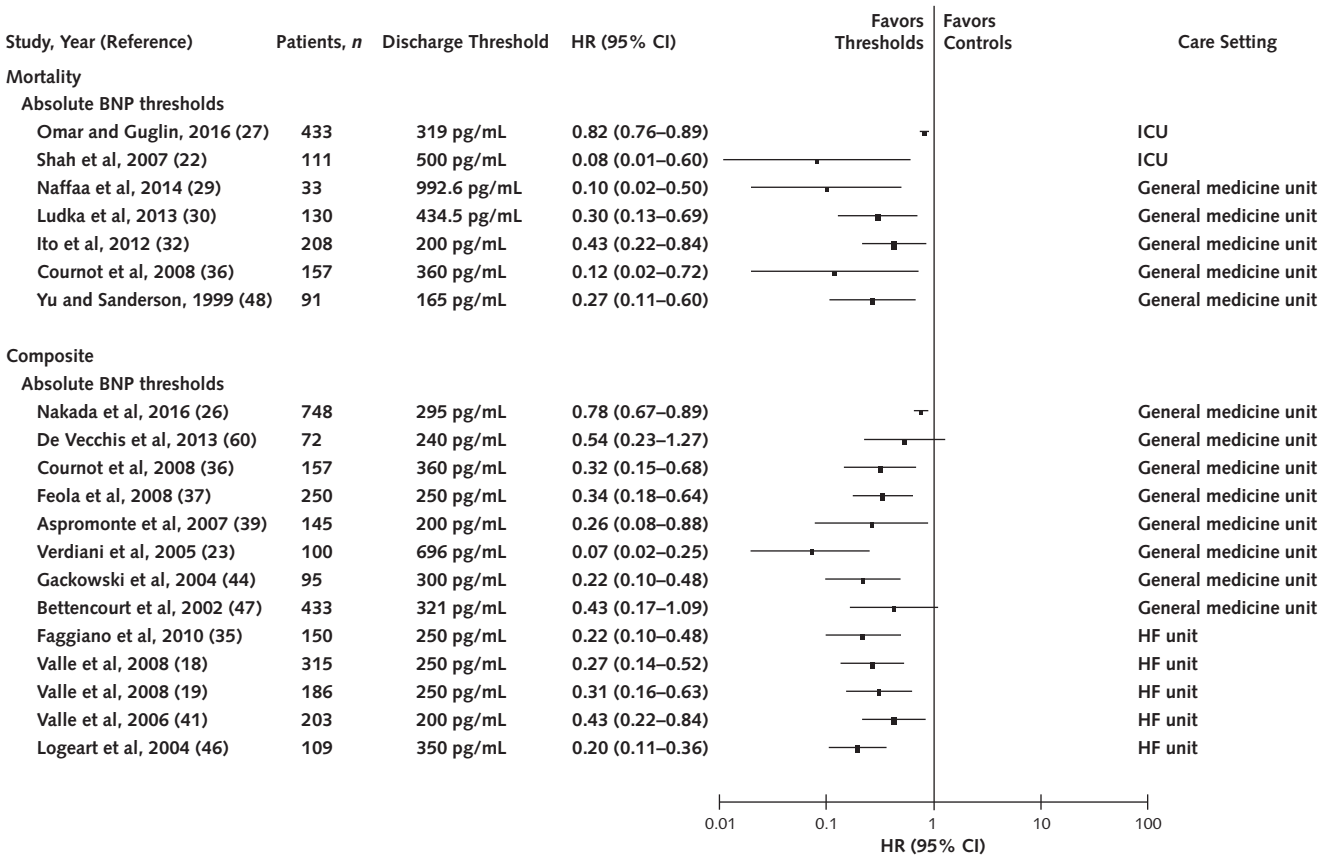
BNP = brain-type natriuretic peptide; HR = hazard ratio.

Appendix Figure 7. Risk for outcomes associated with achievement of an NT-proBNP discharge threshold, by study design.



eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; NT-proBNP = amino-terminal pro–brain-type natriuretic peptide.

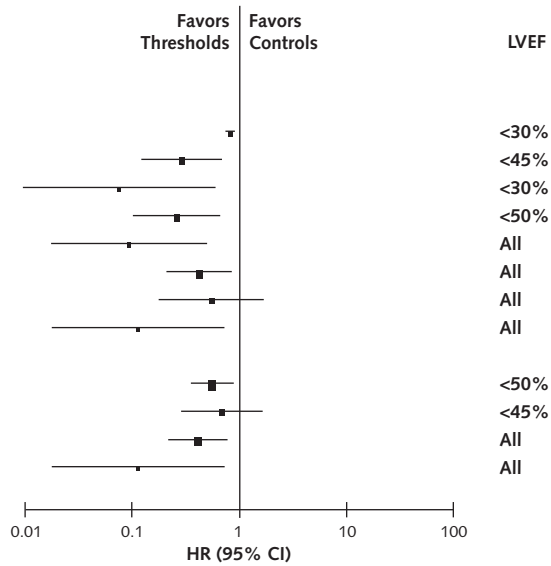
Appendix Figure 8. Risk for outcomes associated with achievement of a BNP discharge threshold, by care setting.



BNP = brain-type natriuretic peptide; HF = heart failure; HR = hazard ratio; ICU = intensive care unit.

Appendix Figure 9. Risk for outcomes associated with achievement of a BNP discharge threshold, by inclusion criteria for LVEF.

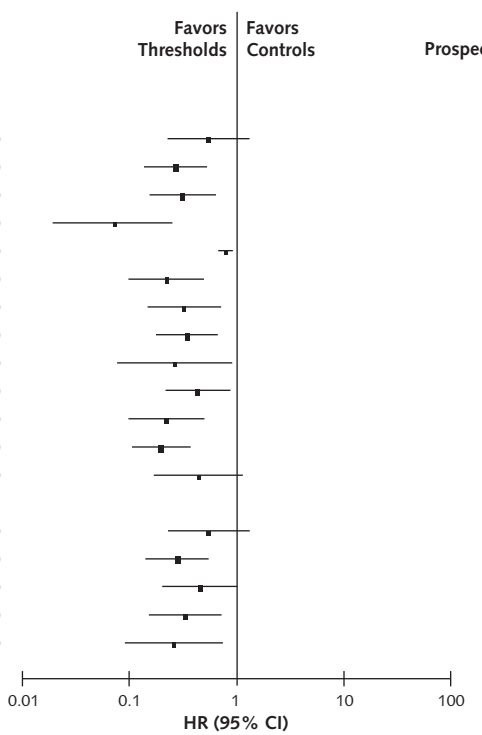
Study, Year (Reference)	Patients, *n*	Discharge Threshold	HR (95% CI)	LVEF
Mortality				
Absolute BNP thresholds				
Omar and Guglin, 2016 (27)	433	319 pg/dL	0.82 (0.76–0.89)	<30%
Ludka et al, 2013 (30)	130	434.5 pg/dL	0.30 (0.13–0.69)	<45%
Shah et al, 2007 (22)	111	500 pg/dL	0.08 (0.01–0.60)	<30%
Yu and Sanderson, 1999 (48)	91	165 pg/dL	0.27 (0.11–0.60)	<50%
Naffaa et al, 2014 (29)	33	992.6 pg/dL	0.10 (0.02–0.50)	All
Ito et al, 2012 (32)	208	200 pg/dL	0.43 (0.22–0.84)	All
Valle et al, 2011 (20)	300	250 pg/dL	0.55 (0.19–1.64)	All
Cournot et al, 2008 (36)	157	360 pg/dL	0.12 (0.02–0.72)	All
Percentage-change BNP thresholds				
Lourenço et al, 2015 (59)	224	30%	0.57 (0.37–0.88)	<50%
Ludka et al, 2013 (30)	130	64%	0.69 (0.30–1.59)	<45%
Noveanu et al, 2011 (33)	171	30%	0.42 (0.23–0.77)	All
Cournot et al, 2008 (36)	157	50%	0.12 (0.02–0.72)	All



BNP = brain-type natriuretic peptide; HR = hazard ratio; LVEF = left ventricular ejection fraction.

Appendix Figure 10. Risk for outcomes associated with achievement of a BNP discharge threshold, by use of thresholds to prospectively make discharge decisions.

Study, Year (Reference)	Patients, *n*	Discharge Threshold	HR (95% CI)	Prospective Decision?
Composite				
Absolute BNP thresholds				
De Vecchis et al, 2013 (60)	72	240 pg/mL	0.54 (0.23–1.27)	Yes
Valle et al, 2008 (18)	315	250 pg/mL	0.27 (0.14–0.52)	Yes
Valle et al, 2008 (19)	186	250 pg/mL	0.31 (0.16–0.63)	Yes
Verdiani et al, 2005 (23)	100	696 pg/mL	0.07 (0.02–0.25)	No
Nakada et al, 2016 (26)	748	295 pg/mL	0.78 (0.67–0.89)	No
Faggiano et al, 2010 (35)	150	250 pg/mL	0.22 (0.10–0.48)	No
Cournot et al, 2008 (36)	157	360 pg/mL	0.32 (0.15–0.68)	No
Feola et al, 2008 (37)	250	250 pg/mL	0.34 (0.18–0.64)	No
Aspromonte et al, 2007 (39)	145	200 pg/mL	0.26 (0.08–0.88)	No
Valle et al, 2006 (41)	203	200 pg/mL	0.43 (0.22–0.84)	No
Gackowski et al, 2004 (44)	95	300 pg/mL	0.22 (0.10–0.48)	No
Logeart et al, 2004 (46)	109	350 pg/mL	0.20 (0.11–0.36)	No
Bettencourt et al, 2002 (47)	433	321 pg/mL	0.43 (0.17–1.09)	No
Percentage-change BNP thresholds				
De Vecchis et al, 2013 (60)	72	30%	0.54 (0.23–1.27)	Yes
Valle et al, 2008 (18)	315	30%	0.27 (0.14–0.52)	Yes
Ruocco et al, 2016 (28)	107	30%	0.44 (0.20–0.97)	No
Cournot et al, 2008 (36)	157	50%	0.32 (0.15–0.68)	No
Cournot et al, 2007 (40)	61	40%	0.25 (0.09–0.69)	No



BNP = brain-type natriuretic peptide; HR = hazard ratio.