Use of Natriuretic Peptide Measurement in the Management of Heart Failure

APPENDICES

APPENDIX A.

Search Strategies

Appendix A. Search Strategies

Medline-OVID
June 25 2012
1. natriuretic peptide, brain/
2. bnp.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. nt-probnp.mp.
4. brain-type natriuretic peptide.mp.
5. bnp1-32.mp.
6. bnp-32.mp.
7. bnp77-108.mp.
8. probnp.mp.
9. nt-probnp1-76.mp.
10. natriuretic factor-32.mp.
11. natriuretic peptide type-b.mp.
12. type-b natriuretic peptide.mp.
13. ventricular natriuretic peptide.mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. limit 14 to english language
16. animals/ not humans/
17. 15 not 16
18. variation.mp.
19. (heart failure or dyspnea or shortness of breath or cardiac failure or systolic failure or diastolic failure or congestive failure or high-output failure or high output failure or low output failure or low-output failure or right-sided failure or right sided failure or left-sided failure or left sided failure or ventricular failure or auricular failure or atrial failure or myocardial failure or cardiac decompensation or heart decompensation or cardiac insufficiency or myocardial insufficiency or CHF or cardiac edema or paroxysmal dyspnea).mp.
20. (general population or unselected or cohort).mp.
21. 18 or 19 or 20
22. 17 and 21

Embase-OVID
June 25 2012
1. Brain Natriuretic Peptide/ct, ec, an, dv [Clinical Trial, Endogenous Compound, Drug Analysis, Drug Development]
2. bnp.tw.
3. nt-probnp.tw.
4. brain-type natriuretic peptide.tw.
5. bnp 1-32.tw.
6. bnp1-32.tw.
7. bnp-32.tw.
8. bnp77-108.tw.
9. bnp 77-108.tw.
10. probnp.tw.

11. nt-probnp1-76.tw.
12. nt-probnp 1-76.tw.
13. natriuretic factor-32.tw.
14. natriuretic peptide type-b.tw.
15. type-b natriuretic peptide.tw.
16. ventricular natriuretic peptide.tw
17. or/1-16
18. human/
19. animal/
20. animal experiment/
21. 19 or 20
22. 18 not 21
23. 17 and 22
24. limit 23 to english language
25. variation.mp.
26. (heart failure or dyspnea or shortness of breath or cardiac failure or systolic failure or diastolic failure or congestive failure or high-output failure or high output failure or low output failure or low-output failure or right-sided failure or right sided failure or left-sided failure or left sided failure or ventricular failure or auricular failure or atrial failure or myocardial failure or cardiac decompensation or heart decompensation or cardiac insufficiency or myocardial insufficiency or CHF or cardiac edema or paroxysmal dyspnea).mp.
27. (general population or unselected or cohort).mp.
28. 25 or 26 or 27
29. 24 and 28
30. limit 29 to "review"
31. 29 not 30

Cochrane-OVID
June 25, 2012
1. Natriuretic Peptide, Brain/me, bi, bl, se, du [Metabolism, Biosynthesis, Blood, Secretion, Diagnostic Use]
2. bnp.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]
3. nt-probnp.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]
4. brain-type natriuretic peptide.tw.
5. bnp1-32.tw.
6. bnp-32.tw.
7. bnp77-108.tw.
8. probnp.tw.
9. nt-probnp1-76.tw.
10. natriuretic factor-32.tw.
11. natriuretic peptide type-b.tw.
12. type-b natriuretic peptide.tw.
13. ventricular natriuretic peptide.tw.
14. or/1-13
15. variation.mp.

16. (heart failure or dyspnea or shortness of breath or cardiac failure or systolic failure or diastolic failure or congestive failure or high-output failure or high output failure or low output failure or low-output failure or right-sided failure or right sided failure or left-sided failure or left sided failure or ventricular failure or auricular failure or atrial failure or myocardial failure or cardiac decompensation or heart decompensation or cardiac insufficiency or myocardial insufficiency or CHF or cardiac edema or paroxysmal dyspnea).mp.
17. (general population or unselected or cohort).mp.
18. 15 or 16 or 17
19. 14 and 18

AMED-OVID
June 25, 2012
1. exp peptides/
2. bnp.tw.
3. nt-probnp.tw.
4. brain-type natriuretic peptide.tw.
5. bnp 1-32.tw.
6. bnp-32.tw.
7. bnp77-108.tw.
8. probnp.tw.
9. nt-probnp1-76.tw.
10. natriuretic factor-32.tw.
11. natriuretic peptide type-b.tw.
12. type-b natriuretic peptide.tw.
13. ventricular natriuretic peptide.tw.
14. or/1-13
15. variation.mp.
16. (heart failure or dyspnea or shortness of breath or cardiac failure or systolic failure or diastolic failure or congestive failure or high-output failure or high output failure or low output failure or low-output failure or right-sided failure or right sided failure or left-sided failure or left sided failure or ventricular failure or auricular failure or atrial failure or myocardial failure or cardiac decompensation or heart decompensation or cardiac insufficiency or myocardial insufficiency or CHF or cardiac edema or paroxysmal dyspnea).mp.
17. (general population or unselected or cohort).mp.
18. 15 or 16 or 17
19. 14 and 18

APPENDIX B.

FDA Cleared Devices

Appendix B. FDA Cleared Devices

Table B-1. Details of FDA approved BNP tests characteristics

Test / Instrument Name	Company Name	510(k) Number
Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA)	Axis-Shield Diagnostics	k033606
ADVIA Centaur® B -Type Natriuretic Peptide (BNP) Assay	Bayer HealthCare LLC	k031038
Bayer Diagnostics ADVIA® Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay	Bayer HealthCare LLC	k043228 k040425
B-type Natriuretic Peptide (BNP) Assay for the ADVIA IMS	Bayer HealthCare LLC	k051265
Triage® B-Type Natriuretic Peptide (BNP) Test	Biosite Incorporated	k051787 k032235 k021317 k010266 k003475
Triage® B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems	Biosite Incorporated	k052789 k033383
Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method	Dade Behring, Inc.	k071767 k042347 k041417
ARCHITECT BNP Reagent Kit	Fujirebio Diagnostics, Inc.	k060964
i-STAT BNP test	i-STAT Corporation	k053597
StatusFirst™ CHF NT-proBNP	Nanogen, Inc.	k051596
Triage® CardioProfilER® Panel	Biosite Incorporated	k080269 k030286
Triage® Profiler S.O.B. ™ (Shortness of Breath Panel)	Biosite Incorporated	k080269 k042723 k040437

Table B-2. Details of FDA approved NT-proBNP tests characteristics

Test / Instrument Name	Company Name	510(k) Number
VIDAS® NT-proBNP	bioMerieux, Inc	k073091
Dimension® Vista™ NT-proBNP (PBNP) Flex® reagent cartridge method (K6423)	Dade Behring, Inc.	k061795
Stratus CS® Acute Care™ NT-proBNP (pBNP) TestPak assay	Dade Behring, Inc.	k071834 k060548 k043476
PATHFAST NTproBNP test	Mitsubishi Kagaku Iatron Inc. c/o Polymedco Inc.	k072189
VITROS Immunodiagnostic NT-proBNP Reagent Pack	Ortho-Clinical Diagnostics, Inc.	k060632
RAMP NT-proBNP Assay	Response Biomedical Corporation	k063662
Elecsys® proBNP II Immunoassay	Roche Diagnostics Corporation	k072437
Elecsys® proBNP II STAT Immunoassay	Roche Diagnostics Corporation	k092649
Elecsys® proBNP Immunoassay	Roche Diagnostics Corporation	k051382 k032646 k022516
Dimension® EXLTm N-termninal Pro-Brain Natriuretic Peptide (NTP) Flex® Reagent Cartridge (RF623)	Siemens Healthcare Diagnostics Inc.	k082645
Dimension Vista® N-terminal Pro-Brain Natriuretic Peptide (PBNP) Flex® Reagent Cartridge (K6423A)	Siemens Healthcare Diagnostics, Inc.	k080578

APPENDIX C.

Study Selection and Criteria Forms

Appendix C. Study Selection and Criteria Forms

Title & Abstract level 1

1. Does citation evaluate BNP in any way? (using any related term: BNP, NTproBNP, proBNP, BNP77-108, nt-proBNP1-76, brain type natriuretic peptide, natriuretic factor, natriuretic peptide type-b, type-b natriuretic peptide, ventricular natriuretic peptide B-type)
Yes
No

Title & Abstract level 2

1. Is this study published in English?
Yes (unsure)
No (stop)
2. Does this study involve humans aged 18 years or older?
Yes/unsure
No (non-human) (Stop)
No (under 18 years) (stop)
3. Does this report describe a primary study?
Yes (unsure)
No (stop)
No, systematic review (stop)
4. Is this a case report n=1?
Yes (stop)
No/unsure (submit)

Title & Abstract level 3 - keyword screen

1. Does this citation contain the word "variation"?
Yes
No

2. Does this citation contain any of the following words "heart failure" OR "dyspnea" OR "shortness of breath" OR "cardiac failure" OR "systolic failure" OR "diastolic failure" OR "congestive failure" OR "high-output failure" OR "high output failure" OR "low-output failure" OR "low output failure" OR "right-sided failure" OR "right sided failure" OR "left-sided failure" OR "left sided failure" OR "ventricular failure" OR "auricular failure" OR "atrial failure" OR "myocardial failure" OR "cardiac decompensation" OR "heart decompensation" OR “cardiac insufficiency” OR “myocardial insufficiency” OR CHF OR "cardiac edema" OR "paroxysmal dyspnea"?
Yes
No

3. Does this citation contain any of the following words: "general population" or "unselected" or "cohort"?
Yes
No

4. Does NOT contain any of the words above
Exclude

Full Text Screen Level 4

1. Is this paper available for viewing?
Yes **No, please gives reasons**
2. Is this study published in English?
Yes
No (stop)
3. Does this study involve humans aged 18 years or older?
Yes
No(non-human)(Stop)
No (under 18 years only)(stop)
4. Does this report describe a primary study?
Yes
No (stop)
No, systematic review (stop)
5. Is this a case report or case series?
Yes case report (n=1) (stop)
Yes, case series (specify number of subjects(s))
No (continue)
6. Was BNP or NT-proBNP measured in serum, plasma or whole blood using an FDA approved method? (please consult FDA approved list)
Yes
No (stop)
Unsure (to be viewed by principal investigators) (continue, and please give reasons for uncertainty)
Note: The following questions (7, 8, 9, 10, & 11) will determine inclusion/exclusion of this article and the Key Question(s) it will be assigned to.
7. Does this study report test accuracy data for the diagnosis of heart failure? *Look for terms such as: sensitivity/specificity, +/- predictive value, ROC curves, likelihood ratios, and test accuracy.*
Yes, in Emergency Department /Urgent Care setting
Yes, in Primary Care setting
Yes, reports diagnostic accuracy but not one of the above populations
No, not a diagnostic study

8. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome? *Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.*
Yes, in a heart failure population
Yes, in general population not selected for disease
Yes, prognosis but not any of the above populations
No, not a prognosis study
9. Is this an RCT comparing treatment guided by BNP or NT-proBNP to usual care?
Yes, in an outpatient setting (patients with chronic HP)
Yes, but in other setting
No, not a therapy study
10. Is biological variation of BNP or NT-proBNP reported? *Look for terms such as biological variation, intra-individual variation, and inter-individual variation used to describe this data.*
Yes **No**
11. Does this study have ALL of the following options ticked: 7c *or* **7d, 8c** *or 8***d, 9c, and 10b (options in CAPS above)?**
Yes No

KQ 1 & 2 Investigators Screening

1. Which location did the study take place?
Emergency Department or Urgent Care Settings or Both
Primary Care Setting (i.e. community or family practice or equivalent)
Both Primary Care setting and Emergency Department/Urgent Care settings (STOP)
None of the above (STOP)
Unclear (continue)
2. Did patients have prior diagnosis of HF?
(Note: We are excluding subject with already known diagnosis of heart failure, which includes acute HF or known exacerbation of stable chronic HF.)
No/ Unclear (continue)
Yes (STOP)
3. Did the study only include patients with one or more of the following conditions: Heart Transplant, Hypertrophic Cardiomyopathy, and Valvular Lesions?
No/ Unclear (continue)
Yes (STOP)
4. Did the study describe patients who are recruited as having signs and symptoms suggestive of HF or at risk of HF?
(Note: only including studies that recruit patients who arrive to emergency or urgent care department with signs or symptoms consistent with HF, and excluding studies that recruit patients already diagnosed with acute HF or known exacerbation of stable chronic HF.)
Yes/ Unclear (continue)
No (STOP)
5. Was this a case report or a case series study?
No/Unclear (continue)

Yes (STOP)

6. Does this study report test accuracy data for the diagnosis of heart failure? Look for terms such as: sensitivity/specificity, +/- predictive value, ROC curves, likelihood ratios, and test accuracy.

Yes/ Unclear (continue)

No (STOP)

7. Does this paper belong in the Diagnosis section?

Yes (continue)

No, not a diagnosis study

Reports diagnostic accuracy but not one of the above populations

Unsure (to be viewed by another investigator)

8. What type of study is this? *Only complete this question if you have answered "Yes (continue)" to question # 7.

Diagnosis and RCT

Diagnosis and Case Control

Diagnosis and Cohort

Diagnosis and Cross-Sectional Design

Not a diagnosis study

Unclear

9. (OPTIONAL) Would you recommend this paper be considered for another section?

No

Yes (which one?)

10. (OPTIONAL) Comments:

KQ 3 & 4 Investigators Screening

1. Which location did the study take place?

Outpatient Clinic or Ambulatory Care or Family Practice

Admitted to hospital

None of the above (STOP)

Unclear (continue)

2. Were participants patients with Heart Failure (HF), with or without co-morbidities?

Yes/ Unclear (continue)

No (STOP)

3. Is this study an RCT/CCT, cohort, before-after or time series?

Yes/ Unclear (continue)

No (STOP)

4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome?

Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.

Yes/ Unclear (continue)

No (STOP)

5. Does this paper belong in the Prognosis section?

Yes (continue)

No, not a prognosis study
Prognosis, but not any of the above populations for KQ3,4; does not have the outcome of interest
Unsure (to be viewed by another investigator)

6. What type of study is this?
***Only complete this question if you have answered "Yes (continue)" to question # 5.**
Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design
Not a prognosis study
Unclear
7. (OPTIONAL) Would you recommend this paper to another section?
No
Yes (which one?)
8. (OPTIONAL) Comments:

KQ 5 Investigators Screening

1. Is the study population drawn from the general population? (e.g. community-based, primary care, family practice, or equivalent)
Yes/ Unclear (continue)
No (stop)
2. Did this study use a specific disease to include or exclude subjects *(i.e. acute coronary syndrome (ACS), CAD, Diabetes, Renal Failure, etc.)*? *(Note: We are only looking for studies that recruit the general population (i.e. population with a mixture of conditions), not a population with a specific disease as inclusion or exclusion criteria).*
No/ Unclear (continue)
Yes (stop)
3. Is the study an RCT/CCT, cohort, before-after or time series?
Yes
No (stop)
Unclear (continue)
4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome?
Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.
Yes/ Unclear (continue)
No (stop)
5. Does this paper belong in the Prognosis section?
Yes (continue)
No, not a prognosis study at all
Prognosis, but not any of the above populations for KQ5; does not have the outcome of interest
Unsure (to be viewed by another investigator)

6. What type of study is this? *Only complete this question if you have answered "Yes (continue)" to question # 5.
Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design
Not a prognosis study
Unclear
7. (OPTIONAL) Would you recommend this paper for consideration in another section?
No Yes (which one?)
8. (OPTIONAL) Comments:

KQ 6 Investigators Screening

1. Are the study patients being treated for chronic HF (exclude if patients are admitted or are known HF patients with acute HF)?
Yes, patients are treated for chronic HF
No (EXCLUDE)(STOP)
2. Was this an RCT where medical therapy was based on BNP/NT-proBNP OR usual care for HF patients (there is no restriction on usual care; only needs to be defined)?
Yes, RCT
No (EXCLUDE)

KQ 7 Investigators Screening

1. Does this study report biological variation data?
Yes
No

KQ 1B & 2B Investigators Screening

1. Which location did the study take place?
Emergency Department or Urgent Care Settings or Both
Primary Care Setting (i.e. community or family practice or equivalent)
Both Primary Care setting and Emergency Department/Urgent Care settings (STOP)
None of the above (STOP)
Unclear (continue)
2. Did patients have prior diagnosis of HF? (Note: We are excluding subject with already known diagnosis of heart failure, which includes acute HF or known exacerbation of stable chronic HF.)
No/ Unclear (continue)
Yes (STOP)
3. Did the study only include patients with one or more of the following conditions: Heart Transplant, Hypertrophic Cardiomyopathy, and Valvular Lesions?
No/ Unclear (continue)

Yes (STOP)

4. Did the study describe patients who are recruited as having signs and symptoms suggestive of HF or at risk of HF? (Note: We are only including studies that recruit patients who arrive to emergency or urgent care department with signs or symptoms consistent with HF, and excluding studies that recruit patients already diagnosed with acute HF or known exacerbation of stable chronic HF.)

Yes/ Unclear (continue)

No (STOP)

5. Was this a case report or a case series study?

No/ Unclear (continue)

Yes (STOP)

6. Does this study report test accuracy data for the diagnosis of heart failure? Look for terms such as: sensitivity/specificity, +/- predictive value, ROC curves, likelihood ratios, and test accuracy.

Yes/ Unclear (continue)

No (STOP)

7. Does this paper belong in the Diagnosis section?

Yes (continue)

No, not a diagnosis study

Reports diagnostic accuracy but not one of the above populations

8. What type of study is this? *Only complete this question if you have answered "Yes (continue)" to question # 7.

Diagnosis and RCT

Diagnosis and Case Control

Diagnosis and Cohort

Diagnosis and Cross-Sectional Design

Not a Diagnosis study

Unclear

9. (OPTIONAL) Would you recommend this paper to another section?

No

Yes (which one?)

10. (OPTIONAL) Comments:

KQ 3B & 4B Investigators Screening

1. Which location did the study take place?

Outpatient Clinic or Ambulatory Care or Family Practice

Admitted to hospital

None of the above (STOP)

2. Were participants patients with Heart Failure (HF), with or without co-morbidities?

Yes

No (STOP)

3. Is this study an RCT/CCT, cohort, before-after or time series?

Yes

No (STOP)

4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome? (Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.)
Yes
No (STOP)
5. Does this paper belong in the Prognosis section?
Yes (continue)
No, not a prognosis study (STOP)
Prognosis but not any of the above populations (STOP)
6. What type of study is this? (*Only complete this question if you have answered "Yes (continue)" to question # 5.
Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design
7. (OPTIONAL) Would you recommend this paper to another section?
No
Yes (which one?)
8. (OPTIONAL) Comments:

KQ 5B Investigators Screening

1. Is the study population drawn from the general population? (e.g. community-based, primary care, family practice, or equivalent)
Yes/ Unclear (continue)
No (STOP)
2. Did this study use a specific disease to include or exclude subjects (i.e. acute coronary syndrome (ACS), CAD, Diabetes, Renal Failure, etc.)? *(Note: We are only looking for studies that recruit the general population (i.e. population with a mixture of conditions), not a population with a specific disease as inclusion or exclusion criteria).*
No/ Unclear (continue)
Yes (STOP)
3. Is the study an RCT/CCT, cohort, before-after or time series?
Yes/ Unclear (continue)
No (STOP)
4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome? (Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.)
Yes/ Unclear (continue)
No (STOP)
5. Does this paper belong in the Prognosis section?
Yes (continue)
No, not a prognosis study
Prognosis but not any of the above populations
6. What type of study is this?
***Only complete this question if you have answered "Yes (continue)" to question # 5.**

Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design
Not a prognosis study
Unclear

7. (OPTIONAL) Would you recommend this paper to another section?

No
Yes (which one?)

8. (OPTIONAL) Comments:

APPENDIX D.

Data Extraction Forms

Appendix D. Extraction Forms

General Data Extraction Form

1. Which peptide was assessed?

- e.g. BNP
- e.g. NT-proBNP
- e.g. Both

2. In what country was the study conducted or administrated?
Please specify the country where the study was conducted. Note that in some papers only the city/province will be reported, e.g. Copenhagen. In such case, please choose "Others" and report the city's name. For countries not listed in the drop-down option, please choose "Others" and specify.

3. What was the study type?
Please specify study type. Note that the provided list may not contain all the study types, but these are the most common. You may also refer to "Study Design Descriptions" for definition.

4. What is the total number of patients included in the study?
Please report all that apply.

Total # enrolled (n) = *Total number of subjects who meet the inclusion criteria of the study/randomized.*

Total treatment (n) (e.g. "n" of index group) = *Total number of patients in each group who are randomized into the BNP/NT-proBNP or clinical intervention.*

Total control (n) (e.g. "n" of reference group) = *Total number of patient who are receiving receiving usual care/standard care/clinical group.*

- Example = 500 patients are enrolled in the study, but only 450 meets the inclusion criteria. After randomization, 225 receives BNP-guided treatment, while 225 receives usual-care. Therefore:

  Total # enrolled (n) = 450
  Total treatment (n) (e.g. "n" of index group) = 225
  Total control (n) (e.g. "n" of reference group) = 225

5. Please report the AGE CHARACTERISTICS for:
Please record as reported.

6. Please report the AGE GROUPS, if applicable:
If the study reported the group age as, e.g. ≤50 yrs or ≥50yrs, please report the sign as <=50 yrs or >=50 yrs.

7. Please report GENDER:
Please record as reported.

8. Please report Race/Ethnicity:
Please record as reported.

9. Please describe the population included in the study:
Please record as reported the population characteristics.

10. Please describe the following outcomes/end-points:

Primary outcome/end-points: *The primary outcome that is measured to see if a given treatment worked (e.g., the number of all-cause mortality, number of hospitalization).*

Secondary outcome/end-points: *Other outcomes reported in the study.*

11. What other medical conditions (co-morbidities) did the patients have? (Check and record all that apply)
Please record as reported.

12. Which test was used to measure BNP or/and NT-proBNP
Please record as reported.

13. List and report (n,%) the adverse events associated with BNP/NT-proBNP testing reported?
Please record as reported. E.g. Hypotension, renal failure, etc.

<u>Key Question: 1 & 2 Data Extraction Form</u>

RefID:

Author:
Please record first author's last name and the year of the publication.

Setting:
- Emergency Department/Urgent Care
- Primary Care (community/family practice or equivalent)

Test
Please specify either BNP or NT-proBNP or both that was tested, and specify unit(s) (e.g. pg/ml; pmol/l).
- BNP
- NT-proBNP

Prevalence
Please report % of prevalence.
(Definition of Prevalence: The proportion of people in a defined group who have a disease, condition or injury. In the context of diagnosis, this is also called "pre-test probability.")

Mean BNP/NT-proBNP
Provide mean of BNP/NT-proBNP and corresponding SD (in brackets) for study samples; Specify units (pg/ml, pmol/l)

Decision Cut Point
For studies that report decision cut points, provide all the cut points in this column with the units (pg/ml, pmol/l). Remember to report all corresponding test performance measures (sens, spec, etc.) in their appropriate columns.

Population
Report all population characteristics: Comorbidities, Age Categories, Gender, and Race Groups. If studies provided results of test performances by these populations (commorbidities, age categories, gender, and race groups), remember to report all test performance measures in their appropriate column).
- Overall
- Age categories (e.g. age>50, age<50)
- Gender (Female/Male)
- Comorbidities (e.g. Non-Dysponea/Dysponea/Diabetes/)

- Race/ethnicity (e.g. White/Hispanic/Caucasian/Asians)

Sens (sensitivity)
Please express sensitivity in proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).

Confidence level
Where reported, specify level of confidence (e.g. 95%, 90%)

Sens.lower/upper (sensitivity lower/upper)
Please express sensitivity's confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).

Spec. (specificity)
Please express specificity as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)

Spec. lower/upper (specificity lower/upper)
Please express specificity confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)

PLR (positive likelihood ratio) *Please record as reported.*

Plr.lower/upper (lower/upper confidence interval for positive likelihood ratio)
Please record as reported.

Negative LR (negative likelihood ratio) *Please record as reported.*

Nlr.lower/upper (lower/upper confidence interval for negative likelihood ratio)
Please record as reported.

TP (true positive) *Please record as reported.*

FP (false positive) *Please record as reported.*

FN (false positive) *Please record as reported.*

TN (true negative) *Please record as reported.*

n (sample size for study) *Please record as reported.*

PPV (positive predictive value) *Please record as reported.*
PPV lower(Positive predictive value lower confidence interval *Please record as reported.*

PPV Upper (Positive predictive value upper confidence interval *Please record as reported.*

NPV (negative predictive value) *Please record as reported.*

NPV lower(Negative predictive value lower confidence interval *Please record as reported.*

NPV Upper (Negative predictive value upper confidence interval *Please record as reported.*

Diagnostic Accuracy *Please record as reported*

AUC (area under the curve) *Please record as reported.*

AUC lower(Area under curve lower confidence interval *Please record as reported.*

AUC upper(Area under curve upper confidence interval *Please record as reported.*

Pre-test Probability *Please record as reported.*
(Definition of Pre-test Probability: The proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence).)

Pre-test Odds *Please record as reported.*
(Definition of Pre-test Odds: The odds that the patient has the target disorder before the test is carried out.)

Post-test Probability *Please record as reported.*
(Definition of Post-test Probability: The proportion of patients with that particular test result who have the target disorder.)

Post-test Odds *Please record as reported.*
(Definition of Post-test Odds: The odds that the patient has the target disorder after the test is carried out.)

<u>Key Question: 3, 4, & 5 Data Extraction Form</u>

RefID:

Screener: *Please record your name.*

Author, Year: *Please record first author's last name and the year of the publication.*

Setting:

- Hospital
- Outpatient Clinic/Ambulatory care
- Family practice

Study Design *Please refer to* ***Study Design Descriptions*** *if needed.*

- Randomized Controlled Trials (RCTs)
- Controlled Clinical Trials (CCTs)
- Cohort
- Before/After/Time-series

n (overall sample size for study and specific populations) *Please record as reported.*

Population

Report all population characteristics: Comorbidities, Age Categories, Gender, Race Groups, Population Sub-types, BNP cut-points, and Prognostic Tools used. If studies provided results or information of outcomes, time-points, admissions/discharge/change, statistical measures (e.g. HR, OR), etc. for specific populations, please remember to report all in their appropriate column).

- Overall
- Age categories (e.g. age>50, age<50)
- Gender (Female/Male)
- Comorbidities (e.g. Non-Dysponea/Dysponea/Diabetes/)
- Race/ethnicity (e.g. White/Hispanic/Caucasian/Asians)
- Population Sub-types Types (e.g. survivors/non-survivors, with/without readmission or death, acute/chronic or chronic with acute, etc.)
- BNP/NT-proBNP cut-points (e.g. BNP >= 541, BNP < 541)
- Prognostic measures (e.g. NYHA, ejection fraction, electrocardiographic measures, etc.).
- Doubling of NT-proBNP
- Quintile 1
- Quintile 2
- Tertile 1

***Please note that population characteristics will vary across studies. Please capture all that is reported. The above list is only an example.**

Specify Population Units
Specify units (pg/ml, pmol/l) for corresponding population characteristics.

Sub-population
Utilize this column for sub-population descriptions. For instance, if study tested a group of survivors (population) within a BNP level or >=541 (sub-population).

- Age categories (e.g. age>50, age<50)
- Gender (Female/Male)
- Comorbidities (e.g. Non-Dysponea/Dysponea/Diabetes/)
- Race/ethnicity (e.g. White/Hispanic/Caucasian/Asians)
- Population Sub-types Types (e.g. survivors/non-survivors, with/without readmission or death, acute/chronic or chronic with acute, etc.)
- BNP/NT-proBNP cut-points (e.g. BNP >= 541, BNP < 541)
- Prognostic Tools (e.g. NYHA, ejection fraction, electrocardiographic measures, etc.).

*__Please note that population characteristics will vary across studies. Please capture all that is reported. The above list is only an example.__

Kaplan-Meier
Please specify if the number of events and timepoints of outcome assessments were extracted from Kaplan-Meier Curve. Please record a "Yes" or "No."

Timepoint of Outcome Assessments
Report all the different times of outcome assessments (e.g. 6 months, during hospital stay). Time of assessments will differ across studies, could be days, weeks, months or years.

Outcome Type
Please report all types of outcomes.

- All-Cause Mortality
- Heart Failure Mortality
- All-Cause Hospitalization
- Number of Hospitalization
- Heart Failure Hospitalization
- Planned Hospitalization
- Unplanned Hospitalization

# of Events *Please record number of events according to the outcomes, as reported in Outcome Type column.*

 # at Risk *Please record number of risk according to the total number of patients in each group.*

BNP/NT-proBNP Admission Levels (Mean)

Report all Mean levels of BNP/NT-proBNP during Admission.

BNP/NT-proBNP Admission Levels (SD) *Please also specify standard deviations of admission levels.*

BNP/NT-proBNP Admission Levels (Median) *Please also specify the median of admission levels.*

BNP/NT-proBNP Admission Levels (IQR) *Please also specify the interquartile range of admission levels.*

BNP/NT-proBNP Discharge Levels (Mean) *Report all Mean levels of BNP/NT-proBNP during Discharge.*

BNP/NT-proBNP Discharge Levels (SD) *Please also specify standard deviations of Discharge levels.*

BNP/NT-proBNP Discharge Levels (Median) *Report all Median levels of BNP/NT-proBNP during Discharge.*

BNP/NT-proBNP Discharge Levels (IQR) *Report all interquartile range of BNP/NT-proBNP during Discharge.*

BNP/NT-proBNP Change (Mean) *If provided, please report the Mean change of BNP/NT-proBNP.*

BNP/NT-proBNP Change (SD) *Please also specify standard deviations of change in BNP/NT-proBNP levels.*

BNP/NT-proBNP Change (Median) *Please also specify the median of change in BNP/NT-proBNP levels.*

BNP/NT-proBNP Change (IQR) *Please also specify interquartile range of change in BNP/NT-proBNP levels.*

Specify BNP/NT-proBNP Units *Specify units (pg/ml, pmol/l) for corresponding BNP/NT-proBNP Levels.*

Confidence Level (%) *Where reported, specify level of confidence (e.g. 95%, 90%)*
Model Used *Specify type of statistical model used. e.g. cox proportional, logistic regression*

Adjusted/Unadjusted *Please report whether the model used was adjusted or unadjusted.*
Covariates in the Model, if Adjusted *If model is adjusted, please report the variable that were adjusted for. E.g. Age, Gender, LVEF, BNP cutpoint, etc.*

HR (Hazard Ratio) *Please record as reported.*

HR LCI/UCI (lower/upper confidence interval for hazard ratio) *Please record as reported.*

RR (Risk Ratio/Relative Risk) *Please record as reported.*

RR LCI/UCI (lower/upper confidence interval for risk ratio) *Please record as reported.*

OR (Odds Ratio) *Please record as reported.*

OR LCI/UCI (lower/upper confidence interval for odds ratio) *Please record as reported.*

Positive LR (positive likelihood ratio) *Please record as reported.*

Positive LR.lower/upper (lower/upper confidence interval for positive likelihood ratio) *Please record as reported.*

Negative LR (negative likelihood ratio) *Please record as reported.*

Negative LR.lower/upper (lower/upper confidence interval for negative likelihood ratio) *Please record as reported.*

Sensitivity *Please express sensitivity in proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).*

Sens.lower/upper (sensitivity lower/upper) *Please express sensitivity's confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).*

Specificity *Please express specificity as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)*
Spec. lower/upper (specificity lower/upper) *Please express specificity confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)*

AUC (Area under the curve) *Please record as a proportion.*

Any Comments *Please use this column for any comments.*

APPENDIX E.

Assessment of Risk of Bias

Appendix E. Assessment of Risk of Bias

Assessment of Risk of Bias: Prognosis Studies

Risk of bias of prognosis studies was assessed using a modified version of the guidelines proposed by Hayden, et al.

To enhance the appropriateness of Hayden's guidelines to this review, several modifications were made to the guidelines prior to commencing the assessment of risk of bias. We modified the tool by adding a seventh area of bias (i.e., study design) for which we asked whether the included studies were designed to test the prognostic value of BNP or NT-proBNP (the studies were not secondary analyses of data collected for other purposes).

The tool was further modified by the revising or adding several domains to the areas of bias, as described in Table 1, and expanded on below:

- Prognostic factor measurement:
  - For the 'other prognostic factors measured appropriately' domain, we decided this domain would only be applicable if a study in question compares BNP or NT-proBNP to some other prognostic indicator
  - We added a new domain: "For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data were reported"
  - We added a second new domain: "For other prognostic factors, the extent of and reasons for indeterminate test results or missing data were reported (applicable when a study in question compares BNP/NT-proBNP to other prognostic indicators)"
- Outcome measurement:
  - We added a new domain: "The study avoided the use of a composite outcome".

Hayden, et al., provide a guide to using their tool, which we also adapted for use with our modified version. The modifications that have been made to the tool involved the elimination of several signaling questions that we felt were not relevant to the review:

- Study Attrition:
  - We dropped "Attempts to collect information on participants who dropped out of the study are described" because authors of included studies would largely be unable to accomplish this task;
- Prognostic Factor Measurement:
  - We eliminated "Adequate proportion of the study sample has complete data for prognostic factors" and "Appropriate methods are used if imputation is used for missing prognostic factor data" because BNP or NT-proBNP is routinely collected and imputation, even if performed, would not likely be reported by study authors;
- Measuring and Accounting for Confounding:
  - We dropped "The method and setting of confounding measurement are the same for all study participants" because BNP or NT-proBNP is the focus of most studies and detailed reporting of confounders would not be of the highest priority for study authors;

- Analysis:
    - We eliminated “The strategy for model building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model” and “There is no selective reporting of results” because we felt that commenting on model building and selective reporting would not be suitable for this review, especially given the diversity of strategies that BNP or NT-proBNP researchers may employ in their work.

The final modification involved a change in the response options used to express the degree of bias. Hayden, et. al. originally suggested ‘yes’, ‘no’, ‘partly’, and ‘unsure’ as possible responses to each domain and potential bias item. However, in accordance with the methodology checklist for prognostic studies adapted from Hayden’s work and developed by the National Institute for Health and Clinical Excellence (NICE), we opted for the simplified response categories of ‘yes’, ‘no’ and ‘unclear’. Within each domain, an answer of ‘no’ corresponds to a high risk of bias, ‘unclear’ corresponds to a possible or unclear risk of bias, and ‘yes’ corresponds to a low risk of bias.

Assessment of Risk of Bias: Diagnosis Studies

The QUADAS-2was used to assess the risk of bias of diagnostic studies. The investigators tailored the QUADAS-2 to this review by discussing whether some of the tool's signaling questions should be removed from consideration. The signaling questions are intended to help researchers judge the risk of bias in each of the four domains on the QUADAS-2. This discussion took place prior to the start of quality assessment. We decided to omit the following signaling questions:

- *“If a threshed was used, was it pre-specified?”*: Many factors must be considered when determining a cut-point for the diagnosis of HF. For example, in the determination and application of a cut-point, an adjustment should be made for the independent effects of variables such as age and gender. Likewise, since no consensus exists on the optimum cut-point for the clinical application of BNP or NT-proBNP, the choice of a pre-specified cut-point means some studies may overestimate accuracy because easy-to-diagnose patients are selected for the study sample. Studies may also underestimate accuracy because difficult cases are selected for the study sample. For these reasons, we removed this signaling question.
- *“Was there an appropriate interval between index test(s) and reference standard”*: Since the inclusion criteria for the diagnosis questions required that all blood samples had to be collected on admission or discharge, we deemed this question to be irrelevant.
- *“Did all patients receive a reference standard?”*: This question was not relevant to the review because the inclusion criteria specified the use of standard diagnostic criteria for determining HF in included studies (the criteria had to be applied independent of BNP or NT-proBNP test values). This question would only be applicable if there are specific reference standards to determine whether these test values are used or if the screening question was not specific enough to exclude studies where only some patients were diagnosed with HF.

Each signalling question requires a ‘yes’, ‘no’, or ‘unclear’ response. We developed decision rules to consolidate 'yes', 'no', or 'unclear' responses to the signaling questions into a single 'yes', 'no', or 'unclear' response for each risk of bias question (one risk of bias question per domain).

The decision rules are shown in Table E-1 below.

Table E-1: Decision Rules to Consolidate Responses to QUADAS-2 Signaling Questions into Responses to QUADAS-2 Risk of Bias Questions

Domain 1: Patient Selection (3 questions)
All yes's* = low risk of bias;
All no's* = high risk of bias; or
All unclear* = unclear.
Mixed categories default to the lowest category:
2 yes, 1 no* = high risk of bias;
2 yes, 1 unclear* = unclear;
2 no, 1 yes* = high risk of bias;
2 no, 1 unclear* = high risk of bias;
2 unclear, 1 no* = high risk of bias;
2 unclear, 1 yes* = unclear; or
1 yes, 1 no, 1 unclear* = unclear.
Domain 2: Index Test (1 question)
Yes* = low risk of bias;
No* = high risk of bias; or
Unclear* = unclear.
Domains 3 and 4: Reference Standard and Flow and Timing (2 questions each domain)
Both yes's* = low risk of bias;
Both no's* = high risk of bias;
Both unclear* = unclear;
1 yes, 1 no* = high risk of bias;
1 yes, 1 unclear* = unclear; or
1 no, 1 unclear* = high risk of bias.

*Mix of responses to signaling questions.

QUADAS-2 requires an assessment of the extent to which each included study is applicable to the review. Applicability is rated 'high', 'low', or 'unclear' and is assessed separately for three questions. We assessed applicability for each question as described below.

- "*Are there concerns that the included patients and setting do not match the review questions?*": Studies excluding patients with chest trauma, hemodialysis, asthma, COPD, and dyspnea clearly due to causes other than HF (e.g., pneumothorax, coronary ischemia, myocardial infraction) were not seen as a threat to applicability (rated high in applicability). Studies excluding patients with any other diagnosis or comorbidity besides the ones mentioned above raised concerns about applicability. For example, studies excluding patients because of increased body mass index may have unclear or low applicability because BNP and NT-proBNP decrease as body mass increases. Studies that excluded patients on certain medications, excluded difficult-to-diagnose patients or included only easy-to-diagnose patients, restricted the sample to males or females only, or restricted the sample to certain age groups, were regarded as having unclear or low applicability.
- "*Are there concerns that the index test, its conduct, or its interpretation differ from the review question?*": Since we included studies that utilized FDA approved assay methods, we determined a priori that concerns about applicability were unlikely to exist in this domain (most studies would be rated high in applicability).
- "*Is there concern that the target condition as defined by the reference standard does not match the review question?*": We employed a broad list of acceptable reference tests in this review, so we determined a priori that concerns about applicability were unlikely to exist for most studies in this domain. However, since HF is typically diagnosed using a battery of tests and criteria, applicability was classified as unclear or low in the case of included studies that employed an unusually large number of tests or criteria. Similarly, applicability was classified as unclear or low in studies that employed a single reference test or criterion.

Investigators with previous experience conducting systematic reviews assessed the quality of all RCTs and cross-sectional studies. For quality assessments conducted using the NOS, Hayden, et al. criteria, and QUADAS-2, investigators trained a pool of raters. Training included a description of the background and objectives of the systematic review, an examination of the quality assessment instruments to explain the meaning of questions and develop a standardized approach to answering the questions, and pilot rating phases to test the instruments and resolve inconsistencies in interpreting and answering questions.

Grading the Strength of the Body of Evidence

In principle, a body of evidence from randomized trials starts with a presumed high strength of evidence, and is downgraded across the domains when there are important overall risk of bias of contributing studies, inconsistency in direction of intervention effect, indirectness of the outcome of interest (e.g., a surrogate outcome rather than a clinical health outcome), and imprecision. For nonrandomized studies, the body of evidence starts with a presumed low strength of evidence but may be upgraded across certain domains. The strength of a body of evidence is graded based on the following four domains: overall risk of bias by outcome, consistency, directness, and precision. A methodologist and a content expert grades the strength of the body of evidence as "High," "Moderate," "Low," or "Insufficient" (Table 2). A third methodologist with clinical background adjudicated to resolve disagreements.

Given the results we found, optional domains such as, dose-response association and existence of confounders, were not applicable in this comparative effectiveness review. Given the uncertainties involved in interpreting asymmetry tests for publication bias,

mainly in the presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.

The strength of evidence was graded insufficient when the following occur: no evidence for an outcome, direction of estimates were inconsistent between studies without an identifiable cause, or the body of evidence from the contributing study/studies was underpowered for the outcome of interest (imprecise estimate). That is, when the effect estimate associated with confidence intervals was not only non-significant, but wide enough such that the clinical action would differ if the upper versus the lower boundary of the CI represented the truth, we rated the estimate as imprecise. If an effect estimate is rated as imprecise, this reflects our uncertainty about clinically important benefits, harms or clinically unimportant differences in effect estimates between the contrasting interventions. Customarily only a subset of important outcomes are chosen to grade the strength of evidence - outcomes that are most meaningful for decision-making given a specific Key Question.

Table E-2

Strength of evidence grades and definitions Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

APPENDIX F.

Quality Assessment Forms

Appendix F. Quality Assessment Forms

Newcastle Ottawa Scale, Case-Control Studies

1. **Is this a Case/Control study?**

Yes (continue)

No (STOP) (specify type of study)

2. Is the case definition adequate?

Yes, with independent validation*

Yes, eg. record linkage or based on self reports

No description

3. Representativeness of the cases

Consecutive or obviously representative series of cases*

Potential for selection biases or not stated

4. Selection of controls

Community controls*

Hospital controls

No description

5. Definition of Controls

No history of disease (endpoint)*

No description of source

6. Comparability of cases and controls on the basis of the design or analysis

Study controls for (select the most important factor)*:

Study controls for any additional factor* (This could be modified to indicate specific control for a second important factor.)

7. Ascertainment of exposure

Secure record (e.g. surgical records)*

Structured interview where blind to case/control status *

Interview not blinded to case/control status

Written self-report or medical record only

No description

8. Same method of ascertainment for cases and controls

Yes*

No

9. Non-response rate

Same rate for both groups*

Non respondents described

Rate different and no designation

10. Were potential confounders measured and adequately addressed in the analysis?

Yes

No

11. Was the statistical analysis described?

Yes

No

12. Did the authors mention missing data in manuscript?

Yes

No

Newcastle Ottawa Scale -Cohort Studies

1. Is this a Cohort study?

Yes (continue)

No (STOP) (specify type of study)

2. Representativeness of the exposed cohort

Truly representative of the average in the community* (please describe the average cohort)

Somewhat representative of the average in the community* (please describe the average cohort)

Selected group of users eg. nurses, volunteers

No description of the derivation of the cohort

3. Selection of the non-exposed cohort

Drawn from the same community as the exposed cohort*

Drawn from a different source

No description of the derivation of the non-exposed cohort

4. Ascertainment of exposure

Secure record (eg. surgical records)*

Structured interview*

Written self-report

No description

5. Demonstration that outcome of interest was not present at start of study

Yes*

No

6. Comparability of cohorts on the basis of the design or analysis

Study controls for (select the most important factor)*:

Study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

No relevant adjustments for confounding

7. Assessment of outcome

Independent blind assessment*

Record linkage*

Self report

No description

8. Was follow up long enough for outcomes to occur

Yes (select an adequate follow up period for outcome of interest)*

No

9. Adequacy of follow up of cohorts

Complete follow up- all subjects accounted for*

Subjects lost to follow up unlikely to introduce bias (small number lost) (report an adequate %)*

Follow up rate and no description of those lost (report an adequate %)

No statement

10. Were potential confounders measured and adequately addressed in the analysis?

Yes

No

Unclear

11. Was the statistical analysis described?

Yes

No

Unclear

12. Did the authors mention missing data in manuscript?

Yes

No

<u>QA: Modified Jadad Scale</u>

1. Is this a RCT study?

Yes (continue)

No (STOP) (specify type of study)

2. Double blinding is reported

Yes (1 point)

No

3. Double blinding is appropriate

Yes (1 point)

No (-1 point)

Not described

4. Reported as randomized

Yes (1 Point)

No

5. Randomization is appropriate

Yes (1 point)

No (-1 point)

Not Described

6. Withdrawals are reported by number and reason per arm

Yes (1 point)

No

7. Jadad Score (/5)

8. Method(s) used to assess adverse events is described

Yes (1 point)

No

9. Method(s) of statistical analysis is described

Yes (1 point)

No

10. Inclusion and/or exclusion criteria reported

Yes (1 point if at least one of the requirements is reported)

No

11. Modified Jadad score (/8)

12. Was the allocation adequately concealed? E.g pharmacy controlled randomization scheme, sequentially numbered opaque, sealed envelope, sequentially numbered / coded identical containers, central randomization by phone?

Yes

No

Unclear

13. Was the analysis based on intention to treat principle?

Yes

No

Unclear

14. Was the sample size justified?

Yes

No

Unclear

15. Was the outliers reported and appropriately dealt with in the analysis?

Yes

No

16. Is the role of the study sponsor/ funder (i.e. manufacturer of the device) appropriate?

Is the role of the study sponsor/ funder (i.e. manufacturer of the device) appropriate?
(This question evaluates the role of the study sponsor in the potentially influencing the study conduct, interpretation, or reporting. We ask raters to judge whether "the role of the study sponsor (i.e. manufacturer of the device) appropriate?".)

For low risk of bias, raters would indicate YES (role appropriate) with respect to the following: 1) The funder/ sponsor is identified, and 2) Their specific input/role within the study is also specified such that there is NO or MINIMAL potential to influence study conduct, interpretation, or reporting. For example, a sponsor may provide a device to the study researchers but then had no subsequent involvement in the study development, conduct and reporting. We are looking for a statement from the authors declaring no involvement.

For high risk of bias the raters indicate NO (role is NOT appropriate) with respect to the following: 1) The funder is identified AND their role/input within the study is not explicitly specified 2) The funder is not identified AND their role/input within the study is not explicitly stated. The category of UNSURE is used when information about the study sponsor, device manufacturer, and any potential conflict of interest of the study authors is conflicting or not well reported within the study.)

Yes

No

Unsure

<u>QA: Cross-Sectional Design</u>

1. Is this a Cross-Sectional study?

Yes (continue)

No (STOP) (specify type of study)

Study Population

2. Did the authors clearly describe the population from which the participants were drawn?

Yes

No

Unclear

3. Were the inclusion and/or exclusion criteria described (no specific criteria)?

Yes

No

Unclear

4. Were the participants in the study representative of the population from which they were recruited?

Yes

No

Unclear

Outcome Measurements

5. Was the outcome defined clearly (i.e., was the measure described in sufficient detail to be replicated)?

Yes

No

Unclear

6. Were those measuring the main outcome unaware of the exposure status?

Yes

No

Unclear

Exposure Measurements

7. Was the exposure defined clearly (i.e., was the test method described in sufficient detail to permit replication)?

Yes

No

Unclear

8. Were those measuring the exposure unaware of outcome status?

Yes

No

Unclear

Statistical Analysis

9. Were potential confounders measured and adequately addressed in the analysis?

Yes

No

Unclear

10. Was the statistical analysis described?

Yes

No

Unclear

11. Were missing data reported?

Yes

No

QA Prognosis: Hayden Criteria

1 Study Participation The study population represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results

1 a. Source population clearly defined.

Yes

No

Unclear

1 b. Study population described.

Yes

No

Unclear

1 c. Study population represents source population, or population of interest.

Yes

No

Comment (optional)

2 Study Attrition Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample)

2 a. Completeness of follow-up described.

Yes

No

Unclear

2 b. Completeness of follow-up adequate.

Yes

No

Unclear

3 Prognostic Factors *The prognostic factors of interest are adequately measured in study participants to sufficiently limit potential bias.*

3 a. BNP/NT-proBNP factors defined.

Yes

No

Unclear

3 b. BNP/NT-proBNP factors measured appropriately.

Yes

No

Unclear

3 c. Other prognostic factors measured appropriately.

Yes

No

Unclear

Not Applicable

3 d. For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported.

Yes

No

Unclear

3 e. For other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported.

Yes

No

Unclear

Not Applicable

4 Outcome Measurement *The outcome(s) of interest are adequately measured in study participants to sufficiently limit bias.*

4 a. Outcome defined.

Yes

No

Unclear

4 b. Outcome measured appropriately.

Yes

No

Unclear

Comment (optional)

4 c. A composite outcome was avoided.

Yes

No

Unclear

Comment (optional)

5 Confounding Measurement *Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest*

5 a. Confounders measured.

Yes

No

Unclear

5 b. Confounders accounted for.

Yes

No

Unclear

6 Analysis *The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results*

6 a. Analysis described.

Yes

No

Unclear

Comment (optional)

7 Study Design *7 a. The study was designed to test the prognostic value of BNP or NT-proBNP (i.e. it was not a secondary analysis of data collected for other purposes).*

Yes

No

Unclear

QA: Diagnostic -QUADAS II

1. Is this a Diagnostic study?

Yes (continue)

No (STOP) (specify type of study)

2. Setting:

Emergency Dept.

Primary Care

Unclear

3. Cut point:

4. Which peptide was assessed?

BNP

Nt-ProBNP

Both

Domain 1: Patient Selection

Methods of patient selection: *(Describe included patients (prior testing, presentation, intended use of index test and setting)*

1. Was a consecutive or random sample of patients enrolled? *(define the population in the box/copy and paste from the article)*

Yes

No

Unclear

2. Was a case-control design avoided?

Yes

No

Unclear

3. Did the study avoid inappropriate exclusions?

Yes

No

Unclear

Domain 1: Risk of Bias (will be judge later)

Could the selection of patients have introduced bias?

Low

High

Unclear

Domain 1: Applicability (please click here for help guide)

Are there concerns that the included patients and setting do not match the review question?

Low

High

Domain 2: Index Test(s)

Index Test(s) in this study:

4. Were the index test results interpreted without knowledge of the results of the reference standard?

Yes

No

Unclear

5. If a threshold was used, was it pre-specified?

Yes

No

Unclear

Domain 2: Risk of Bias (will be judge later)

Could the conduct or interpretation of the index test have introduced bias?

Low

High

Unclear

Domain 2: Applicability (please click here for help guide)

Are there concerns that the index test, its conduct, or its interpretation differ from the review question?

Low

High

Unclear

Domain 3: Reference Standard

Reference standard in this study:

6. Is the reference standard likely to correctly classify the target condition?

Yes

No

Unclear

7. Were the reference standard results interpreted without knowledge of the results of the index test?

Yes

No

Unclear

Domain 3: Risk of Bias (will be judge later)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

High

Unclear

Domain 3: Applicability (please click here for help guide)

Are there concerns that the target condition as defined by the reference standar does not match the question?

Low

High

Unclear

Domain 4: Flow and Timing

Describe any patient who did not receive the index test(s) and/or reference standard.

Describe the time interval and any interventions between index test (s) and reference standard.

8. Was there an appropriate interval between index test(s) and reference standard?

Yes

No

Unclear

9. Did all patients receive a reference standard?

Yes

No

Unclear

10. Did patients receive the same reference standard?

Yes

No

Unclear

11. Were all patients included in the analysis?

Yes

No

Unclear

Domain 4: Risk of Bias (will be judge later)

Could the patient flow have introduced bias?

Low

High

Unclear

Hayden Criteria Reference Sheet

1 Potential Bias	Signalling Comments	Yes	No	Unclear
Study Participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results (Hayden, Cote, and Bombardier2006).	**a. Source population clearly defined**	The study reported ALL of the following: • How the sample was identified (e.g. whether a referral was involved, patient of ambulatory care, etc.); • Place of recruitment (admitted to hospital, outpatient clinic/ambulatory care, hospital setting, community, family practice or equivalent, primary care); • The period of recruitment or the duration of follow-up.	The study DID NOT report ALL of the following: • How the sample was identified (e.g. whether a referral was involved, patient of ambulatory care, etc.); • Place of recruitment (e.g. outpatient clinic/ambulatory care, hospital setting, community, family practice or equivalent); • The period of recruitment or the duration of follow-up.	not reported clearly.
	b. Study population described	The study described ALL of the following: • The inclusion and exclusion criteria for all population groups; • Description of all participants at baseline or the start of the follow-up period; • Whether the population groups came from the general population, or as having HF with acute, chronic, or chronic exacerbation, with or without any co-morbidity.	The study did not describe ALL of the following: • The inclusion and exclusion criteria of the sample; • Description of all participants at the start of the follow-up period. • Whether the population came from the general population or having HF with acute, chronic, or chronic exacerbation, with or without any co-morbidity.	not reported clearly.
	c. Study population represents source population, or population of interest	The study meets ALL of the following criteria: • Did not exclude patients based on certain medications, gender, and BMI (exceptions: gender specific study, or other specific study -e.g. BMI). • Strategies for recruiting patients were similar between groups (Viswanathan M, 2012)	The study DOES NOT meet ALL of the following criteria: • Did not exclude patients based on certain medications, gender, and BMI (exceptions: gender specific study, or other specific study -e.g. BMI). • Strategies for recruiting patients were similar between groups (Viswanathan M,2012). • The population would be representative of those seen in	not reported clearly.

		. • The population would be representative of those seen in practice where BNP/NT-BNP testing is likely to be applied (e.g. outpatient clinics, primary care, etc.). • Inclusion and/or exclusion criteria are applied uniformly to all groups (Viswanathan M2012).	practice where BNP/NT-BNP testing is likely to be applied. • Inclusion and exclusion criteria are applied uniformly to all groups (Viswanathan M, 2012).	
2 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**
Study Attrition Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (Hayden, Cote, and Bombardier2006).	**a. Completeness of follow-up described**	ALL of the following are mentioned: • The study provided a reason for loss of follow-up for ALL TIME POINTS OF OUTCOME ASSESSMENT. • The study provided characteristics for participants who dropped out of the study.	At least ONE of the following is NOT mentioned: • The study provided a reason for loss of follow-up for ALL TIME POINTS OF OUTCOME ASSESSMENT. • The study provided characteristics for participants who dropped out of the study.	not reported clearly.
	b. Completeness of follow-up adequate	ALL of the above criteria are met: • In cohort studies the length of follow-up is not different between the groups, or in case-control studies, the time period between the exposure and outcome are the same for cases and controls (Viswanathan M2012). • There was not a high rate of differential or overall attrition (10% is acceptable) (Viswanathan M2012). • Attrition did not result in a difference in group characteristics between baseline and follow-up.	At least one of the following criteria is not met: • In cohort studies the length of follow-up is not different between the groups, or in case-control studies, the time period between the exposure and outcome are the same for cases and controls (Viswanathan M2012). • There was not a high rate of differential or overall attrition (Viswanathan M2012). • Attrition did not result in a difference in group characteristics between baseline and follow-up (Viswanathan	not reported clearly.

		(Viswanathan M2012)	M2012).	
3 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**
Prognostic Factor Measurement The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (Hayden, Cote, and Bombardier2006).	**a. BNP/NT-proBNP factors defined**	BNP/NT-proBNP cut-points were either pre-specified or an explanation/reasoning for cutpoint/threshold was provided. (note: continuous variables and change in BNP are appropriate)	BNP/NT-proBNP cut-points were NOT either pre-specified and an explanation/reasoning for cutpoint/threshold was NOT provided or a continuous variables or change in BNP variable WAS NOT used.	not reported clearly.
	b. BNP/NT-proBNP factors measured appropriately	The following criteria must be met: • No self-reporting of BNP/NT-proBNP levels were employed. • Method and setting of BNP/NT-proBNP measurement were the same for all study participants.	Self-reporting of BNP/NT-proBNP levels were employed or method and setting of BNP/NT-proBNP measurement were NOT the same for all study participants.	not reported clearly.
	c. Other prognostic factors measured appropriately (if applicable)	The following criteria must be met: • No self-reporting of levels of other prognostic factors employed. • Method and setting of other prognostic factor measurement were the same for all study participants.	Self-reporting of levels of other prognostic factors employed or method and setting of other prognostic factor measurement were NOT the same for all study participants.	not reported clearly.
	d. For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data were reported (Viswanathan M2012).	Study mentioned reasons for indeterminate test results and/or missing values of BNP/NT-proBNP levels.	Study did not mention reasons for indeterminate test results and missing values of BNP/NT-proBNP levels.	Information was unclear to answer if reasons for interdeteminant test results and missing values were reported.
	e. For other prognostic factors, the extent of and reasons for indeterminate test results or missing data were reported (Viswanathan M2012). (if applicable)	Study mentioned reasons for indeterminate test results and/or missing values of other prognostic factors.	Study did not mention reasons for indeterminate test results and missing values of other prognostic factors.	Information was unclear to answer if reasons for interdeteminant test results and missing values were reported.

4 Potential Bias	Signalling Comments	Yes	No	Unclear
Outcome Measurement The outcomes of interest are adequately measured in study participants to sufficiently limit bias (Hayden, Cote, and Bombardier2006).	a. **Outcome defined**	For the primary outcome, the following criteria should be met: • The study defines the primary outcomes as follows: a. mortality as including all (Viswanathan M2012) cause or cardiac related or heart failure related; b. morbidity as including definition of all cause (any episode of HF that requires admission to a hospital bed beyond the emergency room for any length of time), change in NYHA class, or any measure of quality of life. • The outcome under study should be well defined such that it should be clear how the investigators determined whether participants experienced, or did not experience, the outcome. • The same methods for defining the outcome(s) were the same for all participants in the study. Often there may be more than one way of measuring an outcome (for example, physical or laboratory tests, questionnaire, reporting of symptoms).	For the primary outcome, the following criteria are NOT met: • The study defines the primary outcomes as follows: a. mortality as including all (Viswanathan M2012) cause or cardiac related or heart failure related; b. morbidity as including definition of all cause (any episode of HF that requires admission to a hospital bed beyond the emergency room for any length of time), change in NYHA class, or any measure of quality of life. • The outcome under study should be well defined such that it should be clear how the investigators determined whether participants experienced, or did not experience, the outcome. • The same methods for defining the outcome(s) were the same for all participants in the study. Often there may be more than one way of measuring an outcome (for example, physical or laboratory tests, questionnaire, reporting of symptoms).	not reported clearly.
	b. **Outcome measured appropriately**	For the primary outcome, the following criteria must be met: • The method of measurement used should be valid and reliable to limit misclassification. • The authors use a sufficient method for capturing morbidity and mortality. • For mortality, linkage to	For the primary outcome, the following criteria was NOT met: • The method of measurement used should be valid and reliable to limit misclassification. • The authors use a sufficient method for capturing morbidity and mortality. • For mortality, linkage to electronic death records and	not reported clearly.

		electronic death records and hospital registry are good sources, while hospital/medical records are not so reliable (note: family, friends, primary care physicians, hospital records, are not acceptable measurements). • For morbidity, NYHA, Framingham, hospital registries are good sources, while others are not so reliable to detect worsening of heart failure. (note: family, friends, primary care physicians, hospital records, are not acceptable measurements). NOTE: for many studies NYHA and Framingham are sources for establishing initial Heart failure status in these studies. Heart failure is not our outcome for these studies (sometimes worsening of heart failure can be an outcome). Make sure NYHA and Framingham are used to assess the morbidity outcome in question (e.g. all cause hospital readmission, cardiac hospital readmission • All study participants undergo the same measure of outcomes in the same setting.	hospital registry are good sources, while hospital/medical records are not so reliable. • For morbidity, NHYA and Framingham are good sources, while others are not so reliable to detect worsening of heart failure. • All study participants undergo the same measure of outcomes in the same setting.	
	c. **A composite outcome was avoided**	The study avoided the use of composite outcomes that combine morbidity and mortality. However, it is adequate if at least one individual outcome is presented in the analysis. Studies that combine different morbidity outcomes are acceptable.	The study DID NOT avoid the use of composite outcomes that combine morbidity and mortality and at least at least one individual outcome is NOT presented in the analysis.	
5 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**

Confounding Measurement and Account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (Hayden, Cote, and Bombardier2006).	**a. Confounders measured**	the following criteria are met: • Important confounders (age, renal function, BMI (or other measure of height and weight) are considered in the study design or in the analysis. (For renal function look for the following tests: BUN, Glomerular filtration rate (GFR), Creatinine-blood, creatinine clearance and creatinine-urine or the following keywords renal failure, acute renal failure, ARF, primary acute renal failure, chronic renal failure, CRF, acute interstitial nephritis, acute tubular necrosis, azotemia, dialysis, glomerulonephritis, hemodialysis, obstructive renal failure, renal insufficiency, kidneys, acute kidney failure) • There are clear definitions of the important confounders (including dose, level and duration of exposures). • The measurement of all important confounders is valid and reliable.	At least one of the following are NOT met: • Important confounders (age, renal function, BMI (or other measure of height and weight) are considered in the study design or in the analysis. • There are clear definitions of the important confounders (including dose, level and duration of exposures). • The measurement of all important confounders is valid and reliable.	not reported clearly.
	b. Confounders accounted for	Important potential confounders are correctly accounted for in the study design (e.g. matching for key variables, stratification or initial assembly of comparable groups) or in the analysis (multiple regression, etc.).	Important potential confounders are NOT correctly accounted for in the study design (e.g. matching for key variables, stratification or initial assembly of comparable groups) or in the analysis (multiple regression, etc.).	not reported clearly.
6 Analysis	**Signalling Comments**	**Yes**	**No**	**Unclear**
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results (Hayden, Cote, and	**a. Analysis described**	The analysis is clearly described and appropriate for the design of the study. There is no selective reporting of results The presentation of data is sufficient	The analysis is not clearly described	not reported clearly.

Bombardier2006).		to assess the adequacy of the analysis.		
7 Study Design	***Signalling comments***	**Yes**	**No**	**Unclear**
	a. The study was designed to test the prognostic value of BNP or NT-proBNP (i.e.it was not a secondary analysis of data collected for other purposes).	*Study was a prospective cohort study designed to test BNP as a predictive factor.*	*RCT designed to evaluate treatment interventions and then a re-analysis is undertaken. Cohort studies done to evaluate another question where post-hoc BNP analysis is used to demonstrate prognostic association.*	*not reported clearly.*

Adapted from:
Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144:427–437.

National Institute for Health and Clinical Excellence (January 2009) The guidelines manual. London: National Institute for Health and Clinical Excellence. Appendix J: Methodology checklist: prognostic studies 218- 222. Available from: www.nice.org.uk

Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/

Reference List

1. Hayden, J. A., P. Cote, and C. Bombardier. 2006. "Evaluation of the Quality of Prognosis Studies in Systematic Reviews." *Ann.Intern.Med.* 144(6):427-37. doi:144/6/427 [pii].

2. Viswanathan M, Ansari MT Berkman ND Chang S Hartling L McPheeters LM Santaguida PL Shamliyan T Singh K Tsertsvadze A Treadwell JR., Viswanathan M, Ansari MT Berkman ND Chang S Hartling L McPheeters LM Santaguida PL Shamliyan T Singh K Tsertsvadze A Treadwell JR. 2012. "Agency for Healthcare Research and Quality Methods Guide for Comaparative Effectiveness Reviews." *Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions.* AHRQ Publication No.12-EHC047-EF.

QUADAS II Reference Sheet

QUADAS-2 HELP SHEET	
1. Was a consecutive or random sample of patients enrolled?	We are interpreting this to be representative of the spectrum of patients seen within the Emergency Departments, Urgent Care departments, or Primary Care Settings, which should include all levels of severity of symptoms or duration. The population would be representative of those seen in practice where the test is likely to be applied. A study should ideally enrol a consecutive or random sample of eligible patients with suspected disease to prevent the potential for bias. If the study is part of a large study were will need to refer to the referenced article to get a full understanding of the study methods. **Yes:** The study clearly indicates that Consecutive or Random sampling was used. A clear description was given that the study includes ALL OR RANDOMLY CHOSEN eligible subjects seen at the Emergency Departments, Urgent Care departments, or Primary Care Settings, and ensures the sampling method represents the entire population. **No:** The study indicates sampling description other than Consecutive or Random. Samples are not randomly recruited OR are only recruited during certain times in the day or at certain course of the study based on the availabilities of the researcher. Samples are not representative of the population. **Unclear:** No or only partial description of how the patients were enrolled. There is uncertainty whether patients were consecutively or randomly obtained.
2. Was a case control design avoided?	Look for a description of a comparison group. **Yes:** The study clearly states there was no comparison group. E.g. Heart Failure (HF) group vs. a group of individuals without the disease. **No:** The study compares HF individuals with a group of individuals without the disease or other diseases. OR the study only select groups of whom they know in advance during the presentation at the Emergency Departments, Urgent Care departments, or Primary Care Settings. **Unclear:** Vague or partial information is reported about

	whether there was a comparison group.
3. Did the study avoid inappropriate exclusions?	This question only concerns inappropriate exclusions made during initial enrolment. Any exclusions made after analysis is not considered here; question # 11 accounts for this. Please see Table 1 for a description of appropriate and inappropriate exclusions. **Yes:** Inappropriate exclusions were avoided. **No:** There was clear indication of inappropriate exclusion (see Table 1). **Unclear:** Insufficient information to determine whether inappropriate exclusions were made.
4. Were the index test results interpreted without knowledge of the results of the reference standard?	This would almost always be "yes" since we are establishing how well an index test (B-type natriuretic peoptide [BNP] or amino-terminal proBNP [NT-proBNP]) can diagnose or exclude HF compared to the reference standard (various diagnoses of HF failure, other than BNP). We assume this bias to be associated with the process of interpretation of BNP results and is related to "review bias" or blinding. **Yes:** The study clearly indicates that BNP cut-points were decided/specified without the knowledge of the results of the reference standard. **No:** The study clearly states that the decision of BNP cut-points were made with the knowledge of the reference standard results. **Unclear:** There is not enough information given to determined whether BNP cut-points were decided/specified without knowledge of the reference standard. (e.g. no indication of blinding or awareness)
5. If a threshold was used, was it pre-specified?	**Yes:** BNP cut-points were established prior to the diagnosis of HF or analysis. **No:** There is evidence that the cut-points of BNP/NT-proBNP were made such in conjunction to what the judicator said about the diagnosis. Or BNP cut-points were based on the outcome of the ROC, Median, or Mean values; in this case it is not pre-specified and should be a "no".

	Unclear: No indication of whether a pre-specified threshold was made.
6. Is the reference standard likely to correctly classify the target condition?	This will almost always be a "yes". One reference standard (e.g. Cardiologist review of records) is considered reasonable to diagnose HF. Most reference standards are well defined diagnostic instruments for HF (clinical presentation, medical treatments and responses to treatment, electrocardiograms, cardiac catheterization investigations, etc.). **Yes:** At least one reference standard was mentioned to diagnose HF, and if diagnosis was not only based on degree of symptoms' severity or classes. **No:** If the final arbitrator of target condition is based on severity of symptoms, e.g. NYHA classes only OR patient's own self-report of HF. **Unclear:** The authors do not give enough information to determine what reference standard was used.
7. Were the reference standard results interpreted without knowledge of the results of the index test?	The index test in this systematic review is the result of BNP levels. The reference test is the diagnostic instruments for HF (clinical presentation, medical treatments and responses to treatment, electrocardiograms, cardiac catheterization investigations, etc.) other than BNP levels. **Yes**: Diagnosis of HF was made without the knowledge of the BNP or NT-proBNP test levels or determination of HF by reference standard were made blinded to the results of the BNP levels. **No:** The diagnosis of HF was made with the knowledge (unaware) of the BNP or NT-proBNP test results or the study clearly states that BNP levels were known by the rater prior to establishing the reference standard; blinding did not occur. **Unclear:** Some information provided but insufficient to determine this item.
8. Was there an appropriate interval between index test(s) and reference standard?	**Yes:** The blood collection for BNP levels was taken within 2-3 days after/before standard reference was collected (e.g. 2-3 days between blood and echocardiograph were taken). **No:** The blood collection was taken longer than 2-3 days after/ before standard reference was collected.

	Unclear: the researchers do not give sufficient information to determine the interval between index and standard.
9. Did all patients receive a reference standard?	**Yes:** All patients was administered at least one reference standard. (The reference standard used for diagnosis is stated in the methods. If it is not entirely clear, the "n" in the results may help decide.) **No:** Not all patients were administered a reference standard. **Unclear:** Insufficient information to determine that all patients received at least one the reference standard.
10. Did patients receive the same reference standard?	This item concerns to partial verification bias which occurs when not all of the study participants receive the reference standard (in our context, confirmation of the true HF status). This is a form of selection bias. Information to address this can be found in methods and results. **Yes:** Paper clearly states that all patients received the same reference standard. **No:** Paper clearly describes that different reference standards were used among patients. **Unclear:** Insufficient information to determine whether partial verification was present.
11. Were all patients included in the analysis?	**Yes:** All patients enrolled in the study were included for analysis. This does not include patients that were excluded during study enrolment. **No:** Not all patient were included in the analysis because of missing data, withdrawal, etc. (e.g. refID 60198: Of the 95 patients screened, 11 (11.5%) patients were excluded due to suboptimal images) **Unclear**: Insufficient information if all patient were included for analysis.

Table F-1:

Criteria	Appropriate exclusions	Inappropriate exclusions
Age	Study excludes patients younger than 18 years of age.	(Paper specific) Inappropriate if conflicting with objective of the study.
Race	none	(Paper specific) Inappropriate if conflicting with objective of the study.
Gender	none	(Paper specific) Inappropriate if conflicting with objective of the study.
Prior diagnosis/ co-morbidity	Study excludes patients with chest trauma, hemodialysis, asthma, COPD, and Dyspnea clearly due to another cause (e.g. pneumothorax, coronary ischemia, myocardial infarction).	Study excludes patients with any other diagnosis (e.g. exclude patients because of increased BMI, knowing that NPs decrease as BMI increases).
Difficulty or ease of diagnosis	None	Study excludes patients that were too difficult to diagnose or too easy to diagnose.
Medications	None	Study excludes patients on certain medications.
Settings	Study excludes patients recruited at settings other than: non emergency settings, non-urgent care, primary care settings	none
Reference Standard	none	none

Quality Assessment Study Design Description Reference Sheet

Case Control Study
A study that compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls), and looks back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease. Study participants are enrolled based on disease status (i.e., case or control).

Case control studies are observational because no intervention is attempted and no attempt is made to alter the course of the disease. The goal is to retrospectively determine the exposure to the risk factor of interest from each of the two groups of individuals: cases and controls. These studies are designed to estimate odds.

Case control studies are also known as "retrospective studies" and "case-referent studies."

Case Report
A case report is a descriptive study of a single individual (case report) in which the possibility of an association between an observed effect and a specific exposure is based on a detailed clinical evaluation and history of the individual.

Case Series
A case series is a descriptive study that follows a group of patients who all have the same diagnosis or who are all undergoing the same procedure/treatment over a certain period of time. Case series do not employ control groups. Results of case series can generate hypotheses that are useful in designing further studies, including randomized controlled trials. However, no causal inferences should be made from case series regarding the efficacy of the investigated treatment.

Cohort Study
A study design that follows prospectively over time one or more populations (called cohorts) to determine which patient characteristics (risk factors) are associated with the development of a disease or outcome. As the study is conducted, the outcome from participants in each cohort is measured and relationships with specific risk factors are determined.
Prospective Cohort Study
In a cohort study, individuals exposed and not exposed (to suspected risk factors) are followed and compared to assess the extent to which each group experiences an outcome of interest -- often illness or death. Participants who are enrolled in the study do not have the outcome of interest at the enrolment date.

Retrospective Cohort Study
Most cohort studies are prospective; however, cohort studies that have reconstructed exposure data from historical records are referred to as retrospective cohort studies. In these studies, exposure and outcome data are followed up without actually following cases, which can result in considerable savings of time and money.

Randomized Controlled Trial
A study design that randomly assigns participants into a treatment/intervention group or a control group. As the study is conducted, the only expected difference between the treatment/intervention and control groups is the outcome variable being studied.

Before-After Design
A study design in which the dependent variable (such as a clinical outcome) is measured before and after an intervention in the same group of individuals. Comparison of outcome measures taken before and after the intervention is made to assess the effect of treatment.

Cross Sectional Study
Studies that conduct measurements on a group of subjects at one point in time. Cross-sectional studies look at both exposure and outcomes at one point in time and may be used to generate hypotheses for further investigation in prospective cohort studies or RCTs.

Crossover Trial
A two-period study design in which each participant serves as their own control. In the first period of the study, participants receive either the treatment or control. Then, after a "washout" period to minimize the effect of the first period, the participant switches to receiving the control or treatment, depending on which they received in the first period. Randomization is used to assign the order in which the treatment and control conditions are administered.

Time series
The defining feature of time series research designs is that each participant or sample is observed multiple times, and its performance is compared to its own prior performance. In other words, each participant or population serves as its own control.

Quasi-Experimental Study
A study design in which researchers manipulate an active independent variable but do not have full control over the allocation or timing of the intervention. Quasi-Experimental designs are often used when it is not possible to conduct a true experiment with complete random assignment, as is often the case in policy or real-life settings.

Interrupted Time Series Design
Study design in which outcomes are measured repeatedly in a single group of participants both before and after a manipulation or a natural event.

APPENDIX G.

List of Excluded Articles

Appendix G. List of Excluded Articles

Aalbers J. Chronic heart failure treatment benefits from pro-BNP-directed therapy. Cardiovasc J Afr 2011;22(1):52.
Exclude: Not a primary study

Abdelwhab S, Elshinnawy S. Pulmonary hypertension in chronic renal failure patients. Am J Nephrol 2008;28(6):990-7.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abdulla J, Kober L, Torp-Pedersen C. Methods of assessing the functional status of patients with left ventricular systolic dysfunction in interventional studies: Can brain natriuretic peptide measurement be used as surrogate for the traditional methods? Cardiovasc Drugs Ther 2004 May;18(3):219-24.
Exclude: Systematic review

Abdullah SM, Khera A, Das SR, et al. Relation of coronary atherosclerosis determined by electron beam computed tomography and plasma levels of n-terminal pro-brain natriuretic peptide in a multiethnic population-based sample (the Dallas Heart Study). Am J Cardiol 2005 Nov 1;96(9):1284-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abe N, Matsunaga T, Kameda K, et al. Increased level of pericardial insulin-like growth factor-1 in patients with left ventricular dysfunction and advanced heart failure. J Am Coll Cardiol 2006 Oct 3;48(7):1387-95.
Exclude: BNP measure not FDA approved

Abe S, Taguchi I, Inoue T. Does direct inhibition bring direct benefit? Circ J 2012;76(6):1326
Exclude: Not a primary study

Abezov DK, Kamilova UK, Shukurdzhanova SM, et al. Assessment of natriuretic peptide indices and oxidative stress in patients with chronic heart failure. Likars'ka sprava 2010 Jan;Jan-Mar(1-2):53-6.
Exclude: Not in English

Abhayaratna WP, Marwick TH, Smith WT, et al. Characteristics of left ventricular diastolic dysfunction in the community: An echocardiographic survey. Heart 2006;92(9):1259-64.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abhayaratna WP, Marwick TH, Becker NG, et al. Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type natriuretic peptide. Am Heart J 2006 Nov;152(5):941-8.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abraham MR, Olson LJ, Joyner MJ, et al. Angiotensin-converting enzyme genotype modulates pulmonary function and exercise capacity in treated patients with congestive stable heart failure. Circ 2002 Oct 1;106(14):1794-9.
Exclude: BNP measure not FDA approved

Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. J Card Fail 1998 Mar;4(1):37-44.
Exclude: BNP measure not FDA approved

Abraham WT, Anand IS, Klapholz M, et al. Treatment of anemia with darbepoetin alfa in heart failure. Congest Heart Fail 2010;16(3):87-95.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abroug F, Ouanes-Besbes L, Nciri N, et al. Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: Diagnostic performance of cardiac biomarkers. Am J Respir Crit Care Med 2006 Nov 1;174(9):990-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abul Y, Karakurt S, Ozben B, et al. C-reactive protein in acute pulmonary embolism. J Investig Med 2011;59(1):8-14.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abulhul E, McDonald K, Martos R, et al. Long-term statin therapy in patients with systolic heart failure and normal cholesterol: Effects on elevated serum markers of collagen turnover, inflammation, and B-type natriuretic peptide. Clin Ther 2012 Jan;34(1):91-100.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Adamopoulos S, Parissis JT, Iliodromitis EK, et al. Effects of levosimendan versus dobutamine on inflammatory and apoptotic pathways in acutely decompensated chronic heart failure. Am J Cardiol 2006 Jul 1;98(1):102-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Adlam D, Silcocks P, Sparrow N. Using BNP to develop a risk score for heart failure in primary care. Eur Heart J 2005 Jun;26(11):1086-93.
Exclude: BNP measure not FDA approved

Adlbrecht C, Huelsmann M, Berger R, et al. Cost analysis and cost-effectiveness of NT-proBNP-guided heart failure specialist care in addition to home-based nurse care. Eur J Clin Invest 2011;41(3):315-22.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Adlbrecht C, Neuhold S, Hulsmann M, et al. NT-proBNP as a means of triage for the risk of hospitalisation in primary care. European Journal of Preventive Cardiology 2012 Feb;19(1):55-61.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aessopos A, Farmakis D, Polonifi A, et al. Plasma B-type natriuretic peptide concentration in beta-thalassaemia patients. Eur J Heart Fail 2007;9(5):537-41.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aggarwal A, Wong J, Campbell DJ. Carvedilol reduces aldosterone release in systolic heart failure. Heart Lung Circ 2006 Oct;15(5):306-9.
Exclude: BNP measure not FDA approved

Aguiar VB, Ochiai ME, Cardoso JN, et al. Relationship between depression, BNP levels and ventricular impairment in heart failure. Arq Bras Cardiol 2010;95(6):732-7.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ahmed KA, Madhavan M, Prasad A. Brain natriuretic peptide in apical ballooning syndrome (Takotsubo/stress cardiomyopathy): Comparison with acute myocardial infarction. Coron Artery Dis 2012;23(4):259-64.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ahmed W, Zafar S, Alam AY, et al. Plasma levels of B-type natriuretic peptide in patients with unstable angina pectoris or acute myocardial infarction: Prognostic significance and therapeutic implications. Angiol 2007 Jun;58(3):269-74.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ybarra J, Planas F, Navarro-Lopez F, et al. Association between sleep-disordered breathing, aminoterminal pro-brain natriuretic peptide (NT-proBNP) levels and insulin resistance in morbidly obese young women. Eur J Intern Med 2009 Mar;20(2):174-81.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

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Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

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Exclude: BNP measure not FDA approved

Yu CM, Sanderson JE. Plasma brain natriuretic peptide--An independent predictor of cardiovascular mortality in acute heart failure. Eur J Heart Fail 1999 Mar;1(1):59-65.
Exclude: BNP measure not FDA approved

Yu H, Oswald H, Gardiwal A, et al. Comparison of N-terminal pro-brain natriuretic peptide versus electrophysiologic study for predicting future outcomes in patients with an implantable cardioverter defibrillator after myocardial infarction. Am J Cardiol 2007 Aug 15;100(4):635-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Yuan W, Gu Y-Y, Zhang D-F. Measurement of serum soluble ST2 in patients with heart failure and its diagnostic value. Acad J Second Military Med U 2012;33(2):175-8.
Exclude: Not in English

Yufu K, Takahashi N, Nakagawa M, et al. Brain natriuretic peptide and cardiac autonomic function in type 2 diabetic patients. Diab Res Clin Pract 2006 Apr;72(1):12-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Yukiiri K, Hosomi N, Naya T, et al. Plasma brain natriuretic peptide as a surrogate marker for cardioembolic stroke. BMC Neurology 2008;8:45
Exclude: BNP measure not FDA approved

Yun KH, Jeong MH, Oh SK, et al. Preoperative plasma N-terminal pro-brain natriuretic peptide concentration and perioperative cardiovascular risk in

elderly patients. Circ J 2008 Feb;72(2):195-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zafarullah H, Shahbaz AU, Alturkmani R, et al. Elevated serum cobalamin in patients with decompensated biventricular failure. Am J Med Sci 2008 Nov;336(5):383-8.
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Zamora E, Simo R, Lupon J, et al. Serum myostatin levels in chronic heart failure. Rev Esp Cardiol 2010 Aug;63(8):992-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zanchi A, Maillard M, Jornayvaz FR, et al. Effects of the peroxisome proliferator-activated receptor (PPAR)-gamma agonist pioglitazone on renal and hormonal responses to salt in diabetic and hypertensive individuals. Diabetol 2010 Aug;53(8):1568-75.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

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Zapata L, Vera P, Roglan A, et al. B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin. Intensive Care Med 2011 Mar;37(3):477-85.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zdrenghea D, Pop D, Ilea M, et al. The acute effect of Metoprolol upon NT-proBNP level in patients with congestive heart failure. Rom J Intern Med 2009;47(1):35-40.
Exclude: BNP measure not FDA approved

Zeller M, Cottin Y, Laurent Y, et al. N-terminal pro-brain natriuretic peptide levels in patients with non-ST-elevation myocardial infarction. Cardiol 2004;102(1):37-40.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zemljic G, Bunc M, Yazdanbakhsh AP, et al. Levosimendan improves renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. J Card Fail 2007 Aug;13(6):417-21.
Exclude: BNP measure not FDA approved

Zeng C, Wei T, Jin L, et al. Value of B-type natriuretic peptide in diagnosing left ventricular dysfunction in dialysis-dependent patients. Intern Med J 2006 Sep;36(9):552-7.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zeng Q-X, Wei M-F, Zhang W, et al. Level of natriuretic peptide determines outcome in atrial fibrillation. J Atrial Fibrillation 2010;1(10):559-68.
Exclude: BNP measure not FDA approved

Zhang J, Fu X, Jia X, et al. B-type natriuretic peptide for prevention of contrast-induced nephropathy in patients with heart failure undergoing primary percutaneous coronary intervention. Acta Radiol 2010 Jul;51(6):641-8.
Exclude: BNP measure not FDA approved

Zhao Q, Wu TG, Lin Y, et al. Low-dose nesiritide improves renal function in heart failure patients following acute myocardial infarction. Heart Ves 2010 Mar;25(2):97-103.
Exclude: BNP measure not FDA approved

Zhao SQ, Hu YM, Li Q, et al. The clinical value of rapid assay for plasma B-type natriuretic peptide in differentiating congestive heart failure from pulmonary causes of dyspnoea. Int J Clin Pract 2008 Feb;62(2):214-20.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zhao YT, Shao L, Teng LL, et al. Effects of n-3 polyunsaturated fatty acid therapy on plasma inflammatory markers and N-terminal pro-brain natriuretic peptide in elderly patients with chronic heart failure. J Int Med Res 2009 Nov;37(6):1831-41.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zhao ZH, Liu ZH, Luo Q, et al. The effects of noninvasive positive pressure ventilation treatment on plasma concentration of amino terminal-pro brain natriuretic peptide in congestive heart failure in patients with sleep apnea. Chin J Intern Med 2006 May;45(5):386-8.
Exclude: Not in English

Zhao ZH, Liu ZH, Luo Q, et al. Positive pressure ventilation treatment reduces plasma levels of amino

terminal-pro brain natriuretic peptide in congestive heart failure patients with sleep apnea. Circ J 2006 May;70(5):572-4.
Exclude: BNP measure not FDA approved

Zhou B, Yang J, Yang X, et al. Usefulness of the Echocardiographic Multi-Parameter Score (EMPS) in evaluating left ventricular global heart function. Tex Heart Inst J 2011;38(1):27-34.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zhou J, Shi H, Zhang J, et al. Rationale and design of the beta-blocker in heart failure with normal left ventricular ejection fraction (beta-PRESERVE) study. Eur J Heart Fail 2010 Feb;12(2):181-5.
Exclude: Not a primary study

Zhou L, Giacherio D, Cooling L, et al. Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. Transfusion 2005 Jul;45(7):1056-63.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zhu BL, Ishikawa T, Michiue T, et al. Postmortem pericardial natriuretic peptides as markers of cardiac function in medico-legal autopsies. Int J Legal Med 2007 Jan;121(1):28-35.
Exclude: BNP measure not FDA approved

Zhu D, Wang F, Yu H, et al. Catestatin is useful in detecting patients with stage B heart failure. Biomarkers 2011 Dec;16(8):691-7.
Exclude: BNP measure not FDA approved

Zhubrina ES, Ovchinnikov AG, Seredenina EM, et al. Optimization of use of beta-adrenoblockers in the treatment of chronic heart failure in the outpatient setting. Ter Arkh 2009;81(11):35-40.
Exclude: Not in English

Zielinski T, Sobieszczanska-Malek M, Browarek A, et al. The influence of the recipient's body weight on the probability to obtain a heart transplant-POLKARD HF registry. Transplant Proc 2009 Oct;41(8):3166-70.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zile MR, DeSantis SM, Baicu CF, et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. Circ 2011 May 1;4(3):246-56.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zimmermann O, Bienek-Ziolkowski M, Wolf B, et al. Myocardial inflammation and non-ischaemic heart failure: Is there a role for C-reactive protein? Basic Res Cardiol 2009 Sep;104(5):591-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zoccali C, Mallamaci F, Benedetto FA, et al. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. J Am Soc Nephrol 2001 Jul;12(7):1508-15.
Exclude: BNP measure not FDA approved

Zoccali C, Tripepi G, Mallamaci F. Predictors of cardiovascular death in ESRD. Semin Nephrol 2005;25(6):358-62.
Exclude: Not a primary study

Zondag W, Agterof MJ, Schutgens RE, et al. Repeated NT-proBNP testing and risk for adverse outcome after acute pulmonary embolism. Thromb Haemost 2011 Dec;106(6):1226-7.
Exclude: Not a primary study

Zuber M, Kipfer P, Attenhofer Jost CH. Usefulness of acoustic cardiography to resolve ambiguous values of B-type natriuretic Peptide levels in patients with suspected heart failure. Am J Cardiol 2007 Sep 1;100(5):866-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zuber M, Cuculi F, Attenhofer Jost CH, et al. Value of brain natriuretic peptides in primary care patients with the clinical diagnosis of chronic heart failure. Scand Cardiovasc J 2009;43(5):324-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Zugck C, Gerhards A, Kell R, et al. Brain natriuretic peptide (BNP) is superior to atrial natriuretic peptide (ANP), endothelin and norepinephrine as prognostic indicator in patients with congestive heart failure. J Kardiol 2001;8(7-8):286-92.
Exclude: Not in English

Zugck C, Haunstetter A, Kruger C, et al. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. J Am Coll Cardiol 2002 May 15;39(10):1615-22.
Exclude: BNP measure not FDA approved

Zver S, Zadnik V, Bunc M, et al. Cardiac toxicity of high-dose cyclophosphamide in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Int J Hematol 2007 Jun;85(5):408-14.
Exclude: BNP measure not FDA approved

APPENDIX H.

KQ1 Evidence Set

Appendix H. KQ1 Evidence Set - Table of Contents

Tables

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Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Alibay,[1] 2005 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=45), cardiac heart failure (n=60), pulmonary disease (n=55); Reference Standard: 2 cardiologists	Evaluated the influence of creatinine clearance, Age, gender and BMI on plasma BNP and NT-proBNP levels	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=160, Mean age: 80.13y, % Males:38 HF Prevalence: 37.5%	50	99	31	1.43	0.03	NR
					100	98	47	1.85	0.04	NR
					150	94	61	2.41	0.10	0.82
					200	87	64	2.42	0.20	NR
Arenja, [2] 2011 Switzerland	Cohort (BASEL); Ethnicity: NR Comorbidities: hypertension (n=452), CAD (n=212), historical MI (n=111), chronic kidney disease (n=187); Reference Standards: 2 independent cardiologists	To extend this finding to AHF using a sensitive cardiac troponin I (s-cTnI) assay. Secondary aim was to investigate whether quantification of cardiomyocyte damage by s-cTnI would also be useful diagnostically to differentiate between AHF and noncardiac causes of acute dyspnoea.	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	dyspnea (n= 667,age= 76(64-83)y, %males=53); HF prevalence=56.5%	NR	NR	NR	NR	NR	0.96
Arques,[3] 2007 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=19), CAD (n=6), diabetes mellitus (n=10), previous HF (n=16), history of chronic pulmonary disease (n=11); Reference Standard: 2 cardiologists; 1 chest physician	Emergency diagnosis of CHF with a normal left ventricular ejection fraction	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, ≥70y n=41, Mean age: 84y, % Males:41 HF Prevalence: 53.7%	200	96	74	3.63	0.06	NR
					253	86	90	8.23	0.15	0.928
					≥253	96	90	9.10	0.05	NR
					≥253	96	90	9.10	0.05	NR
					≥200	96	84	6.04	0.05	NR
					≥200	96	79	4.55	0.06	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Barcarse,[4] 2004 USA	Cross-sectional (Independent study); Ethnicity: Caucasian (n=78), African-American (n=10), Hispanic (n=6), Asian (n=4); Comorbidities: Hypertension (n=73), CAD (n=44), stroke (n=14), atrial fibrillation (n=13), COPD (n=37), diabetes mellitus (n=41), MI (n=40), CHF (n=58), asthma (n=13), pulmonary embolism (n=3), valvular heart disease (n=14); Reference Standard: 1 cardiologist	Cardiac death, readmission, or visit to the ED within 90 days	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test	Acute SOB n=98, Mean age: 64.6 1.2), % Males:100 HF Prevalence: 58%	110	NR	NR	NR	NR	0.979
				Diagnose CHF, BNP>100 n=33, Mean age: NR % Males: NR HF Prevalence: 58%	590	NR	NR	NR	NR	0.64
Boldanova,[5] 2010 Switzerland	Cross-sectional (BASEL); Ethnicity: NR Comorbidities: Hypertension (n=237), CAD (n=225), stroke (n=91), COPD (n=140), renal disease (n=112), any pulmonary disease (n=226), deep vein thrombosis (n=41), depressive disorder (n=36), previous heart failure (n=64); Reference Standard: 1 physician	Diagnostic accuracy of BNP Prognostic value of BNP (one year mortality)	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=452, Mean age: NR % Males: NR HF Prevalence: 49.3%	NR	NR	NR	NR	NR	NR
				Dyspnea, previous history of HF n=64, Mean age: 73 11)y, % Males:61 HF Prevalence: 84%	100	96	45	1.75	0.09	NR
					403	80	77	3.48	0.26	0.84
					500	76	77	3.30	0.31	NR
				Dyspnea, no previous history of HF n=388, Mean age: 73 11)y, % Males:52 HF Prevalence: 43.6%	100	94	59	2.29	0.10	NR
					289	81	83	4.76	0.23	0.883
					500	68	99	68.00	0.32	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[6] 2005 France	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=153), COPD (n=127), MI (n=124), previous CHF (n=128); Reference Standard: Urgentists	Diagnostic-accuracy study	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=381, Mean age: 79±12, % Males: NR HF Prevalence: 30.2%	NR	NR	NR	NR	NR	NR
				Dyspnea, GFR <30 n=41, Mean age: 83 (11)y, % Males: NR HF Prevalence: 48.8%	515	82	89	7.45	0.20	0.89
				Dyspnea, GFR 59-30 n=187, Mean age: 81(10)y, % Males: NR HF Prevalence: 34.2%	480	74	81	3.89	0.32	0.799
				Dyspnea, 89-60 n=141, Mean age: 74(13)y, % Males: NR HF Prevalence: 19.9%	290	76	88	6.33	0.27	0.842
Chenevier-Gobeaux,[7] 2008 France	Cross-sectional (Ray 2005); Ethnicity: NR Chenevier-Gobeaux 2005); Comorbidities: Hypertension (n=272), CAD (n=180), COPD (n=167), previous HF (n=138), malignancy (n=94); Reference Standard: physicians	CHF	BNP [TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=570, Mean age: NR % Males:48 HF Prevalence: 44.4%	NR	NR	NR	NR	NR	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[7] 2008 France (cont'd)	(repeated data) Cross-sectional (Ray 2005); Ethnicity: NR Chenevier-Gobeaux 2005); Comorbidities: Hypertension (n=272), CAD (n=180), COPD (n=167), previous HF (n=138), malignancy (n=94); Reference Standard: physicians	(repeated data) CHF	(repeated data) BNP [TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, ≥85y n=210, Mean age: NR % Males:35 HF Prevalence: 52%	250	85	64	2.36	0.23	NR
					290	80	69	2.58	0.29	0.797
					380	70	73	2.59	0.41	NR
					400	67	75	2.68	0.44	NR
					500	60	79	2.86	0.51	NR
					590	55	85	3.67	0.53	NR
				Acute dyspnea, <85y n=360, Mean age: NR % Males:52 HF Prevalence: 40%	270	73	83	4.29	0.33	0.835
Chenevier-Gobeaux,[8] 2010 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=152), prior AMI/angina (n=124), COPD (n=125), previous CHF (n=125); Reference Standard: 2 emergency department physicians	Determine the relationship between the estimated glomerular filtration rate (eGFR) and MR-proANP concentrations in dyspnea emergency patients and to compare the diagnostic performance of MR-proANP with that of NT-proBNP and BNP with respect to renal function	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, > 60 ys, n=378, Mean age: 78(12)y, % Males:50 HF Prevalence: 30.16%	100 ng/L	99	41	1.68	0.02	0.82
				Tertile 3 eGFR >= 58.6 ml/min/1.73 m2) n=126, Mean age: 73(13)y, % Males:68 HF Prevalence: 17.46%	210 ng/L	86	71	2.97	0.20	0.85

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[8] 2010 France (cont'd)	(repeated data) Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=152), prior AMI/angina (n=124), COPD (n=125), previous CHF (n=125); Reference Standard: 2 emergency department physicians	(repeated data) Determine the relationship between the estimated glomerular filtration rate (eGFR) and MR-proANP concentrations in dyspnea emergency patients and to compare the diagnostic performance of MR-proANP with that of NT-proBNP and BNP with respect to renal function	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Tertile 2 eGFR between 44.3 and 58.5 ml/min/1.73m2) n=126, Mean age: 79(11)y, % Males:44 HF Prevalence: 34.13%	280 ng/L	88	72	3.14	0.17	0.86
				Tertile 1 eGFR<44.3 ml/ min/1.73 m2), n=126, Mean age: 83(10)y, % Males:39 HF Prevalence: 38.89%	550 ng/L	85	65	2.43	0.23	0.76
Choi,[9] 2007 Korea	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=183), COPD (n=56), diabetes mellitus (n=80), renal disease (n=15), angina (n=70), Hypertension plus diabetes (n=97), Hypertension plus COPD (n=51), Hypertension plus renal failure (n=44); Reference Standard: the final diagnosis of CHF was defined by transthoracic echocardiography.	Determining the cut off value for diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=1,040, Mean age: NR % Males:56 HF Prevalence: 36.3%	12.5	100	28	1.39	0.00	0.961
					100	99	67	3.00	0.02	NR
					191	96	84	5.82	0.05	NR
					296.5	91	91	10.52	0.10	0.961
					400	85	96	22.29	0.16	NR
					496	70	97	25.96	0.31	NR
					601	61	98	26.35	0.40	NR
					983.5	40	99	33.25	0.61	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chung,[10] 2006 Australia	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Historical MI (n=25), History of HF (n=80), History of respiratory disease (n=93), History of HF and respiratory disease (n=48); Reference Standard: 1 cardiologist	Accurate diagnosis of patients with history of HF using BNP	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Patients with dyspnea , all n=143, Mean age: 79(10), % Males:44 HF Prevalence: 50.3%	100	100	41	1.65	0.00	0.85
					400	87	76	3.63	0.17	NR
				History of HF n=80, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.74
				No history of HF n=63, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.94
				LVEF <50% n=67, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.64
				LVEF ≥50% n=39, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.87
				High serum creatinine n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.81
				Low serum creatinine n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.9

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chung,[10] 2006 Australia (cont'd)	(repeated data) Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Historical MI (n=25), History of HF (n=80), History of respiratory disease (n=93), History of HF and respiratory disease (n=48); Reference Standard: 1 cardiologist	(repeated data) Accurate diagnosis of patients with history of HF using BNP	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Initial inter-emergency department likelihood of HF n=44, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.79
				Low or high likelihood of HF n=9, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.86
				Patients > 79 years n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.85
				Patients < 79 years n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.88
Collins,[11] 2006 USA	Cross-sectional (Independent study); Ethnicity: Caucasian (n=166), other (n=177); Comorbidities: Hypertension (n=214), CAD (n=116), congestive HF (n=164), valvular heart disease (n=100), cardiomyopathy (n=65); Reference Standard: 2 senior cardiology fellows	Diagnosis of HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=NR Mean age: NR % Males: NR HF Prevalence: 38.8%	"indeterminate zone" (100 to <= 500 pg/ml)	NR	NR	NR	NR	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Coste,[12] 2006 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: history of HF (n=174); Reference Standard: 2 cardiologists	Diagnosis of acute or decompensated HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=699, Mean age: 72.8y(14.3) % Males:68 HF Prevalence: 60%	NR	NR	NR	NR	NR	NR
				Acute dyspnea , no history CHF n=525, Mean age: NR % Males: NR HF Prevalence: NR%	The cutoff points delimiting the gray zones glow=167 ng/L (95% bootstrap CI: 108 to 219) and gup= 472 ng/L (95% bootstrap CI: 390 to 501)	NR	NR	18.25	0.05	NR
				Acute dyspnea , history of CHF n=174, Mean age: NR % Males: NR HF Prevalence: NR%	gup=334 ng/L (95% bootstrap CI 178 to 465); glow=0	NR	NR	3.35	0.01	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Daniels,[13] 2006 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=618); Comorbidities: COPD (n=542), Diabetes mellitus (n=347), Myocardial infarction (n=384), CHF (n=456); Reference Standard: 2 cardiologists	How obesity affects cutpoints for BNP in diagnosis of heart failure	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=1,368, Mean age: 65y, % Males:56 HF Prevalence: 46.1%	NR	NR	NR	NR	NR	NR
				Dyspnea , BMI <25 n=526, Mean age: 67.3y % Males:55.7 HF Prevalence: 47%	100	94	65	2.63	0.10	0.9
				Dyspnea, 25 ≤BMI <35 n=595, Mean age: 63.2y % Males:58 HF Prevalence: 46.2%	100	92	76	3.88	0.10	0.91
				Dyspnea , BMI z35 n=247, Mean age: 56.7y, % Males:46.3 HF Prevalence: 44.1%	100	77	84	4.85	0.27	0.88
				Dyspnea , BMI <25 n=526, Mean age: 67.3, % Males:55.7 HF Prevalence: 47%	100	90	NR	NR	NR	NR
				Dyspnea , 25 ≤BMI <35 n=595, Mean age: 63.2y, % Males:58 HF Prevalence: 46.2%	110	90	NR	NR	NR	NR
				Dyspnea , BMI z35 n=247, Mean age: 56.7y, % Males:46.3 HF Prevalence: 44.1%	54	90	NR	NR	NR	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Dao,[14] 2001 USA	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: CAD (n=100), COPD (n=90), CHF (n=75); Reference Standard: 2 cardiologists	Final diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	dyspnea, all n=250, Mean age: 63y, % Males:94 HF Prevalence: 38.8%	80	98	92	12.25	0.02	0.98
					100	94	94	15.67	0.06	NR
					115	90	96	22.50	0.10	NR
					120	90	96	22.50	0.10	NR
					150	87	97	29.00	0.13	NR
Defilippi,[15] 2007 USA	Cohort (Independent study); Ethnicity: African-American (n=318); Inclusion criteria = patients with the complaint of dyspnea who presented to the Carolinas Medical Center emergency department who underwent BNP measurement; Comorbidities: Hypertension (n=555), CAD (n=263), atrial fibrillation (n=175), diabetes mellitus (n=305), prior HF (n=287); Reference Standard: 1 cardiologist	All-cause mortality compared the diagnostic accuracies of NT-proBNP and BNP for diagnosing decompensated HF and predicting 1-year all-cause mortality)	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=831, Mean age: NR % Males:45.7 HF Prevalence: 52.6%	NR	NR	NR	NR	NR	NR
				No kidney disease eGFR>= 60 n=438, Mean age: 63.5 16.0)y, % Males:43.8 HF Prevalence: 45%	100 ng/L	90	37	1.42	0.27	0.95
				Kidney disease eGFR <60 n=393, Mean age: 69.3y(13.1) % Males:47.8 HF Prevalence: 61%	200 ng/L	82	53	1.74	0.34	0.68

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Dieplinger,[16] 2009 Austria	Cross-sectional (Mueller et al 2005, Gegenhuber et al 2006); Ethnicity: NR Comorbidities: Hypertension (n=141), CAD (n=117), atrial fibrillation (n=83), diabetes mellitus (n=58), history of HF (n=75), NYHA II (n=59), NYHA III (n=53), NYHA IV (n=25); Reference Standard: Framingham score for HF plus echocardiographic evidence of systolic or diastolic dysfunction	Evaluate the utility of established and novel biomarkers for the diagnosis of acute destabilised HF in patients with SOB presenting to an emergency department	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	Dyspnea n=251, Mean age: NR % Males: NR HF Prevalence: 54.6%	160ng/L	90	73	3.33	0.14	0.92
				Dyspnea attributable to acute emergency department HF n=137, Mean age: 69-82y, % Males:93 HF Prevalence: 46.2%	NR	NR	NR	NR	NR	NR
				Dyspnea not attributable to HF n=114, Mean age: 68-82y, % Males:95 HF Prevalence: 8.3%	NR	NR	NR	NR	NR	NR
Gorissen,[17] 2007 The Netherlands	Cross-sectional (Independent study); Acute dyspnea , all n=80, Mean age: 43–90yrs, % males=55; HF Prevalence=50% Ethnicity: NR Comorbidities: NR Reference Standard: consensus on clinical dx (cardiac + pulmonary)	Diagnostic-accuracy study	BNP Centaur (ADVIA - Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=160, Mean age: 80.13y, % Males:38 HF Prevalence: 37.5%	138 ng/L (Centaur)	65	88	5.42	0.40	0.775
					225 ng/L (Triage)	73	78	3.32	0.35	0.783
				Acute dyspnea , <65 n=17, Mean age: NR % Males: NR HF Prevalence: NR%	78 ng/L (Triage)	100	55	2.22	0.00	0.75
					91 ng/L (Centaur)	100	55	2.22	0.00	0.705
				Acute dyspnea , 65-75 n=23, Mean age: NR % Males: NR HF Prevalence: NR%	260 ng/L (Triage)	82	83	4.82	0.22	0.795
					188 ng/L (Centaur)	73	83	4.29	0.33	0.773

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gorissen,[17] 2007 The Netherlands (cont'd)	(repeated data) Cross-sectional (Independent study); Acute dyspnea , all n=80, Mean age: 43–90yrs, % males=55; HF Prevalence=50% Ethnicity: NR Comorbidities: NR Reference Standard: consensus on clinical dx (cardiac + pulmonary)	(repeated data) Diagnostic-accuracy study	(repeated data) BNP Centaur (ADVIA - Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea , >75 n=40, Mean age: NR % Males: NR HF Prevalence: NR%	309 ng/L (Triage)	68	71	2.34	0.45	0.765
					247 ng/L (Centaur)	68	77	2.96	0.42	0.767
				Acute dyspnea , GFR >60 n=40, Mean age: NR % Males: NR HF Prevalence: NR%	202 ng/L (Triage)	81	63	2.19	0.30	0.797
					127 ng/L (Triage)	73	85	4.87	0.32	0.799
				Acute dyspnea , GFR <60 n=40, Mean age: NR % Males: NR HF Prevalence: NR%	229 ng/L(Centaur)	64	70	2.13	0.51	0.669
					309 ng/L (Centaur)	64	74	2.46	0.49	0.69
Gruson,[18] 2008 Belgium	Cohort (Independent study); Ethnicity: NR Comorbidities: NR Reference Standard: 1 cardiologist	Diagnostic accuracy of NT-proBNP in patients in the emergency department (ED) with dyspnea and/or chest pain.	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Patients with dyspnea and/or chest pain with cardiovascular and/or pulmonary disorders), all n=137, Mean age: 69y, % Males:56.2 HF Prevalence: 22.6%	NR	NR	NR	NR	NR	0.93
Gruson,[19] 2009 Belgium	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=10), renal disease (n=17), pulmonary disorders (n=21), pulmonary embolism (n=19), ; Reference Standard: clinicians	To evaluate the SOB panel and to assess its reliability in patients presenting in ED with dyspnea and/or atypical thoracic pain	SOB BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Dyspnea, all n=97, Mean age: 30–95y, % Males:43 HF Prevalence: 19.6%	NR	100	59	2.44	0.00	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gruson,[20] 2012 Belgium	Cohort (Independent Study); Ethnicity= NR Comorbidities= hypertension (n=69), atrial fibrillation (n=11), diabetes mellitus (n=30), historical MI (n=20); Reference Standard= clinicians	To evaluate the diagnostic accuracy of circulating levels of proBNP in patients admitted to ED with dyspnea and/or thoracic pain. Moreover, we compared the performances of proBNP assay to two commercial assays for BNP and Nt-proBNP.	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	dyspnea and/or chest pain, all (n=156, mean= 67y, %males=54.5); HF Prevalence= 29.5%	100 ng/L	NR	NR	NR	NR	0.91
Havelka,[21] 2011 USA	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: NR Reference Standard: discharge diagnosis	Diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=54, Mean age:, % Males: 80y* HF Prevalence: NR%	NR	NR	NR	NR	NR	0.77
Knudsen,[22] 2004a Norway	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=52), Angina (n=47), Atrial Fibrillation (n=39), COPD (n=73), Diabetes mellitus (n=24), Historical MI (n=56), CABG (n=14); Reference Standard: 2 cardiologists		BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=155, Mean age: NR % Males:44.5 HF Prevalence: 48.3%	100	NR	NR	NR	NR	NR
				Acute dyspnea, women n=86, Mean age: 78y, % Males: NR HF Prevalence: 40.7%	50	100	37	1.59	0.00	NR
					100	94	55	2.09	0.10	NR
					150	91	59	2.22	0.15	NR
					200	89	63	2.38	0.18	0.86

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Knudsen,[22] 2004a Norway (cont'd)	(repeated data) Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=52), Angina (n=47), Atrial Fibrillation (n=39), COPD (n=73), Diabetes mellitus (n=24), Historical MI (n=56), CABG (n=14); Reference Standard: 2 cardiologists		(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=69, Mean age: 74y, % Males: NR HF Prevalence: 58%	50	95	38	1.53	0.13	NR
					100	90	55	2.01	0.18	NR
					150	93	62	2.44	0.12	NR
					200	90	72	3.26	0.14	0.9
				Acute dyspnea, >76y n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.88
				Acute dyspnea, <76y n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.82
Knudsen,[23] 2004b Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=340), African-American (n=495); Comorbidities: Hypertension (n=547), Acute MI (n=250); Reference Standard: 2 cardiologists, Framingham, NHANES		BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, All n=880, Mean age: 64y, % Males:55 HF Prevalence: 51%	100	90	75	3.60	0.13	NR
					200	80	87	6.15	0.23	NR
					300	71	90	7.10	0.32	NR
					400	64	92	8.00	0.39	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Knudsen,[24] 2005 Multi-national study	Cohort (Breathing Not Properly Study) Ethnicity: NR Comorbidities: diabetes mellitus (n=325), MI (n=353), congestive HF (n=480), arterial Hypertension (n=799); Reference Standard: 2 cardiologists	Diagnosis of acute HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=1,431, Mean age: NR % Males: NR HF Prevalence: 46.1%	NR	NR	NR	NR	NR	NR
				Atrial fibrillation n=292, Mean age: 67–827y, % Males:61.3 HF Prevalence: 46.6%	≥50	99	21	1.24	0.07	NR
					≥100	95	40	1.57	0.14	NR
					≥200	85	73	3.12	0.20	0.084
					≥300	74	80	3.63	0.32	NR
					≥400	64	86	4.70	0.41	NR
					≥500	55	88	4.50	0.51	NR
					≥600	47	89	4.27	0.60	NR
					≥700	43	89	3.86	0.65	NR
					≥800	36	93	5.24	0.69	NR
				No atrial fibrillation n=1,139, Mean age: 49–74y, % Males:59.1 HF Prevalence: 30.2%	≥50	96	65	2.75	0.06	NR
					≥100	89	79	4.15	0.15	NR
					≥200	79	88	6.69	0.24	0.91
					≥300	71	91	7.96	0.32	NR
					≥400	62	93	8.56	0.41	NR
					≥500	55	94	9.03	0.48	NR
					≥600	50	95	9.42	0.53	NR
					≥700	47	96	11.80	0.55	NR
					≥800	47	96	13.06	0.55	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Knudsen,[24] 2005 Multi-national study (cont'd)	(repeated data) Cohort (Breathing Not Properly Study) Ethnicity: NR Comorbidities: diabetes mellitus (n=325), MI (n=353), congestive HF (n=480), arterial Hypertension (n=799); Reference Standard: 2 cardiologists	(repeated data) Diagnosis of acute HF	(repeated data) BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Atrial fibrillation by ECG upon admission n=158, Mean age: NR % Males: NR HF Prevalence: NR%		NR	NR	NR	NR	0.8
				History of atrial fibrillation but no current af n=134, Mean age: NR % Males: HF Prevalence: NR%		NR	NR	NR	NR	0.86
Lainchbury,[25] 2003 New Zealand	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: CAD (n=88), COPD (n=86), previous HF (n=52); Reference Standard: 2 cardiologists	Final clinical diagnosis	BNP- Biosite point-of-care assay [TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, all n=205, Mean age: 70 14), % Males:49 HF Prevalence: 34.1%	20 pmol/L	97	44	1.73	0.07	NR
					30 pmol/L	97	49	1.90	0.06	NR
					60 pmol/L	94	70	3.13	0.09	0.89
					80 pmol/L	83	78	3.77	0.22	NR
					100 pmol/L	77	84	4.81	0.27	NR
			BNP- local research assay (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		33 pmol/L	87	82	4.83	0.16	NR
			BNP- local research assay (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		44 pmol/L	88	82	4.89	0.15	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Logeart,[26] 2002 France	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=65), Prior AMI/angina (n=53), Diabetes mellitus (n=23), Previous CHF (n=80); Reference Standard: 2 cardiologists and 1 pneumologist	No specified end point other than diagnosis	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, all n=163, Mean age: 67y, % Males:66.8 HF Prevalence: 70.1%	80	97	27	1.33	0.11	NR
					100	96	31	1.39	0.13	NR
					150	93	45	1.69	0.16	NR
					200	93	56	2.11	0.13	NR
					250	91	68	2.84	0.13	NR
					300	88	87	6.77	0.14	0.93
					400	79	93	11.29	0.23	NR
Lokuge,[27] 2010 Australia	RCT (SOB); Inclusion criteria: Patients presenting to the Alfred and the Northern Hospital EDs with a chief complaint of dyspnea; Ethnicity: NR Comorbidities: Hypertension (n=308), atrial fibrillation (n=172), COPD (n=388), diabetes mellitus (n=121), ischemic heart disease (n=253), prior HF (n=220), renal failure (n=69); Reference Standard: 1 cardiologist, emerg.or resp.	Accuracy of HF diagnosis	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	Dyspnea n=306, Mean age: 74 11)y, % Males:54 HF Prevalence: 48.4%	101	92	51	1.88	0.16	0.87
					265*	83	81	4.37	0.21	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Maisel,[28] 2002 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: COPD (n=650), diabetes mellitus (n=397), MI (n=523), CHF (n=523); Reference Standard: 2 cardiologists	Final diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=1,586 Mean age: 64y % Males:56 HF Prevalence: 47%	50	97	62	2.55	0.05	NR
					80	93	74	3.58	0.09	NR
					100	90	76	3.75	0.13	0.91
					125	87	79	4.14	0.16	NR
					150	85	83	5.00	0.18	NR
Maisel,[29] 2003 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: Hypertension (n=879), Prior AMI/angina (n=308), Atrial fibrillation (n=256), COPD (n=600), Diabetes mellitus (n=367), Myocardial infarction (n=385), CHF (n=527), CABG (n=176); Reference Standard: 2 cardiologists	This study examines B-type natriuretic peptide (BNP) levels in patients with systolic versus non-systolic dysfunction presenting with SOB for the purpose of diagnosis of HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=1,586, Mean age: 64y, % Males:56 HF Prevalence: 47%	100	90	73	3.33	0.14	0.9
					200	81	85	5.40	0.22	NR
					300	73	89	6.64	0.30	NR
					400	63	91	7.00	0.41	NR
				CHF n=452, Mean age: 64y, % Males:56 HF Prevalence: 47%	100	95	14	1.10	0.36	NR
					200	89	NR	NR	NR	NR
					300	83	39	1.36	0.44	0.66
					400	74	50	1.48	0.52	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Maisel,[30] 2004 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: NR Reference Standard: 2 cardiologists	Final diagnosis of CHF or non-CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=1,586 Mean age: 64yrs % Males=56 HF Prevalence: 47%	100	90	73	3.34	0.13	NR
					200	81	85	5.46	0.22	NR
					300	73	89	6.36	0.31	NR
					400	63	91	7.04	0.41	NR
				18 to 69 yrs n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	86	82	4.69	0.17	0.915
					200	77	91	8.45	0.25	NR
					300	69	94	11.10	0.33	NR
					400	60	95	11.23	0.43	NR
				70 to 105 yrs n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	94	53	2.00	0.12	0.844
					200	85	72	3.03	0.21	NR
					300	75	77	3.27	0.32	NR
					400	65	83	3.85	0.42	NR
				Male n=883, Mean age: NR % Males: 100 HF Prevalence: 47.7%	100	92	76	3.84	0.10	0.918
					200	84	88	6.93	0.18	NR
					300	73	90	7.49	0.30	NR
					400	64	93	9.00	0.39	NR
				n=703 Mean age: NR % Males: NR HF Prevalence: 45.7%	100	88	59	2.16	0.20	0.87
					200	78	82	4.27	0.27	NR
					300	72	87	5.40	0.32	NR
					400	61	89	5.55	0.44	NR
				Caucasian n=773 Mean age: NR % Males: NR HF Prevalence: 49.9%	100	93	69	2.96	0.10	0.888
					200	82	82	4.63	0.21	NR
					300	72	86	5.11	0.33	NR
					400	60	90	5.86	0.44	NR
				African-American n=715 Mean age: NR % Males: NR HF Prevalence: 43.9%	100	87	76	3.61	0.17	0.903
					200	81	88	6.45	0.22	NR
					300	74	91	8.24	0.28	NR
					400	66	93	8.79	0.37	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Maisel,[31] 2010 Multi-national study	Cross-sectional (BACH); Ethnicity: Caucasian (n=1090), African-American (n=476), other (n=60); Comorbidities: arrhythmia (n=405), dyslipidemia (n=570), Hypertension (n=1080), CAD (n=504), obstructive lung disease (n=201). prior AMI/angina (n=61), stroke (n=165), ACS (n=38), COPD (n=471), diabetes mellitus (n=462), historical MI (n=300), asthma (n=318), pneumonia (n=112), pulmonary embolism (n=85), chronic renal insufficiency (n=246); Reference Standard: 2 cardiologists	Diagnosis of AHF, where the non-inferiority of MR-proANP compared with BNP was evaluated and 90-day survival, where the superiority of the utility of MR-proADM versus BNP for predicting survival over a period of 90 days	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea, all n=1,641, Mean age: NR % Males: NR HF Prevalence: 34.6%	100	96	62	2.51	0.07	0.91
					300	NR	NR	NR	NR	0.9
McCullough,[32] 2002a Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=230), African-American (n=161), other (n=26); Comorbidities: Hypertension (n=196), prior AMI/angina (n=58), AF (n=54), diabetes mellitus (n=66), historical MI (n=60), MI (n=60), prior CABG (n=26), prior CHD (n=125); Reference Standard: 2 cardiologists, Framingham, NHANES	Diagnosis of HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=417, Mean age: 62.2y, % Males:55.2 HF Prevalence: 20.9%	100	93	77	4.10	0.09	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
McCullough,[33] 2002b Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: Hypertension (n=854), prior AMI/angina (n=371), atrial fibrillation (n=245), COPD (n=580), diabetes mellitus (n=356), stable angina (n=205), prior CHF (n=511), prior CABG (n=168); Reference Standard: 2 cardiologists	Diagnostic accuracy	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=1,538, Mean age: 64y, % Males:56 HF Prevalence: 47%	100	90	73	3.33	0.14	0.9
Morrison,[34] 2002 USA	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=209), CAD (n=173), COPD (n=128), coronary artery bypass graft (n=71), CHF (n=135); Reference Standard: 2 cardiologists, Framingham criteria, echocardiography, nuclear medicine, ejection fractions, or left ventriculography done at cardiac catheterization.	The purpose of this study was to determine if BNP levels could accurately differentiate CHF from dyspnea of pulmonary etiology.	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=321, Mean age: NR % Males: NR HF Prevalence: 42%	94	86	98	43.00	0.14	0.99
					105	86	94	14.33	0.15	NR
					135	90	90	9.00	0.11	NR
					195	94	85	6.27	0.07	NR
					240	96	79	4.57	0.05	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Mueller,[35] 2005 & Gegenhuber,[36] 2006 Austria	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=117), atrial fibrillation (n=83), diabetes mellitus (n=58), renal disease (n=74), arterial Hypertension (n=141); Reference Standard: Framingham	Diagnostic accuracy of BNP/NT-proBNP	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	Dyspnea all n=251, Mean age: 58-82y, % Males:93 HF Prevalence: 55%	100 ng/L	96	61	2.46	0.07	NR
					118 ng/L	95	64	2.64	0.08	NR
					160 ng/L	90	73	3.33	0.14	NR
					295 ng/L	80	86	5.71	0.23	NR
Noveanu,[37] 2009 Switzerland	RCT (BASEL); Ethnicity: NR Comorbidities: Hypertension (n=237), CAD (n=225), COPD (n=140), diabetes mellitus (n=103), renal disease (n=112), asthma (n=29), pulmonary embolism (n=31); Reference Standard: internal med specialist	360 days mortality, 360-D in-hospital, 360 day treatment cost, in-hospital mortality, Time to treatment; Hospital admission; Time to discharge, Initial treatment cost	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=452, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	NR
				SOB, BMI >30 n=86, Mean age: 72 15)y, % Males:59 HF Prevalence: 44%	100	91	68	2.84	0.13	NR
					182	85	83	5.00	0.18	0.884
					500	56	96	14.00	0.46	NR
				SOB, BMI <30 n=366, Mean age: 65 14), % Males: HF Prevalence: 50%	100	96	56	2.18	0.07	NR
					298	84	81	4.42	0.20	0.885
					500	73	89	6.64	0.30	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Pahle,[38] 2009 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: NR Comorbidities: Hypertension (n=879), atrial fibrillation (n=145), diabetes mellitus (n=353), historical MI (n=362), previous HF (n=503); Reference Standard: 2 cardiologists, Framingham, NHANES	Utility of BNP measurement for diagnosing HF in the emergency department	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=1,583, Mean age: 64 17)y, % Males:56 HF Prevalence: 47%	NR	NR	NR	NR	NR	NR
				Dyspnea, history of hypertension n=879, Mean age: 56-77y, % Males:54 HF Prevalence: 54.3%	50	97	56	2.20	0.05	NR
					100	90	72	3.21	0.14	NR
					120	88	76	3.67	0.16	NR
					140	86	78	3.91	0.18	NR
					160	85	80	4.25	0.19	NR
					194	NR	NR	NR	NR	0.88
					180	83	83	4.88	0.20	NR
					200	82	85	5.47	0.21	NR
					300	74	88	6.17	0.30	NR
				Dyspnea, no history of hypertension n=608, Mean age: 45-75y, % Males:60 HF Prevalence: 34.5%	50	98	70	3.27	0.03	NR
					100	90	83	5.29	0.12	NR
					115	NR	NR	NR	NR	0.93
					120	87	85	5.80	0.15	NR
					140	83	88	6.92	0.19	NR
					160	82	89	7.45	0.20	NR
					180	80	92	10.00	0.22	NR
					200	79	93	11.29	0.23	NR
					300	68	95	13.60	0.34	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Pahle,[38] 2009 Multi-national study (cont'd)	(repeated data) Cross-sectional (Breathing Not Properly Study) Ethnicity: NR Comorbidities: Hypertension (n=879), atrial fibrillation (n=145), diabetes mellitus (n=353), historical MI (n=362), previous HF (n=503); Reference Standard: 2 cardiologists, Framingham, NHANES	(repeated data) Utility of BNP measurement for diagnosing HF in the emergency department	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, elevate emergency department BP n=843, Mean age: 54=78y, % Males:51.8 HF Prevalence: 51.7%	50	97	61	2.49	0.05	NR
					100	91	78	4.14	0.12	NR
					120	88	80	4.40	0.15	NR
					140	87	82	4.83	0.16	NR
					150	NR	NR	NR	NR	0.9
					160	85	84	5.31	0.18	NR
					180	82	87	6.31	0.21	NR
					200	81	87	6.23	0.22	NR
					300	72	91	8.00	0.31	NR
				Dyspnea, no elevate emergency department BP n=740, Mean age: 49-76y, % Males:60 HF Prevalence: 42.4%	50	97	63	2.62	0.05	NR
					100	89	76	3.71	0.14	NR
					120	87	78	3.95	0.17	NR
					140	84	81	4.42	0.20	NR
					160	84	84	5.25	0.19	NR
					180	82	87	6.31	0.21	NR
					200	81	89	7.36	0.21	NR
					205	NR	NR	NR	NR	0.9
					300	73	91	8.11	0.30	NR
Parrinelo,[39] 2008 Italy	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=196), diabetes mellitus (n=56), ischemic heart disease (n=72), previous CHF (n=80), chronic obstructive pulmonary disease or asthma (n=112); Reference Standard: cardiologist, Framingham	Diagnosis of acute decompensated heart failure	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	SOB n=292, Mean age:67.5y, % Males:53.5 HF Prevalence: 58.9%	≥100	95	88	7.58	0.06	NR
					≥127	95	93	14.15	0.06	0.97

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Potocki,[40] 2010 Germany	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=195), CAD (n=80), COPD (n=98), diabetes mellitus (n=52), chronic kidney disease (n=80), previous HF (n=69); Reference Standard: 2 cardiologists	Compare the accuracy of MR-proANP with that of NT-proBNP to diagnose HF	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Micro-particle Enzyme Immunoassay (MEIA))	Dyspnea n=287, Mean age: 77 68–83)y, % Males:52 HF Prevalence: 53.7%	BNP	NR	NR	NR	NR	NR
Ray,[41] 2005 France	Cross-sectional (EPIDASA STUDY); Ethnicity: NR Comorbidities: chronic respiratory failure (n=35), cardiac disease (n=64); Reference Standard: 2 independent experts (pulmonologist, cardiologist, emergency physician, or geriatric or internal physician)	Final diagnosis (CPE or no CPE)	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, 65 and older n=202, Mean age: 65–100y, % Males:49 HF Prevalence: 43.6%	250	73	91	8.11	0.30	0.85
Ray,[42] 2006 France	Cross-sectional (EPIDASA study) Ethnicity: NR Comorbidities: cardiac insufficiency (n=63), chronic respiratory insufficiency (n=76), venous thromboembolic disease (n=36); Reference Standard: 2 of cardiologists, pulmonologist, general medicine intern., geriatrician, emergency department physician	Diagnosis of cardiac pulmonary edema or no CPE	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea >65 yrs n=308, Mean age: 80y, % Males:49 HF Prevalence: 45.7%	100	90	59	2.20	0.17	NR
					150	85	71	2.93	0.21	NR
					200	82	84	5.13	0.21	NR
					250	78	90	7.80	0.24	0.874
					300	72	92	9.00	0.30	NR
					350	67	92	8.38	0.36	NR
					400	60	95	12.00	0.42	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC

Ro,[43] 2011
 	
USA
	Cross-Sectional Design (Independent Study);
	Ethnicity:
	caucasian (n=231), African American (n=8), hispanic (n=9), asian (n=1), other unspecified (n=1);
	Comorbidities:
	hypertension (n=196), CAD (n=143), acute MI (n=101), COPD (n=63), diabetes melitus (n=98), pulmonary embolism (n=13), chronic kidney disease (n=48), stable angina (n=44), unstable angina (n=21);
	Reference Standard:
	cardiologist, discharge diagnosis, echo
		To compare the ease of use, performance, and diagnostic accuracy of Triage BNP (Biosite, San Diego, CA) and i-STAT BNP (Abbott, East Windsor, NJ) POC devices in patients with symp-toms suggestive of heart failure in an ED setting.	I-STAT BNP		100	94.4	43.3	1.66	0.13	0.84

			BNP (TRIAGE - BNP Test) I-STAT BNP (i-STAT BNP test)		100	87.7	52.5	1.85	0.23	0.81
Rogers,[44] 2009a Multi-national study	Cohort (HEARD-IT); Ethnicity: Caucasian (n=344), African-American (n=370); Comorbidities: history of HF (n=384), Reference Standard: 2 cardiologists	To create a model that adjusts B-type natriuretic peptide (BNP) for specific covariates to better distinguish cardiac from non-cardiac dyspnea	BNP (Abbott AxSYM® BNP MEIA, ADVIA - Centaur®, BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=740, Mean age: NR % Males: NR HF Prevalence: 49.7%	100	96	69	3.10	0.06	0.937
					400	NR	93	NR	NR	NR
					Adjust BNP cut-off with 96% sen	96	73	3.56	0.05	0.948

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Rogers,[45] 2009b USA	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: atrial fibrillation (n=107), COPD (n=43), history of HF (n=164); Reference Standard: 4 physicians	Diagnostic performance for BNP, distinguishing cardiac from non-cardiac dyspnea	BNP (i-STAT BNP test)	Dyspnea, all n=335, Mean age: 72 11)y, % Males: NR HF Prevalence: 42.1%	100	91	54	1.98	0.17	0.858
					400	NR	92	NR	NR	NR
				Dyspnea, age >= 75 years n=171, Mean age: NR % Males: NR HF Prevalence: NR%	100	94	41	1.59	0.15	NR
					184	91	66	2.68	0.14	NR
				Dyspnea, atrial fibrillation n=109, Mean age: NR % Males: NR HF Prevalence: NR%	100	92	26	1.24	0.31	NR
					150	91	39	1.49	0.23	NR
					449	91	78	4.14	0.12	NR
				Dyspnea, creatinine>= 2 mg/dl n=47, Mean age: NR % Males: NR HF Prevalence: NR%	100	100	30	1.43	0.00	NR
				Dyspnea, BMI >= 35 kg/m2 n=85, Mean age: NR % Males: NR HF Prevalence: NR%	25	91	25	1.21	0.36	NR
					100	64	61	1.64	0.59	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Sanz,[46] 2006 Spain	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: systolic dysfunction (n=5), atrial fibrillation (n=8), COPD (n=11), ischemic heart disease (n=5), cardiomyopathy hypertensive (n=9), valvular (n=7); Reference Standard: Symptoms and signs and the following clinical and laboratory emergency department: physical examination, blood test, ECG, chest x-radiography, and in some cases, echocardiography criteria (10)	The aim of this study was to evaluate the value of NT-proBNP and BNP in patients with acute dyspnea in the ED. diagnostic accuracy of different assays.	BNP - ADVIA (ADVIA - Centaur® BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=100, Mean age: 75 14.77)y, % Males:67 HF Prevalence: NR%	79	95	96	22.16	0.05	NR
					100	86	98	39.09	0.14	NR
					116	93	96	21.11	0.07	NR
					100	95	89	8.58	0.05	NR
					NR	NR	NR	NR	NR	0.965
					NR	NR	NR	NR	NR	0.975
Shah,[47] 2009a NR	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=267), CAD (n=178), atrial fibrillation (n=81), diabetes mellitus (n=121), CHF or cardiomyopathy (n=147); Reference Standard: panel of experts and antihypertensive and lipid lowering treatment to prevent heart attack trial criteria	Mortality after one-year	BNP (TRIAGE - BNP Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea n=412, Mean age: NR % Males: NR HF Prevalence: 37%	100	NR	NR	NR	NR	NR
				Acute dyspnea, LVEF ≤40% n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.88

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Shah,[47] 2009a NR (cont'd)	(repeated data) Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=267), CAD (n=178), atrial fibrillation (n=81), diabetes mellitus (n=121), CHF or cardiomyopathy (n=147); Reference Standard: panel of experts and antihypertensive and lipid lowering treatment to prevent heart attack trial criteria	(repeated data) Mortality after one year	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea, LVEF≥50% n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.57
				Acute dyspnea, dx of diastolic function n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.67
Shah,[48] 2009b USA	Cohort (Independent study); Ethnicity: Caucasian (n=136), African-American (n=264), other (n=12); Comorbidities: Hypertension (n=268), CAD (n=177), diabetes mellitus (n=124), historical MI (n=99), renal disease (n=140), heart failure (n=148); Reference Standard: 2 physicians	1 year all-cause mortality	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea n=412 Mean age: NR % Males: NR HF Prevalence: 35.7%	100	NR	NR	NR	NR	0.9
Steg,[49] 2005 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: NR Comorbidities: NR Reference Standard: 2 cardiologists, Framingham, NHANES	Confirmation of the diagnosis CHF or non-CHF patients	BNP (TRIAGE – BNP Test)	Dyspnea n=709 Mean age: 66.4 14.7)y % Males:43.3 HF Prevalence: 69%	50	95	50	1.90	0.10	NR
					80	92	72	3.29	0.11	NR
					100	89	73	3.30	0.15	NR
					125	83	83	4.88	0.20	NR
					150	84	80	4.20	0.20	NR
					162	86	79	4.10	0.18	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Villacorta,[50] 2002 Brazil	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=36), CAD (n=30), prior AMI/angina (n=18), atrial fibrillation (n=8), COPD (n=31), renal disease (n=6), coronary (n=14), previous CHD (n=26); Reference Standard: 1 cardiologist	Ability of BNP in diagnosing CHF	BNP (TRIAGE - BNP Test)	Acute dyspnea n=70, Mean age: 72.4y % Males: NR HF Prevalence: 51.4%	200	100	97	33.33	0.00	0.99
Wang,[51] 2010 Taiwan	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=38), CAD (n=18), COPD (n=13), diabetes mellitus (n=25), prior HF (n=15); Reference Standard: 2 cardiologists	Diagnosing AHF in patients with acute dyspnea with available plasma BNP	BNP (Abbott AxSYM® BNP MEIA)	Acute dyspnea n=84 Mean age: 73y % Males: 48 HF Prevalence: 58.3%	100	94	34	1.43	0.18	NR
					500	65	74	2.54	0.47	NR

Table H-1. Evidence Tables: Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (cont'd)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Wu,[52] 2004 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: Hypertension (n=679), prior AMI/angina (n=308), atrial fibrillation (n=256), COPD (n=600), historical (n=385), prior CABG (n=176), prior (n=527); Reference Standard: 2 cardiologists	Effect of diabetes on BNP concentrations in patients presenting to the ED with dyspnea	BNP (TRIAGE - BNP) Test	Dyspnea all n=1,586 Mean age: NR % Males: NR HF Prevalence: 46.6%	100ng/L	NR	NR	NR	NR	NR
				Dyspnea, without diabetes n=1,219 Mean age: 65.6(13.02)y % Males:59.4 HF Prevalence: 40%	100ng/L	NR	NR	NR	NR	0.88
				Dyspnea, with diabetes n=367 Mean age: 63.5(17.6)y % Males:5.4 HF Prevalence: 59%	100ng/L	NR	NR	NR	NR	0.878

Abbreviations: AHF = acute heart failure; AMI = acute myocardial infarction; AUC = area under the Curve; BACH = Biomarkers in Acute Heart Failure; BASEL = B-type natriuretic peptide for Acute Shortness of Breath Evaluation; BMI = body mass index; BP = blood pressure; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CAGB = coronary artery bypass graft; CHD = chronic heart disease; CHF = chronic heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPE = cardiogenic pulmonary edema; ECG = electrocardiogram; ED = emergency department; eGFR = estimated glomerular filtration rate; EPIDASA = Epidemiological study of acute dyspnea in elderly patients; GFR = glomerular filtration rate; glow = lower gray zone; gup = upper gray zone; HEARD-IT = Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment; HF = heart failure; KD = kidney disease; kg/m2 = kilograms per meter squared; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; LVEF = left ventricular ejection fraction; MEIA = microparticle enzyme immunoassay; mg/dL = milligram per deciliter; MI = myocardial infarction; mL/min/1.73m2 = milliliter per minute per 1.73 meters squared; MR-proANP = midregional pro-A-type natriuretic peptide; ng/L = Nanogram per liter; NHANES = National Health and Nutrition Examination Survey; NR = Not reported; NT-proBNP = N-Terminal proBNP; NYHA = New York Heart Association; pg/mL = Picograms per milliliter; RCT = Randomized controlled trial; SOB = Shortness of breath; USA = United States of America; yrs = years

Figure H-1. Summary Sensitivity (ED BNP, 100±5 pg/ml cutpoint), random effect

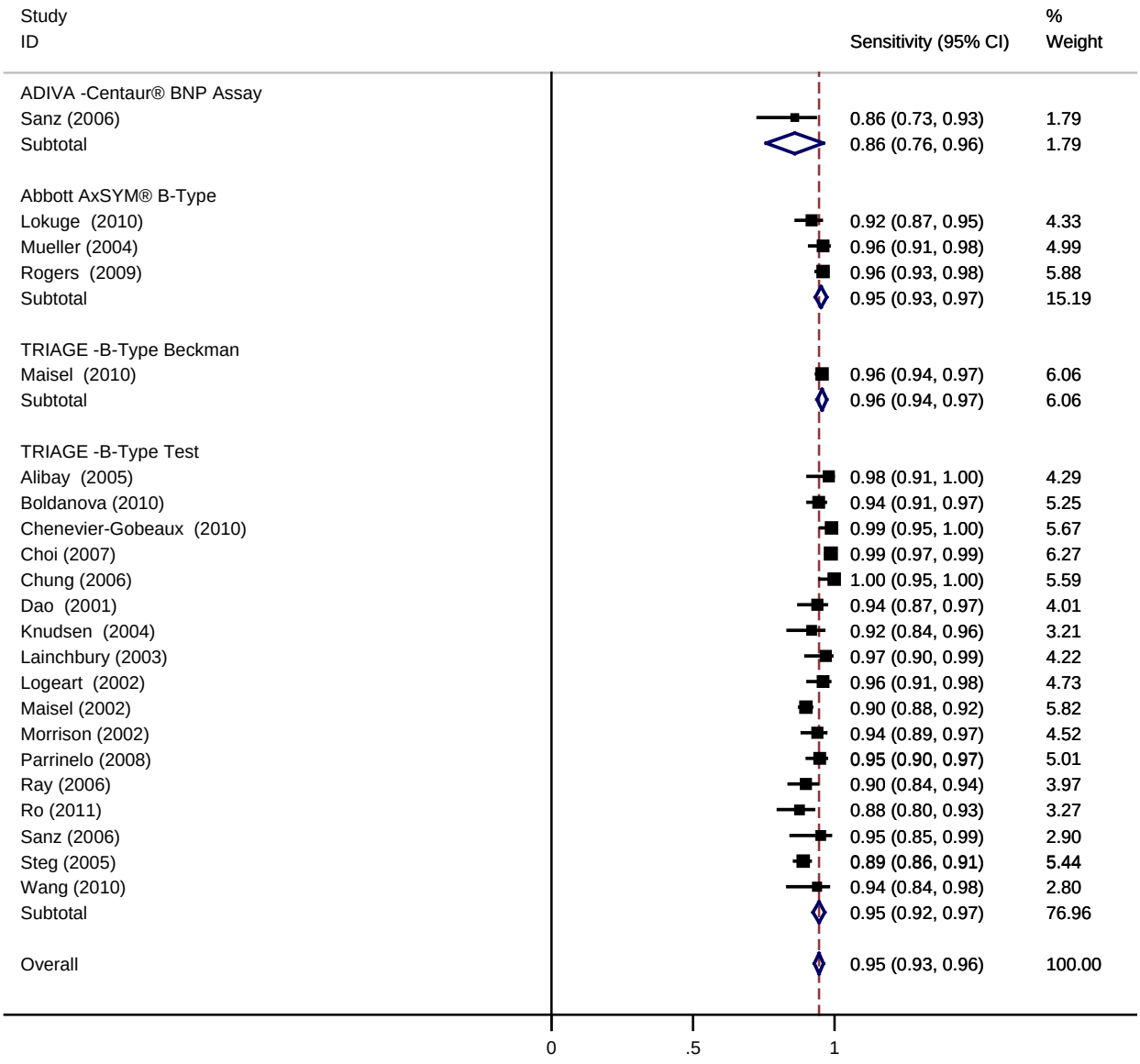


Figure H-2. Summary Sensitivity (ED BNP, lowest cutpoint [pg/ml]), random effect

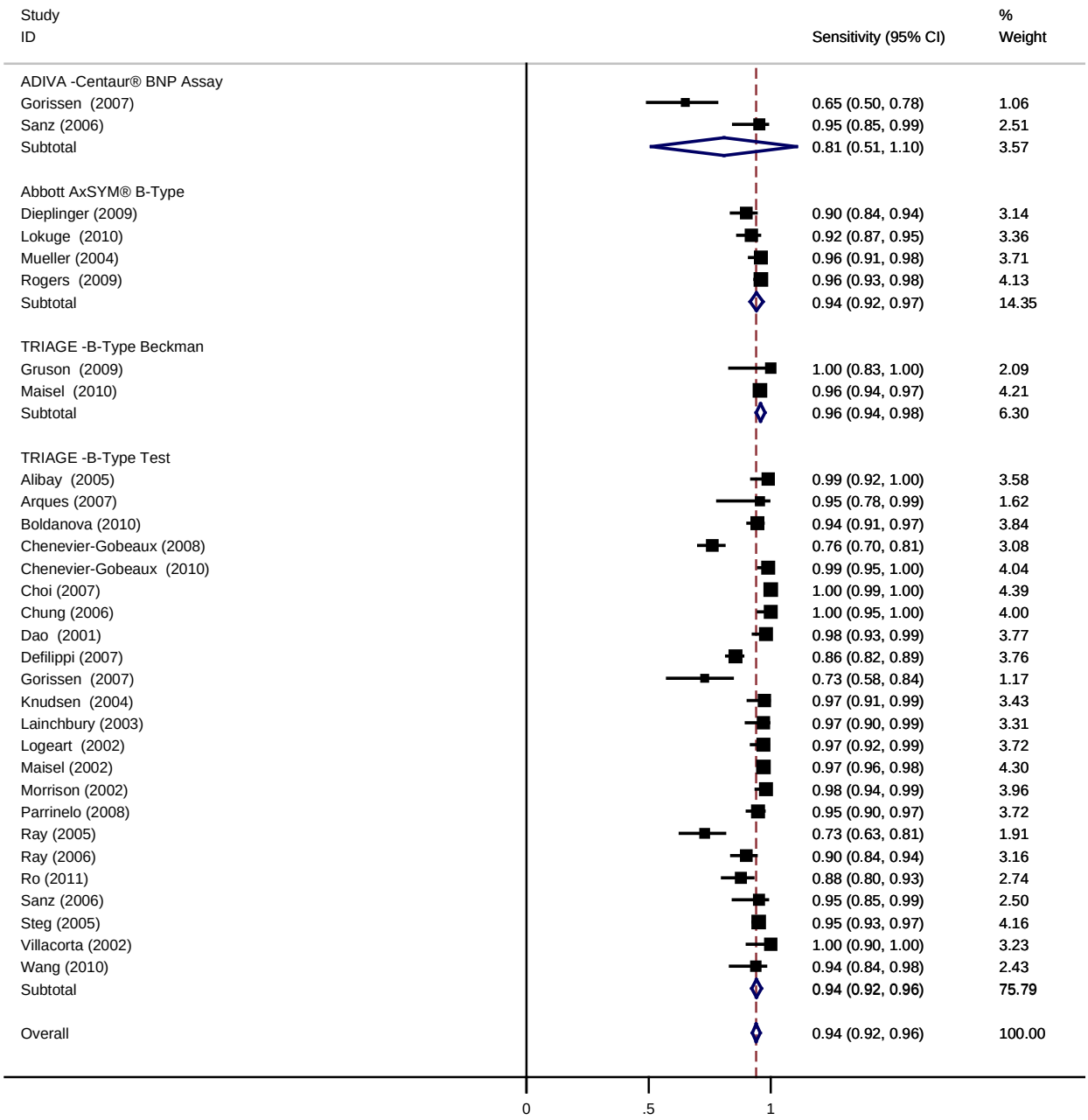


Figure H-3. Summary Sensitivity (ED BNP, optimum cutpoint [pg/ml]), random effect

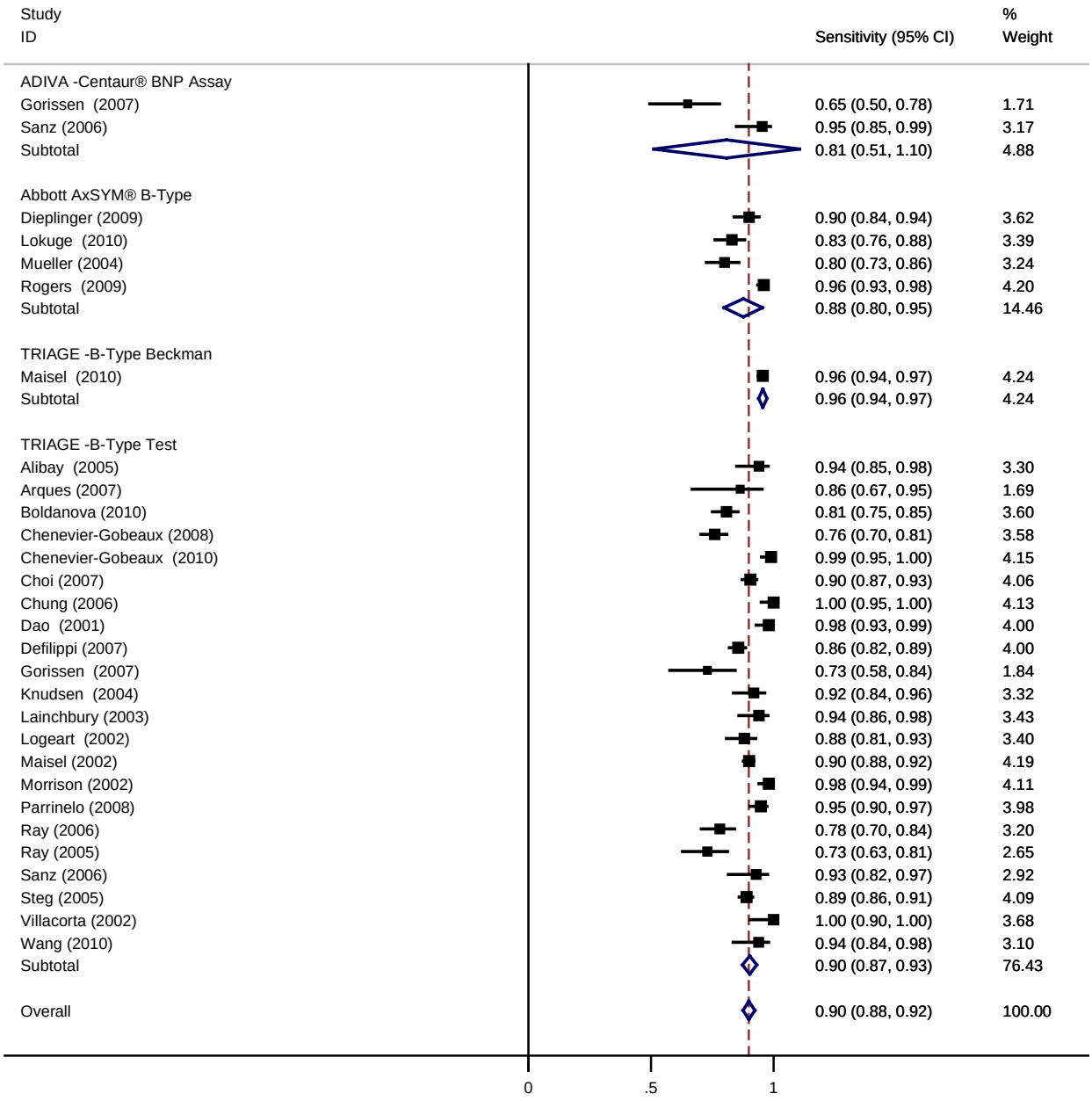


Figure H-4. Summary Specificity (ED BNP, 100±5 pg/ml cutpoint), random effect

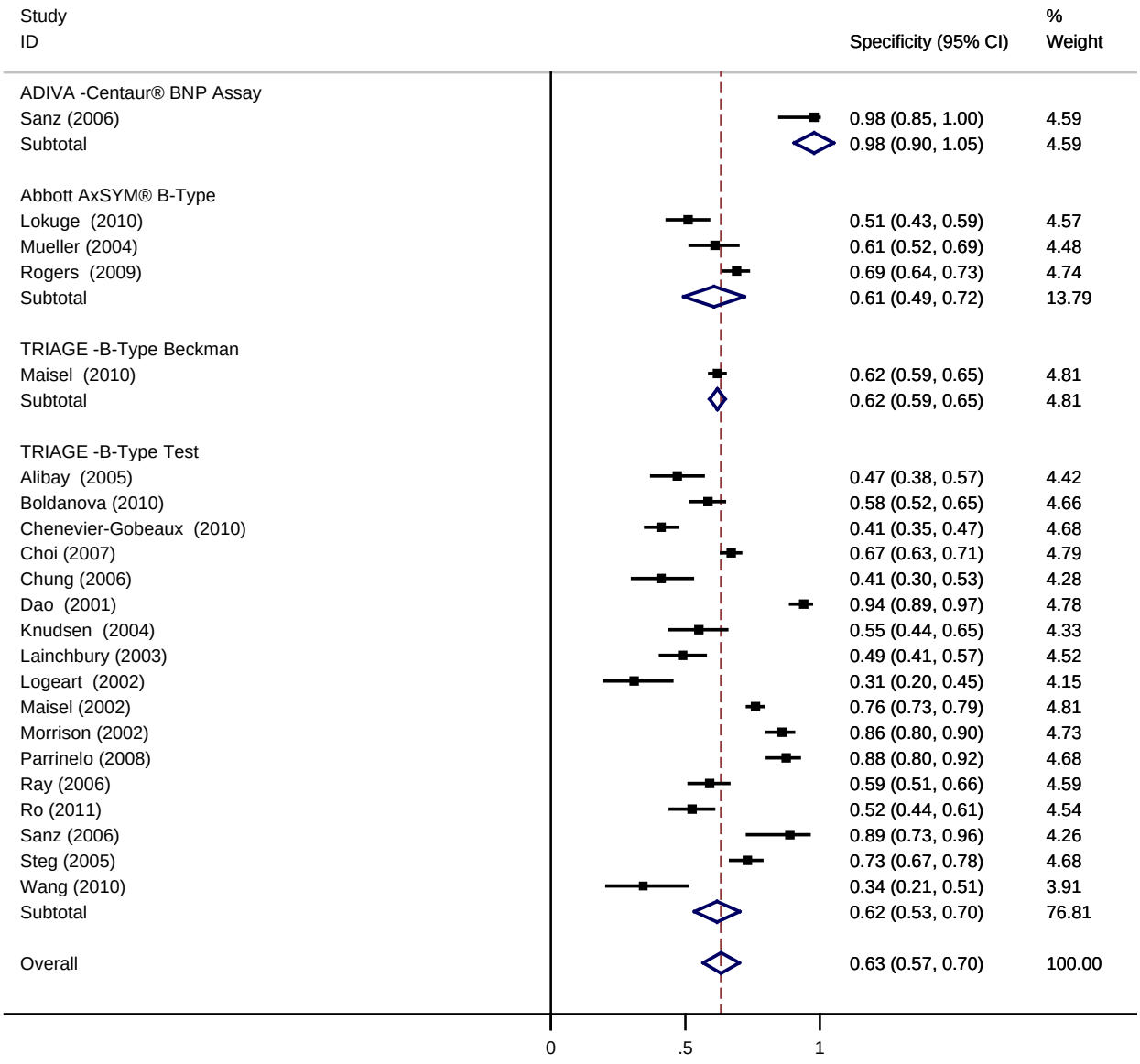


Figure H-5. Summary Specificity (ED BNP, lowest cutpoint [pg/ml]), random effect

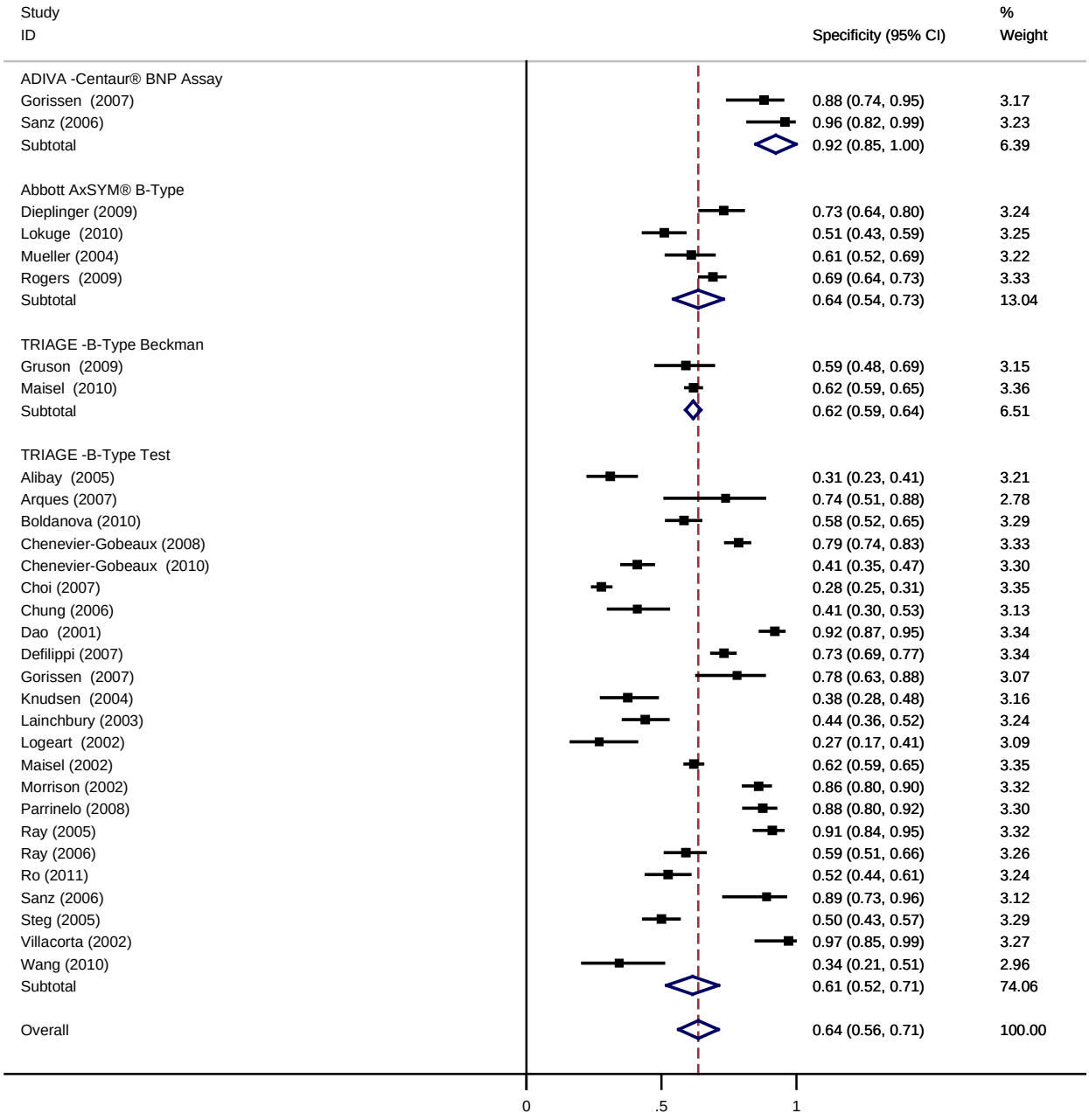


Figure H-6. Summary Specificity (ED BNP, optimum cutpoint [pg/ml]), random effect

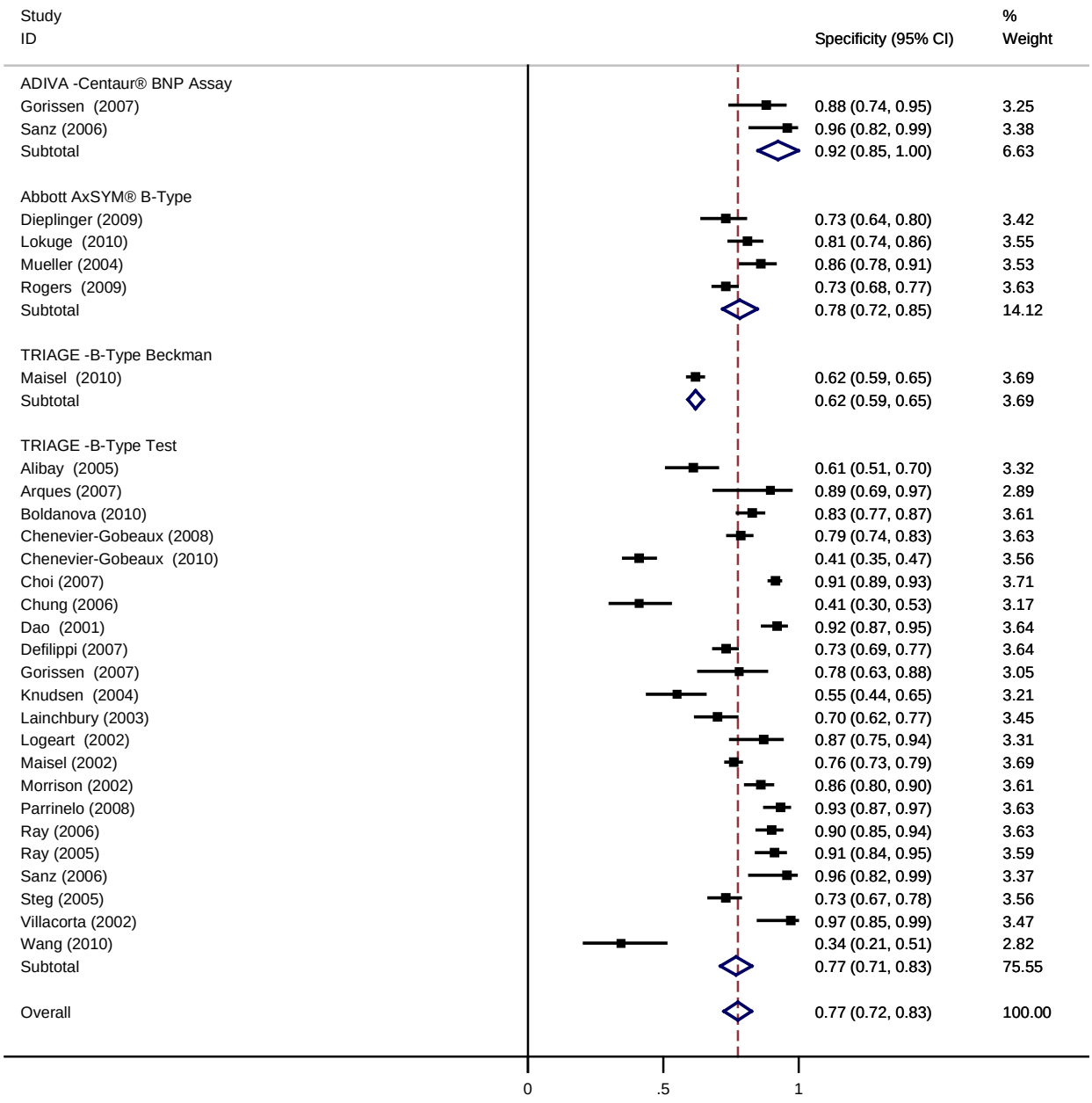


Figure H-7. Summary LR+ (ED BNP, 100±5 pg/ml cutpoint), random effect

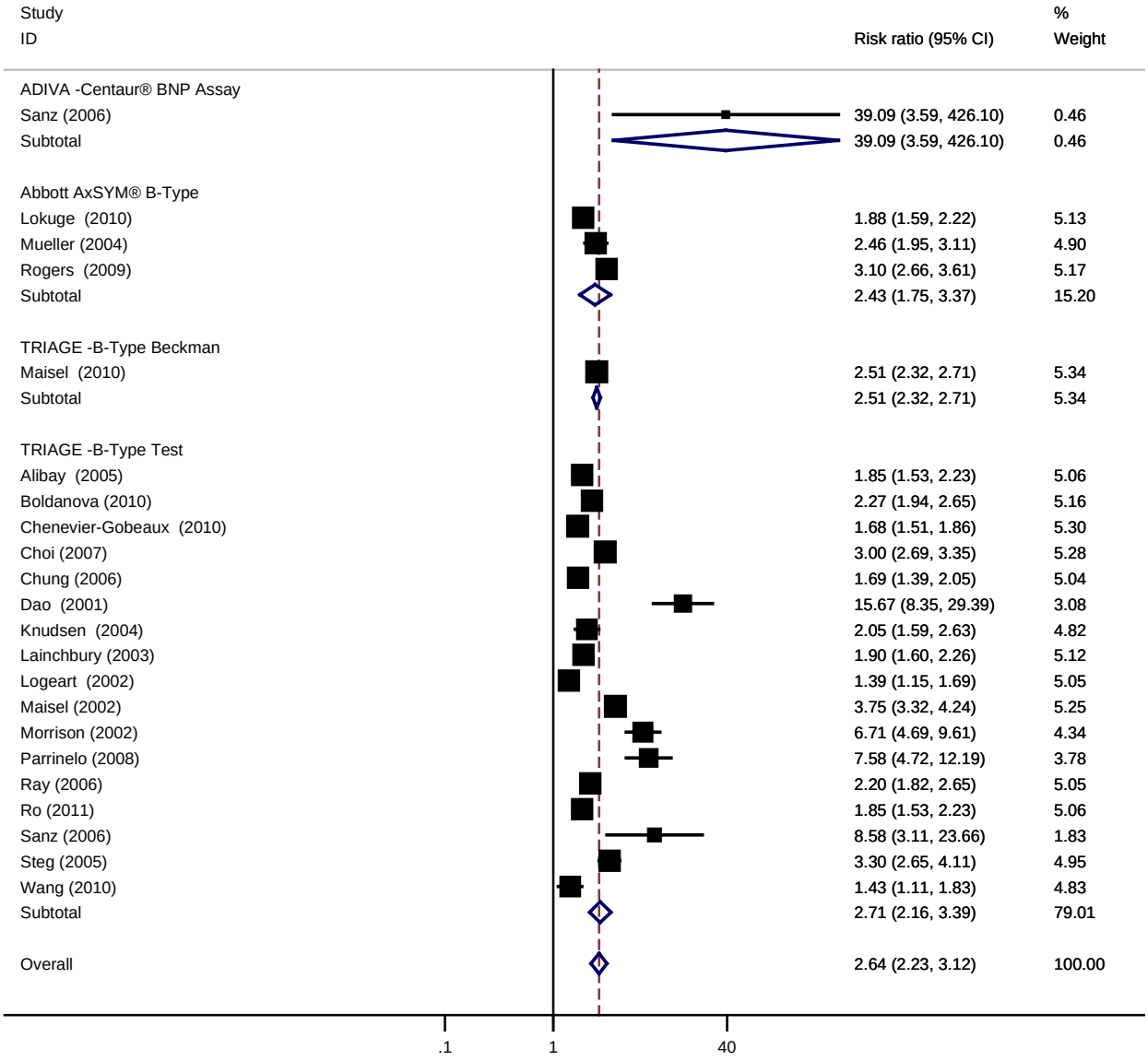


Figure H-8. Summary LR+ (ED BNP, lowest cutpoint [pg/ml]), random effect

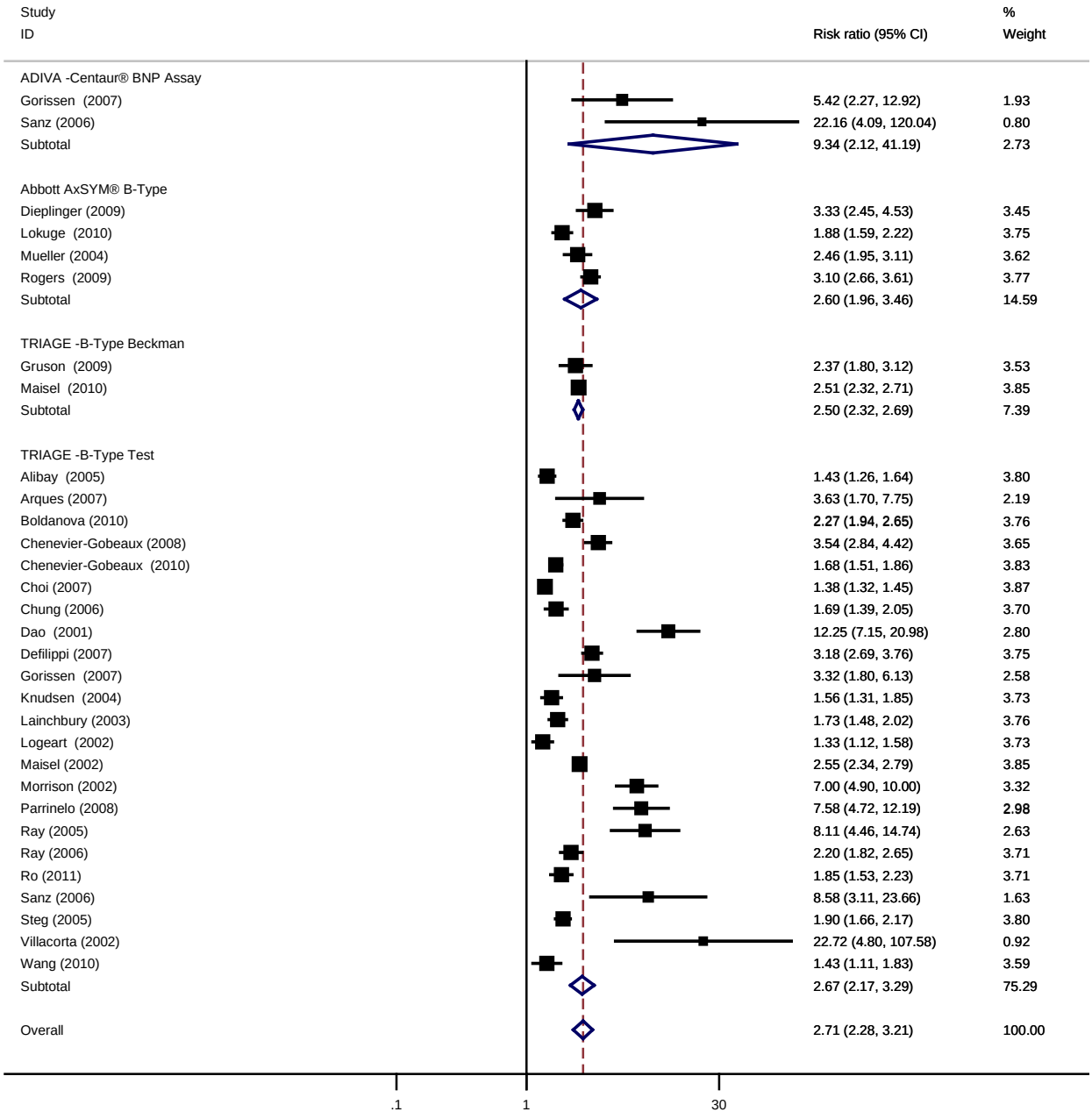


Figure H-9. Summary LR+ (ED BNP, optimum cutpoint [pg/ml]), random effect

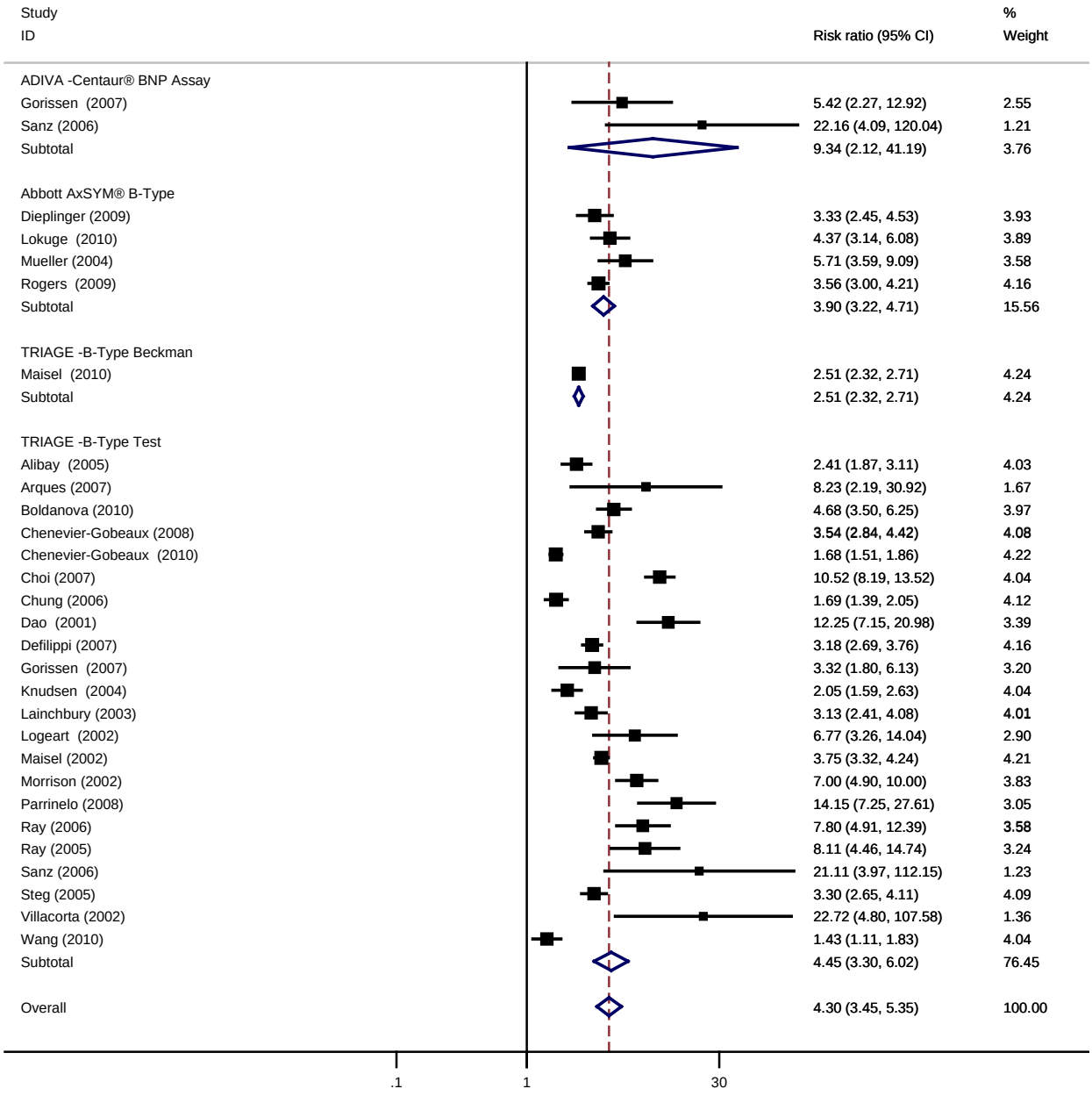


Figure H-10. Summary LR- (ED BNP, 100±5 pg/ml cutpoint), random effect

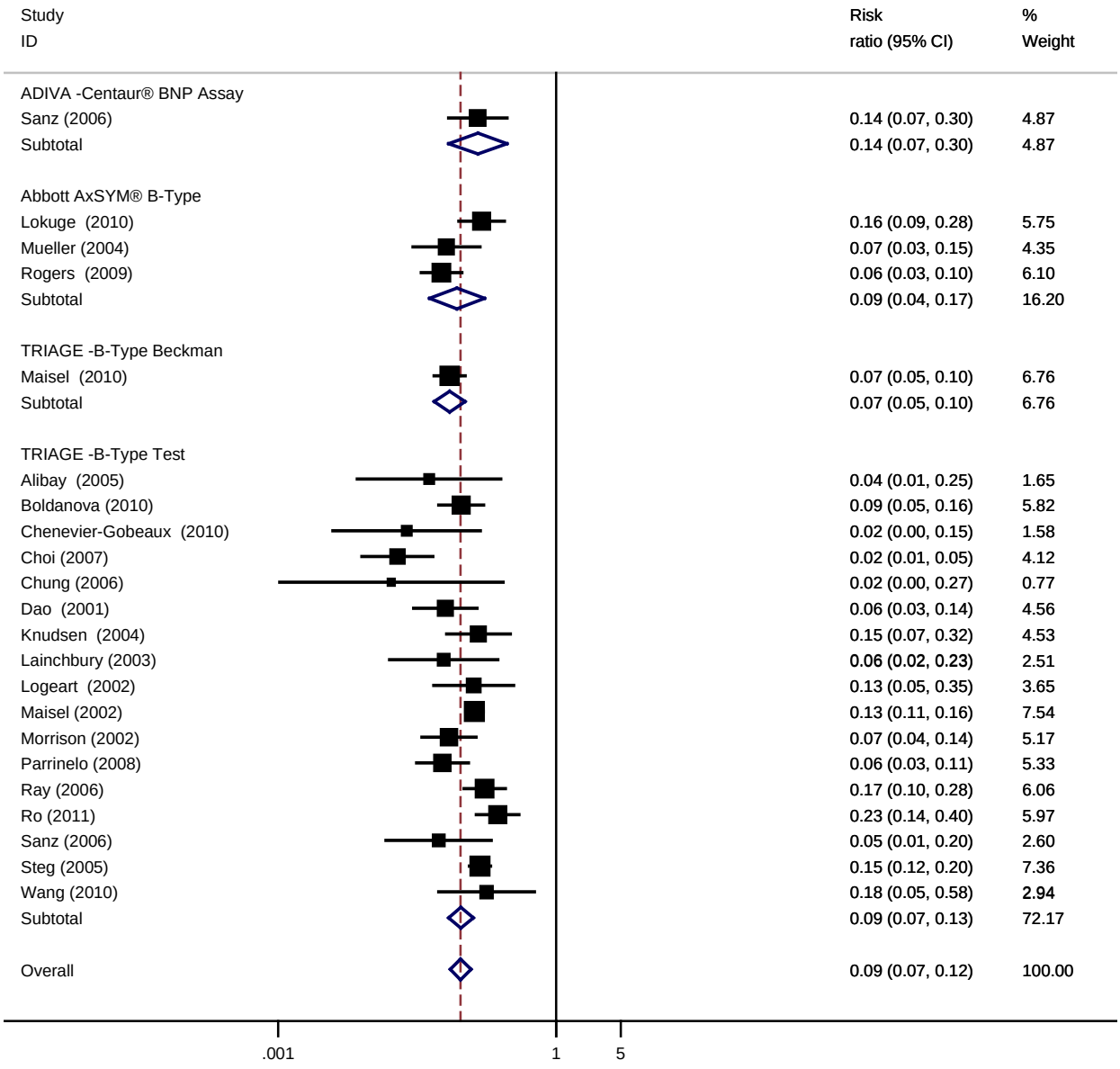


Figure H-11. Summary LR- (ED BNP, lowest cutpoint [pg/ml]), random effect

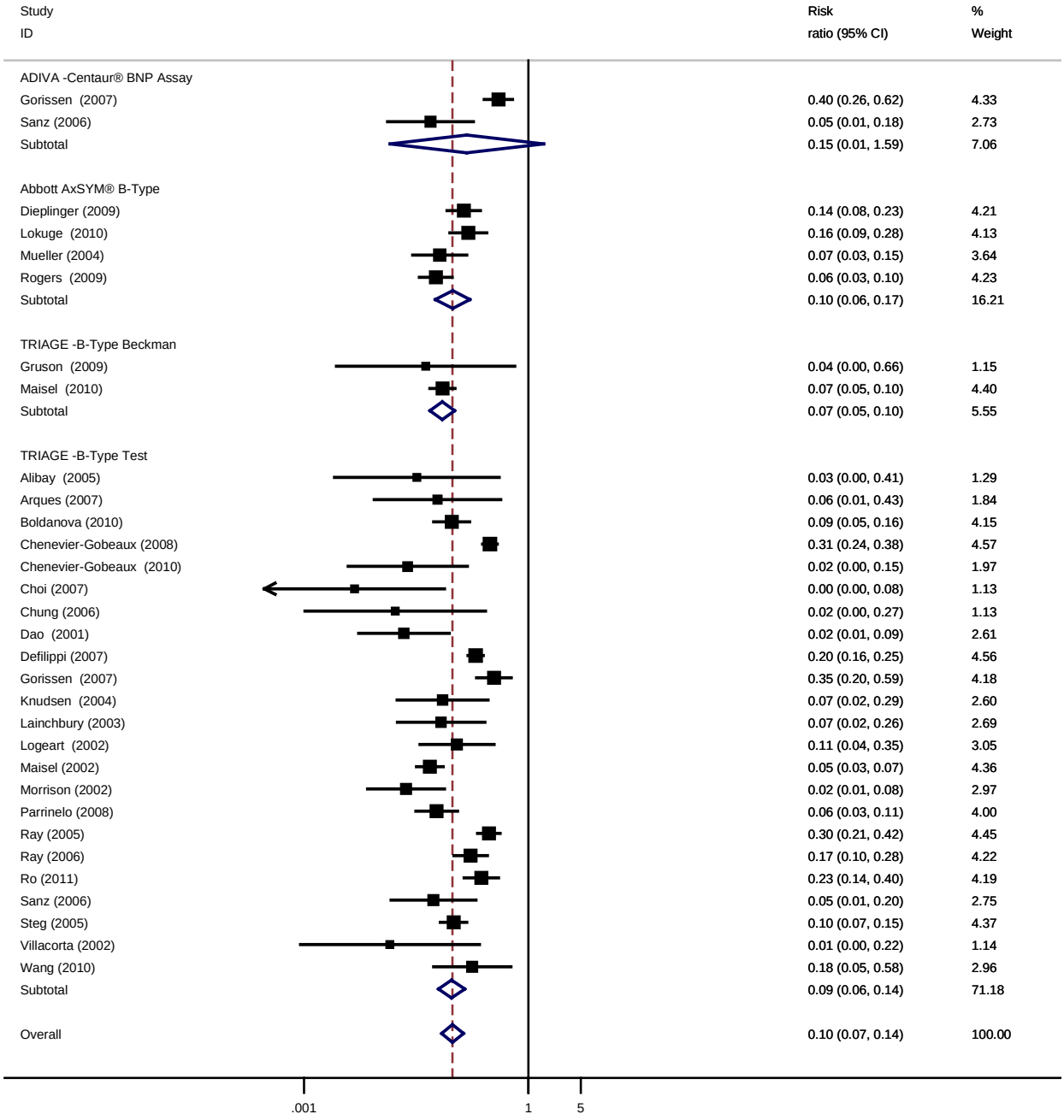


Figure H-12. Summary LR- (ED BNP, optimum cutpoint [pg/ml]), random effect

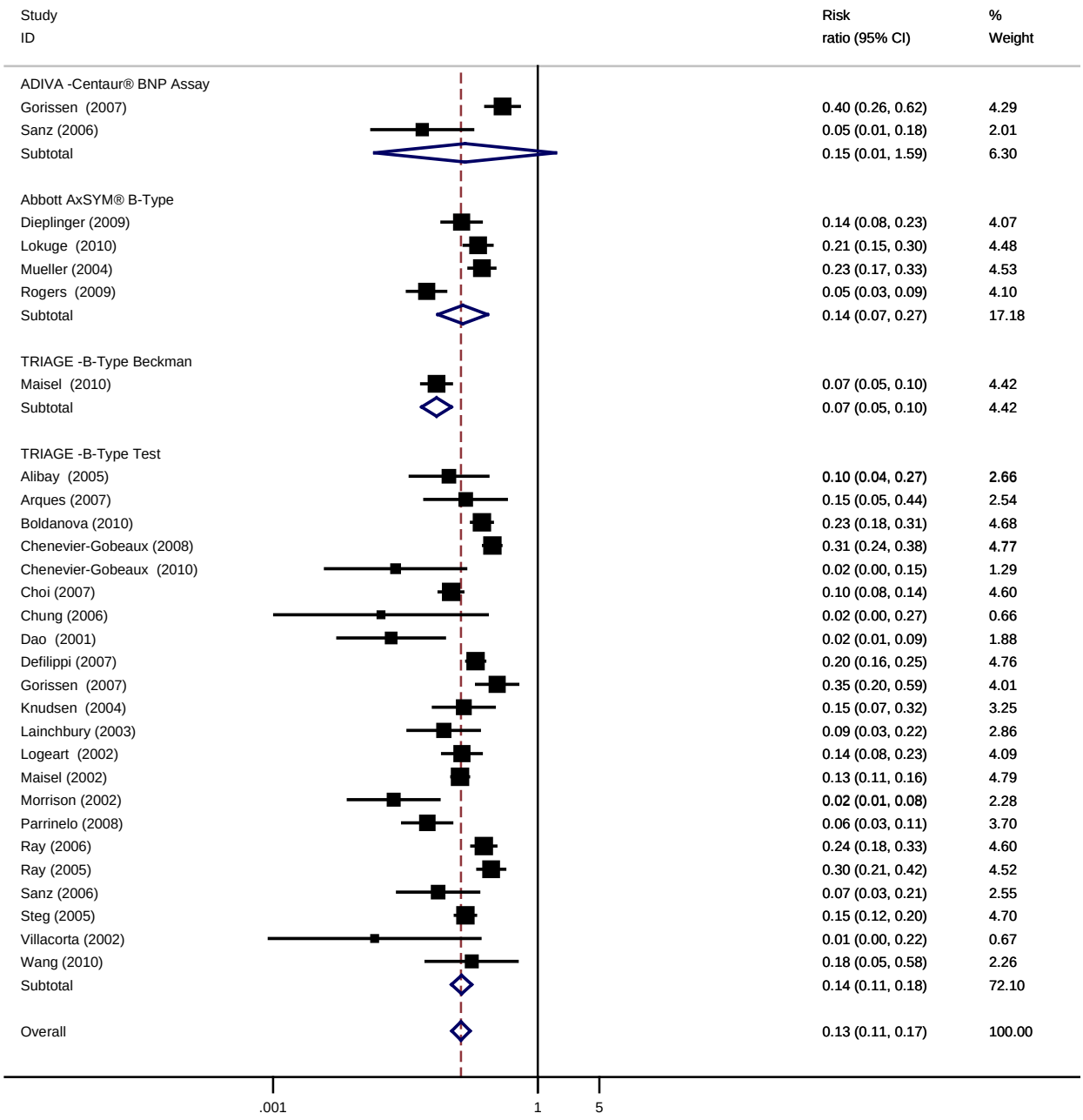


Figure H-13. Summary log DOR (ED BNP, 100±5 pg/ml cutpoint), random effect

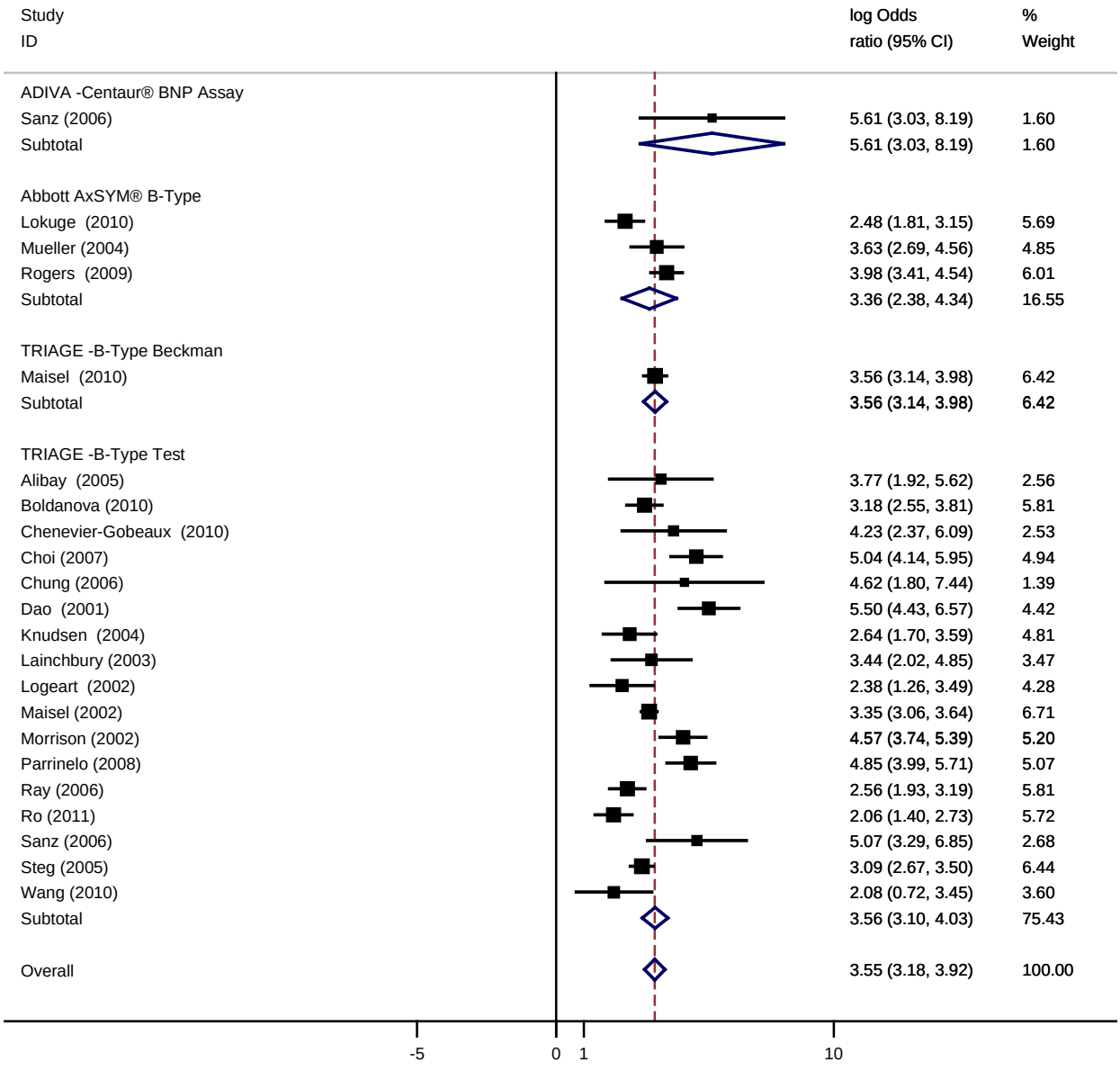


Figure H-14. Summary log DOR (ED BNP, lowest cutpoint [pg/ml]), random effect

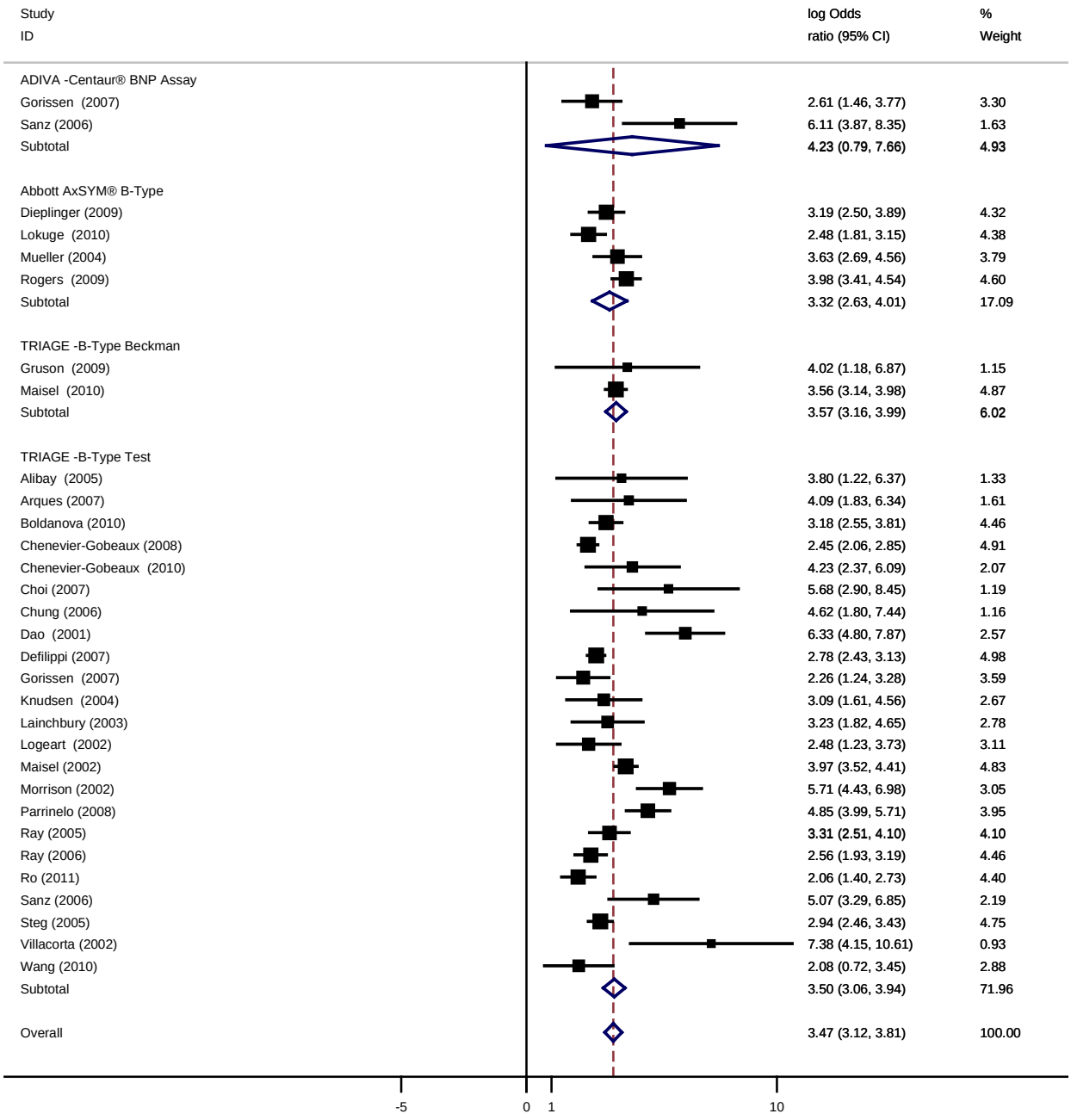


Figure H-15. Summary log DOR (ED BNP, optimum cutpoint [pg/ml]), random effect

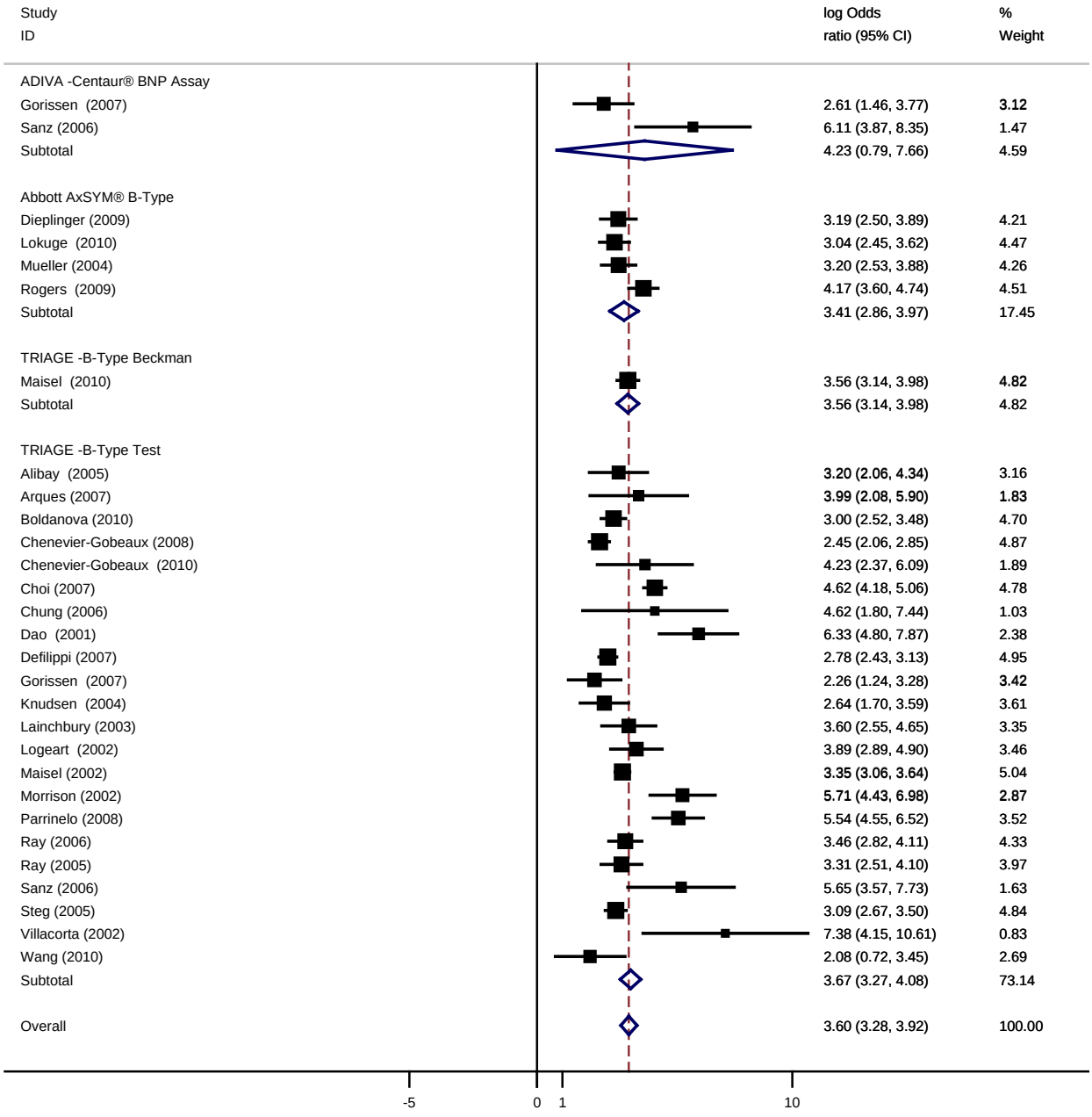


Figure H-16. Summary ROC-curve (ED BNP, 100±5 pg/ml cutpoint), random effect

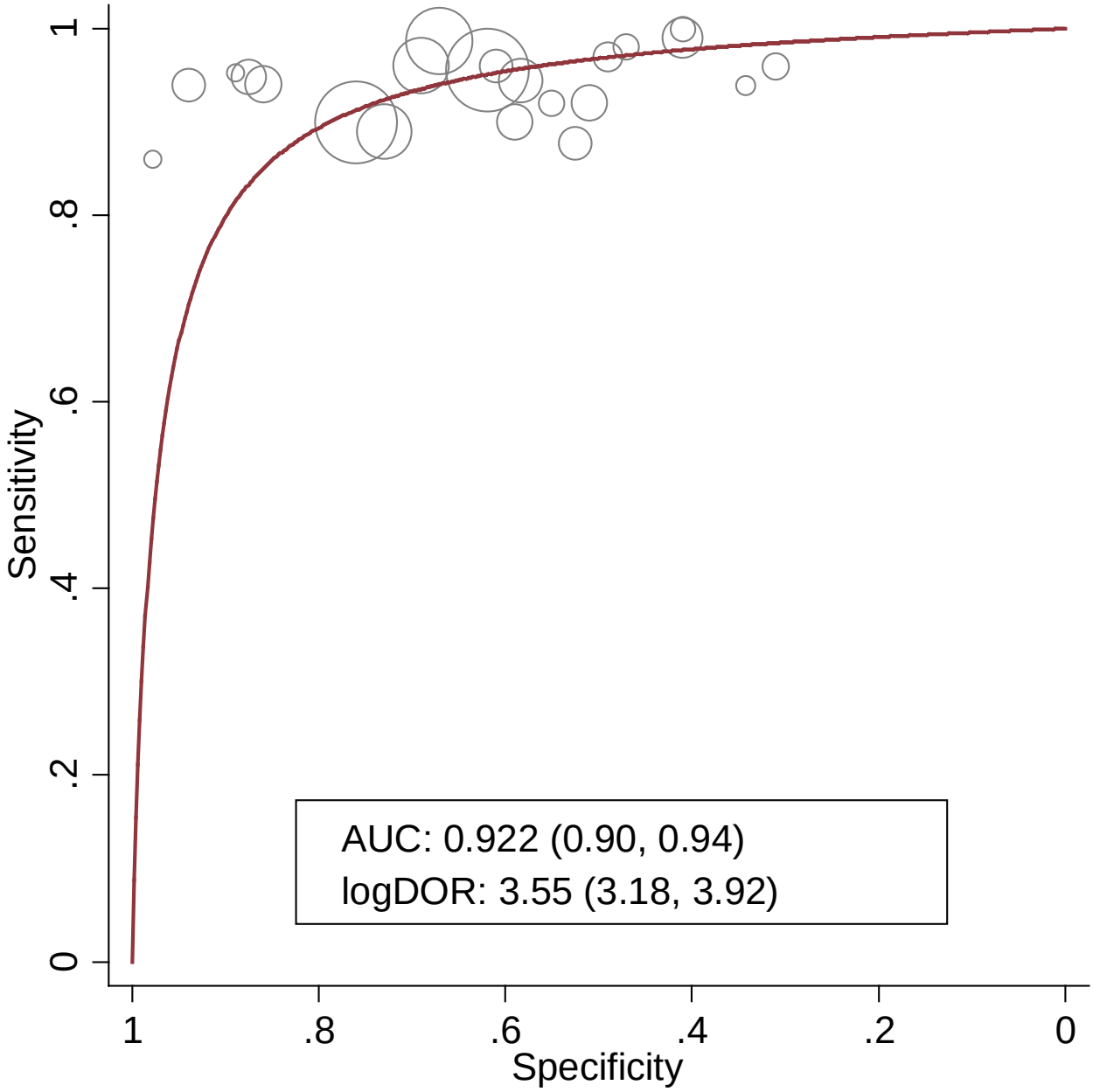


Figure H-17. Summary ROC-curve (ED BNP, lowest cutpoint [pg/ml]), random effect

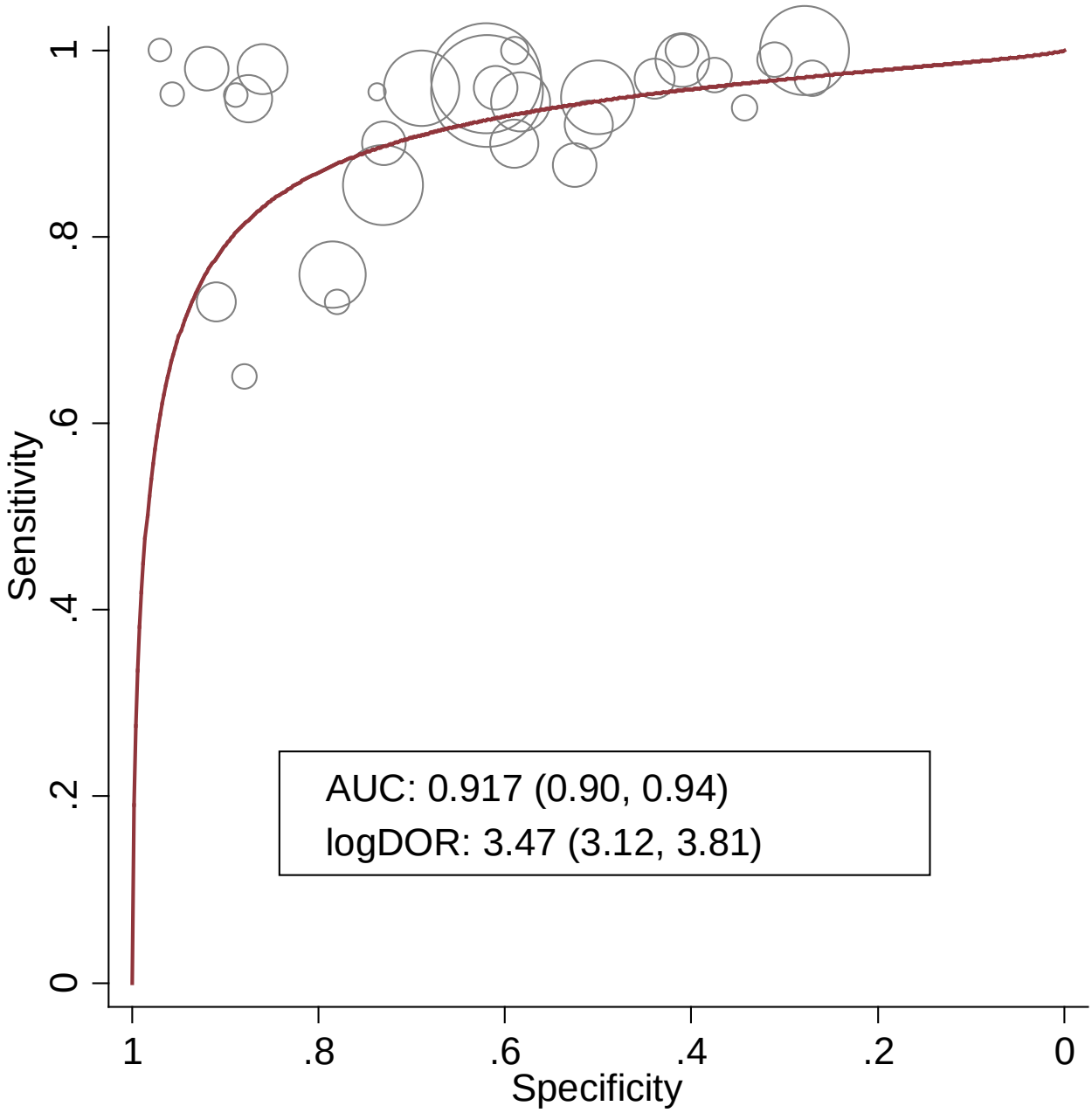


Figure H-18. Summary ROC-curve (ED BNP, optimum cutpoint [pg/ml]), random effect

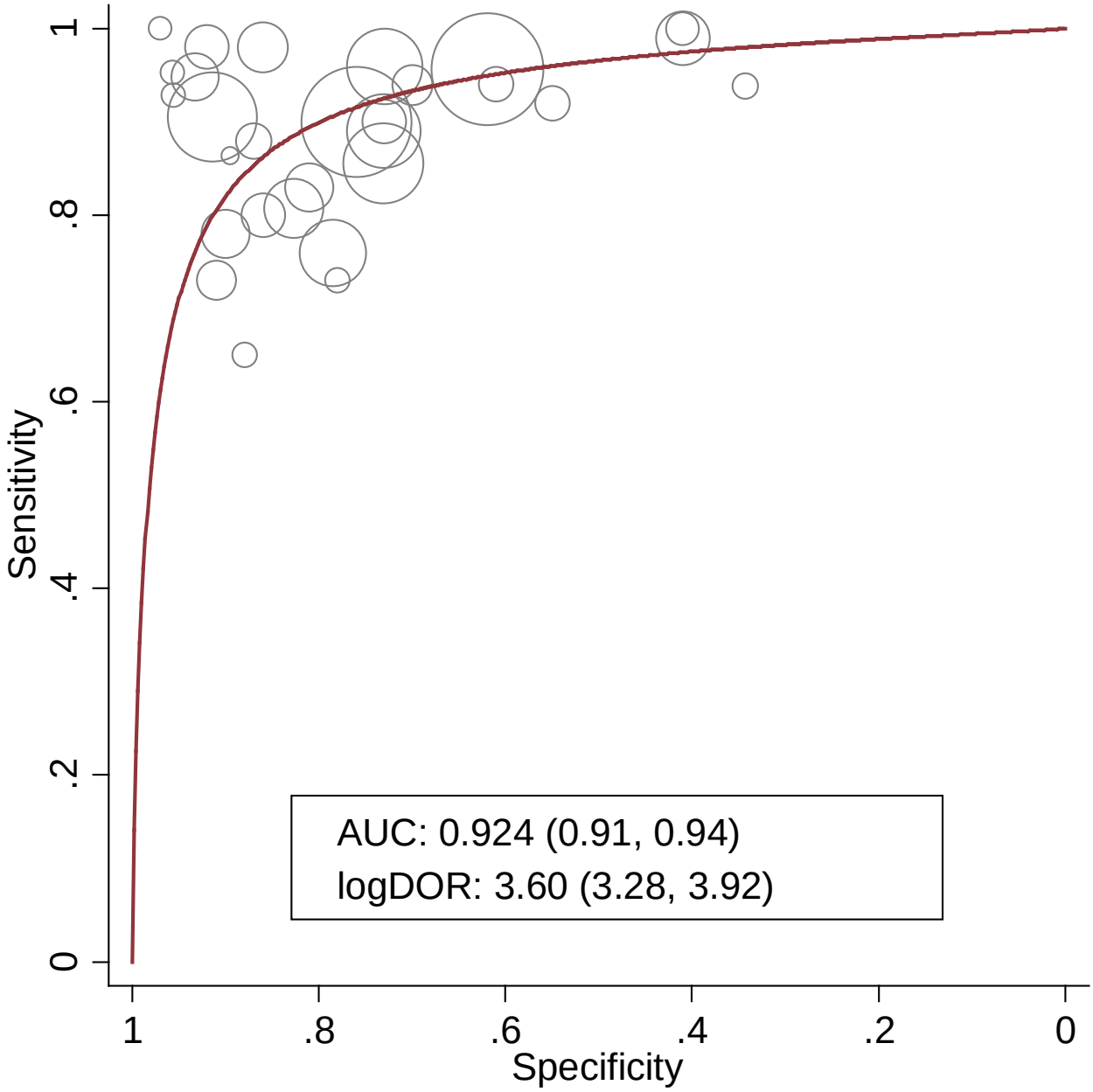


Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Alibay,[1] 2005 France	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=45), Cardiac Heart Failure (n=60), Pulmonary Disease (n=55); Reference standard: 2 Cardiologists	To examine the analytical correlation between non-radio-immunometric plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP), and to evaluate whether NT-proBNP or BNP was superior in the emergency diagnosis of heart failure and whether this was influenced by age, gender, body mass index (BMI) and renal function. Data were collected prospectively from patients admitted to the emergency department for acute dyspnea.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=160 age= 80.1(13.5)y, %males=47.5 HF Prev=38%	280	100	5	1.05	0.00	NR
					600	100	51	2.04	0.00	NR
					1,000	97	63	2.62	0.05	NR
					1,250	87	66	2.56	0.20	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Anwaruddin,[53] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: (n=293), AA=trial fibrillation (n=80), Diabetes (n=37), Historical MI (n=79), Previous CHF (n=151); Reference standard: 2 Cardiologists	60 day mortality and diagnosis of CHF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=(GFR<30) 78.0(7.6)y; (GFR 30-59) 73.1(12.4)y; (GFR60-89) 60.7(15.7)y; (GFR≥90) 51.3(15.7)y, %males=59.3 HF Prev=35%; 140 patients underwent echo.	450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	NR	NR	NR	NR	NR
				GFR ≥60 ml/min/1.73 m2 n=NR age=NR %males=NR HF Prev=21%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	85	88	7.08	0.17	0.95
					450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	97	68	3.03	0.04	0.88
					1200	89	72	3.18	0.15	NR
				GFR < 44 ml/min/1.73 m2 n=NR age=NR %males=NR HF Prev=NR%	1200	92	70	3.07	0.11	0.89

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Bayes-Genıs,[54] 2004 Spain	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Dyslipidemia (n=19), Hypertension (n=58), Prior AMI/angina (n=31), COPD (n=51), Diabetes (n=37), CHF (n=40); Reference standard: 2 Cardiologists	Utility of NT-proBNP for the diagnosis of ventricular dysfunction and to evaluate the changes in NT-proBNP concentrations after intensive treatment initiated during admission.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=89 age=(Decompensated HF) 71(10)y; (Masked HF) 76(7)y; normal) 62(13)y, %males=60.67 HF Prev=83%; 30 cut for ruling out cardiac origin dyspnea;115 to rule in.	30 pmol/L	98.6	46.7	1.85	0.03	NR
					50 pmol/L	95.7	60	2.39	0.07	NR
					70 pmol/L	94.3	73.3	3.53	0.08	NR
					90 pmol/L	91.4	73.3	3.42	0.12	NR
					115 pmol/L	91.4	93.3	13.64	0.09	0.96
					130 pmol/L	90	93.3	13.43	0.11	NR
Bayes-Genis,[55] 2007 Multinational Study	Cross-Sectional (ICON); Ethnicity: NR Comorbidities: Hypertension (n=586), CAD (n=430), Obstructive lung disease (n=412), Prior AMI/angina (n=267), AF (n=232), Diabetes (n=275), Prior HF (n=373); Reference standard: Cardiologists/physicians	Mortality at 1 year diagnostic accuracy	NT-proBNP (ELECSYS -proBNP Immunoassay)	Lean, BMI lower than 25.0 n=412 age=70.5(15.7)y, %males=48.8 HF Prev=NR%	NR	NR	NR	5.34	0.02	NR
				Overweight, BMI of 25.0 to 29.9 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	13.32	0.03	NR
				obese, BMI>=30.0 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	7.54	0.08	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Behnes,[56] 2009 Germany	Cross-Sectional (MANPRO); Ethnicity: NR Comorbidities: Arrhythmia (n=107), HBP (n=268), CAD (n=157), Stroke (n=11), Vascular disease (n=62), COPD (n=96), Diabetes (n=120), IHD (n=111), MI (n=89), Renal disease (n=72), CHD (n=194), VHD (n=177), hypercholesterolemia (n=122), DVT (n=10); Reference standard: 1 Physician	Hospitalization and admission to intensive care	NT-proBNP (DIMENSION -NT-proBNP (PBNP) Flex® reagent cartridge method)	Acute dyspnea/peripheral edema n=401 age=67.4y, %males=5 HF Prev=30%	100	98	27	1.34	0.07	NR
					200	98	40	1.63	0.05	NR
					300	96	48	1.85	0.08	0.85
					400	94	54	2.04	0.11	NR
Behnes,[57] 2011 Germany	Cross-Sectional (MANPRO); Ethnicity: NR Comorbidities: Hypertension (n=268), CAD (n=157), Acute MI (n=89), AF (n=107), COPD (n=96), Diabetes (n=120), Renal disease (n=72) hypercholesterolemia (n=122), CHF systolic (n=91), CHF diastolic (n=76), Pneumonia (n=42); Reference standard: Diagnoses of AF and CHF were based on clinically assessed final diagnoses of the individual hospital stay of each individual patient according to European Guidelines	Association of serum levels of TGF-beta 1 and AF and CHF	NT-proBNP (DIMENSION -NT-proBNP (PBNP) Flex® reagent cartridge method)	Dyspnea n=401 age=67.4y, %males=5 HF Prev=30%	NR	NR	NR	NR	NR	NR
				Dyspnea n=NR age=NR %males=NR HF Prev=27%	270	0.95	NR	NR	NR	0.73
				Dyspnea n=NR age=NR %males=NR HF Prev=30%	300	NR	NR	NR	NR	0.85

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Berdague,[58] 2006 France	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Respiratory insufficiency (n=42), Asymptomatic left ventricular (n=44), Pulmonary Embolism (n=11); Reference standard: 2 Cardiologists	Value of NT-proBNP assay for etiologic diagnosis of acute dyspnea in elderly patients in the emergency setting.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea,>70. n=254 age=81(7)y, %males=48 HF Prev=56%	1,000	97	49	1.90	0.06	NR
					1,200	97	65	2.77	0.05	NR
					1,630	92	55	2.04	0.15	NR
					2,000	87	72	3.11	0.18	NR
					2,300	81	75	3.24	0.25	NR
					3,000	75	80	3.75	0.31	NR
					4,500	64	86	4.57	0.42	NR
					5,500	58	87	4.46	0.48	NR
Chenevier-Gobeaux,[6] 2005 France	Cross-Sectional (Independent study); Ethnicity: NR Hypertension (n=153), COPD (n=127), Myocardial infarction (n=124), Previous CHF (n=128); Reference standard: 2 urgentists	(i) To determine correlations between eGFR and brain natriuretic peptide (NT-proBNP and BNP) levels in patients with cardiac-related dyspnea or non-cardiac- related dyspnea , and (ii) to determine the influence of eGFR on NT-proBNP and BNP values in the diagnosis of cardiac-related dyspnea in patients presented by night to the Emergency Department (ED).	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=381 age=79(1y, %males=NR HF Prev=30%	NR	NR	NR	NR	NR	NR
				eGFR≥90,CKD Level1 n=NR age=NR %males=NR HF Prev=8%	NR	NR	NR	NR	NR	NR
				eGFR 60-89 ml/min/1.73 m2, CKD Level 2 n=NR age=NR %males=NR HF Prev=20%	1,360	77	86	5.50	0.27	0.8476

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[6] 2005 France (cont'd)	(repeated data) Cross-Sectional (Independent study); Ethnicity: NR Hypertension (n=153), COPD (n=127), Myocardial infarction (n=124), Previous CHF (n=128); Reference standard: 2 urgentists	(repeated data) (i) To determine correlations between eGFR and brain natriuretic peptide (NT-proBNP and BNP) levels in patients with cardiac-related dyspnea or non-cardiac- related dyspnea , and (ii) to determine the influence of eGFR on NT-proBNP and BNP values in the diagnosis of cardiac-related dyspnea in patients presented by night to the Emergency Department (ED).	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	eGFR 30-59 ml/min/1.73 m2, CKD Level 3 n=NR age=NR %males=NR HF Prev=34%	1,980	62	80	3.10	0.48	0.7314
				eGFR 15–29 ml/min/1.73 m2; CKD Level 4 n=NR age=NR %males=NR HF Prev=45%	6,550	82	79	3.90	0.23	0.8025
Chenevier-Gobeaux,[7] 2008 France	Cohort (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=272), CAD (n=180), COPD (n=167), Previous HF (n=138), Malignancy (n=94); Reference Standard: 2 Emergency physicians or a pulmonologist and cardiologist	CHF (To evaluate the accuracy of BNP and NT-proBNP for the diagnosis of CHF (CHF) in dyspnea patients aged <85 years admitted to the Emergency Department (ED), and to define threshold values in this oldest-old population.)	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea (all) n=570 age=(<85 non CHF) 75(6)y; (<85 CHF) 77(6)y; (≥85 non CHF) 91(4)y; (≥85 CHF) 90(4)y, %males=47.89 HF Prev=44%	NR	NR	NR	NR	NR	NR
					1,700	74	77	3.22	0.34	0.786
					1,750	85	59	2.07	0.25	NR
					2,100	82	63	2.22	0.29	NR
					2800	74	70	2.47	0.37	NR
					3300	69	75	2.76	0.41	NR
					4900	57	80	2.85	0.54	NR
					6000	53	85	3.53	0.55	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[8] 2010 France	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: hypertension (n=152), prior AMI/angina (n=124), COPD (n=125), Previous CHF (n=125); Reference standard: 2 emergency physicians	To determine the relationship between the estimated glomerular filtration rate (eGFR) and MR-proANP concentrations in dyspnea emergency patients and to compare the diagnostic performance of MR-proANP with that of NT-proBNP and BNP with respect to renal function	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea (age 60+) n=378 age=78(1y) %males=50.26 HF Prev=30%	300 ng/L	100	27	1.37	0.00	NR
				Tertile 3 (eGFR >=58.6 mL/min/1.73 m2) n=NR age=NR %males=NR HF Prev=17%	>1,500 ng/L	82	82	4.56	0.22	NR
				Tertile 2 (eGFR between 44.3 and 58.5 mL/min/1.73m2) n=NR age=NR %males=NR HF Prev=34%	>1,700 ng/L	88	71	3.03	0.17	NR
				Tertile 1 (eGFR<44.3 mL/min/1.73 m2), n=NR age=NR %males=NR HF Prev=39%	>4,000 ng/L	79	60	1.98	0.35	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
deFilippi,[15] 2007 USA	Cohort (Independent study); Ethnicity: African-American (n=318); Comorbidities: Hypertension (n=555), CAD (n=263), Atrial Fibrillation (n=175), Diabetes (n=305), Prior HF (n=287); Reference standard: 2 Cardiologists	Compared the diagnostic accuracies of NT-proBNP and BNP for diagnosing decompensated HF and predicting 1-year all-cause mortality, and to determine whether the natriuretic peptide cutoffs derived from previously published studies of prospectively recruited all-comers cohorts remained optimal in this clinician-selected cohort	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=831 age=(eGFR<60) 69.3 (13.y) (eGFR≥60) 63.5(16)y, %males=45.7 HF Prev=53%	NR	NR	NR	NR	NR	NR
				eGFR<60 n=NR age=NR %males=NR HF Prev=61%	1,200 ng/L	81	49	1.59	0.39	NR
				eGFR≥60 n=NR age=NR %males=NR HF Prev=45%	900 ng/L for age≥50 ,450 ng/L for age<50	81	52	1.70	0.36	NR
Gorrisen,[17] 2007 Netherlands	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: NR Reference standard: 1 Cardiologist, 1 Pulmonologist	To evaluate the analytical and diagnostic performance of two different BNP tests and one NT-pro-BNP test in the diagnosis of CHF in the ED.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=80 age=74(10)y, %males=55 HF Prev=50%	1,550 ng/L	80	65	2.29	0.31	0.774
				< 65 years n=NR age=NR %males=NR HF Prev=NR%	591 ng/L	55	100	NA	0.45	0.614
				65–75 years n=NR age=NR %males=NR HF Prev=NR%	1,922 ng/L	75	73	2.78	0.34	0.75

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gorrisen,[17] 2007 Netherlands (cont'd)	(repeated data) Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: NR Reference standard: 1 Cardiologist, 1 Pulmonologist	(repeated data) To evaluate the analytical and diagnostic performance of two different BNP tests and one NT-pro-BNP test in the diagnosis of CHF in the ED.	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	> 75 years n=NR age=NR %males=NR HF Prev=NR%	1737 ng/L	71	84	4.44	0.35	0.831
				GFR >60 mL/min/1.73 m2 n=NR age=NR %males=NR HF Prev=NR%	1118 ng/L	85	73	3.15	0.21	0.781
				GFR <=60 mL/min/1.73 m2 n=NR age=NR %males=NR HF Prev=NR%	2,592 ng/L	70	64	1.94	0.47	0.702
Green,[59] 2008 USA	Cohort (PRIDE); Ethnicity: NR Comorbidities: Hypertension (n=293), CAD (n=166), Obstructive lung disease (n=217), Diabetes (n=156), Historical MI (n=77), Prior heart failure (n=151); Reference standard: 2 Cardiologists	Adverse outcomes, including death and rehospitalization	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=592 age=(Clinical uncertainty present) 69(14)y; (Clinical uncertainty absent) 59(18)y, %males=50.5 HF Prev=34%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75;1,800 pg/mL in >75 years	NR	NR	NR	NR	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Green,[59] 2008 USA (cont'd)	(repeated data) Cohort (PRIDE); Ethnicity: NR Comorbidities: Hypertension (n=293), CAD (n=166), Obstructive lung disease (n=217), Diabetes (n=156), Historical MI (n=77), Prior heart failure (n=151); Reference standard: 2 Cardiologists	(repeated data) Adverse outcomes, including death and rehospitalization	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Clinical certainty group n=NR age=NR %males=NR HF Prev=24%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75; 1,800 pg/mL in >75 years	92	86	6.57	0.09	0.88
				Clinical uncertainty group n=NR age=NR %males=NR) HF Prev=56%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75;1800pg/mL in >75 years	90	84	5.63	0.12	NR
Gruson,[18] 2008 Belgium	Cohort (Independent study); Ethnicity: NR Comorbidities: NR Reference standard: 1 cardiologist	To evaluate the diagnostic accuracy of circulating N-terminal- pro-atrial natriuretic peptide (Nt-proANP), the extremity of the proANP amino-terminal fragment, assessed by radio-immunoassay, in patients admitted to the ED with dyspnea and/or chest pain. Moreover, we compared the performances of Nt-proANP assay to two commercial assays for BNP and Nt-proBNP.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea (CHF) n=137 age=69y, %males=56 HF Prev=23%	NR	NR	NR	NR	NR	O.91

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gruson,[20] 2012 Belgium	Cohort (Independent Study); Ethnicity=NR Comorbidities=hypertension (n=69), AF (n=11), diabetes mellitus (n=30), historical MI (n=20); Reference Standard=clinicians	To evaluate the diag- nostic accuracy of circulating levels of proBNP in patients admitted to ED with dyspnea and/or thoracic pain. Moreover, we compared the performances of proBNP assay to two commercial assays for BNP and Nt-proBNP.	NT-proBNP (ELECSY-proBNP Immunoassay)	dyspnea and/or chest pain, all (n=156, mean=67y, %males=54.5); HF Prevalance=29.5 %	100 ng/L	NR	NR	NR	NR	0.92
Januzzi,[60] 2005 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Arrhythmia (n=102), Caucasian (n=188), Hypertension (n=294), CAD (n=166), Prior AMI/angina (n=79), COPD (n=216); Reference standard: 2 Cardiologists	Comparison of NT-proBNP results with the clinical assessment of the managing physician for identifying acute CHF	NT-proBNP (ELECSYS -proBNP Immunoassay)	All patients n=599 age=(Acute CHF) 72.8(13.6)y; no acute CHF) 56.9(16.3)y, %males=5 HF Prev=35%	300	99	68	3.09	0.01	NR
					450	98	76	4.08	0.03	NR
					600	96	81	5.05	0.05	NR
				Dyspnea n=NR age=NR %males=NR HF Prev=34.89%	900	90	85	6.00	0.12	0.94

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Januzzi,[60] 2005 USA (cont'd)	(repeated data) Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Arrhythmia (n=102), Caucasian (n=188), Hypertension (n=294), CAD (n=166), Prior AMI/angina (n=79), COPD (n=216); Reference standard: 2 Cardiologists	(repeated data) Comparison of NT-proBNP results with the clinical assessment of the managing physician for identifying acute CHF	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	All patients n=599 age=(Acute CHF) 72.8(13.6)y; no acute CHF) 56.9(16.3)y, %males=5 HF Prev=35%	1000	87	86	6.21	0.15	NR
				<50 years old n=NR age=NR %males=NR HF Prev=NR%	450	93	95	18.60	0.07	0.98
				≥50 yrs old n=NR age=NR %males=NR HF Prev=NR%	900	91	80	4.55	0.11	0.93
				<50 years old n=NR age=NR %males=NR HF Prev=NR%	900	73	96	18.25	0.28	NR
Januzzi,[61] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: African-American (n=46); Comorbidities: Hypertension (n=666), CAD (n=502), COPD (n=465), Historical MI (n=314), Prior HF (n=427); Reference standard: 2 Cardiologists	To establish broader standards for NT-proBNP testing in a study involving four sites in three continents.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=1256 age=68.3(15.9)y, %males=5 HF Prev=57%	300	99	60	2.48	0.02	NR
					Age specific cutpoint	90	84	5.63	0.12	NR
				<50 years old n=NR age=NR %males=NR HF Prev=%	450	97	93	13.86	0.03	0.99

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Januzzi,[61] 2006 USA (cont'd)	(repeated data) Cross-Sectional (PRIDE); Ethnicity: African-American (n=46); Comorbidities: Hypertension (n=666), CAD (n=502), COPD (n=465), Historical MI (n=314), Prior HF (n=427); Reference standard: 2 Cardiologists	(repeated data) To establish broader standards for NT-proBNP testing in a study involving four sites in three continents.	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	50-75 years old n=NR age=NR %males=NR HF Prev=%	900	90	82	5.00	0.12	0.93
				>75 years old n=NR age=NR %males=NR HF Prev=%	1800	85	73	3.15	0.21	0.86
Krauser,[62] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: African-American (n=44); Comorbidities: Hypertension (n=292), CAD (n=167), Acute MI (n=78), AF (n=75), Diabetes (n=157), Heart failure (n=150); Reference standard: 2 Cardiologists	The utility of NT- proBNP for the diagnosis and exclusion of HF in African-American and female patients with acute dyspnea.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=(men) 61.7(16)y, %males=(women) 63.2(17)y) HF Prev=35%	NR	NR	NR	NR	NR	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Krauser,[62] 2006 USA (cont'd)	(repeated data) Cross-Sectional (PRIDE); Ethnicity: African-American (n=44); Comorbidities: Hypertension (n=292), CAD (n=167), Acute MI (n=78), AF (n=75), Diabetes (n=157), Heart failure (n=150); Reference standard: 2 Cardiologists	(repeated data) The utility of NT- proBNP for the diagnosis and exclusion of HF in African-American and female patients with acute dyspnea.	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	African American n=NR age=NR %males=NR HF Prev=30%	optimal diagnostic cutpoints of 450 pg/mL (age <50 years), 900 pg/mL (age 50 to 75 years) and 1,800 pg/mL (age >75 years)	100	90	10.00	0.00	0.96
				Non-African-American n=NR age=NR %males=NR HF Prev=35%	NR	NR	NR	NA	NA	0.94
Krauser,[62] 2006 USA (cont'd)	(repeated data) Cross-Sectional (PRIDE); Ethnicity: African-American (n=44); Comorbidities: Hypertension (n=292), CAD (n=167), Acute MI (n=78), AF (n=75), Diabetes (n=157), Heart failure (n=150); Reference standard: 2 Cardiologists	(repeated data) The utility of NT- proBNP for the diagnosis and exclusion of HF in African-American and female patients with acute dyspnea.	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Female n=NR age=NR %males=NR HF Prev=35%	optimal diagnostic cutpoints of 450 pg/mL (age <50 years), 900 pg/mL (age 50 to 75 yrs) and 1,800 pg/mL (age >75 yrs)	89	90	8.90	0.12	0.95
				Male n=NR age=NR %males=NR HF Prev=35%	NR	NR	NR	NR	NR	0.94

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Lainchbury,[25] 2003 New Zealand	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=88), COPD (n=86), Previous heart failure (n=52); Reference standard: 2 Cardiologists	Final clinical diagnosis	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=205 age=70(14)y, %males=49 HF Prev=34%; Echo performed in 171 patients.	140	87	71	3.00	0.18	0.76
					240	83	82	4.61	0.21	0.83
					340	80	87	6.15	0.23	0.85
					440	74	90	7.40	0.29	0.85
					540	68	92	8.50	0.35	0.84
Liteplo,[63] 2009 USA	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=37), AF (n=23), COPD (n=29), Diabetes (n=21), Renal disease (n=17), Asthma (n=6), Prior CHF (n=46); Reference standard: 2 emergency physicians.	Optimal protocol and test threshold for the US test to diagnose CHF, to compare the diagnostic efficiency of US with NT-ProBNP levels in diagnosing CHF, and to determine if US adds incremental diagnostic information when combined with NT-ProBNP	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=94 age=74(14)y, %males=59 HF Prev=43%	450/900/1800	85	62.96	2.29	0.24	

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Martinez-Rumayor,[64] 2010 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Hypertension (n=292), CAD (n=168), COPD (n=70), Diabetes (n=157), Historical MI (n=77), Asthma (n=94), Cardiomyopathy (n=63), History of prior HF (n=150); Reference standard: 2 Cardiologists	To define more clearly the relationship between the information provided by the chest radiograph (CXR)and the natriuretic peptide (NT-proBNP) test as part of the evaluation of dyspneic patients presenting to the emergency department with suspected acute HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected AHF n=599 age= normal CXR) 59y*, %males=(Abnormal CXR) 71y* HF Prev=35%	'Rule in cut-off points', (450/900/1800 pg/ ml for ages <50/50–75/>75 years)	90	86	6.43	0.12	NR
				Normal CXR n=NR age=NR %males=NR HF Prev=21%	NR	NR	NR	NR	NR	0.94
				Abnormal CXR n=NR age=NR %males=NR HF Prev=56%	NR	NR	NR	NR	NR	0.92
Mueller,[35] 2005 & Gegenhuber,[36] 2006 Austria	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=117), AF (n=83), Diabetes (n=58), Renal disease (n=74), Arterial hypertension (n=141); Reference standard: 1 Internist, Framingham criteria	To compare head to head the diagnostic accuracy of BNP and NT-proBNP with respect to CHF in patients consulting ED with SOB as a chief complaint and to assess appropriate cut off concentrations for this clinical setting by means of two currently developed commercially available assays for BNP and NT-proBNP.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=251 age=(HF) 76y, (no CHF) 69y %males=NR HF Prev=55%	292 ng/L	95	53	2.02	0.09	NR
					125/450 ng/L	94	46	1.74	0.13	NR
					476 ng/L	90	65	2.57	0.15	NR
					825 ng/L	87	81	4.58	0.16	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Moe,[65] 2007 Canada	Cross-Sectional (BACH); Ethnicity: Caucasian (n=464); Comorbidities: Hypertension (n=266), COPD (n=145), Diabetes (n=127), Historical MI (n=151), HF/left ventricular dysfunction (n=171); Reference standard: 2 Cardiologists	The duration of the initial ED visit and the total direct medical costs of treatment as primary end points and initial hospital length of stay, in-hospital and 60-day mortality, and rehospitalization	NT-proBNP (ELECSYS -proBNP Immunoassay))	Dyspnea n=500 age=70yrs %males=51.6 HF Prev=46%	NR	NR	NR	NR	NR	0.86
				NT-proBNP group n=NR age=NR %males=NR HF Prev=NR	NR	NR	NR	NR	NR	NR
				Usual care n=NR age=NR %males=NR HF Prev=NR	NR	NR	NR	NR	NR	NR
Nazerian,[66] 2010 Italy	Cohort (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=84), AF (n=50), COPD (n=49), Ischemic heart disease (n=47), Previous CHF (n=30), Rest dyspnea (n=83), Heart enlargement (n=64), Orthopnea (n=40); Reference standard: 2 Cardiologists, 1 respiratory physician, Boston criteria for CHF.	Outcome measure was Acute Left Ventricular Heart Failure (aimed for Diagnostic Accuracy of Emergency Doppler Echocardiography for Identification of Acute Left Ventricular Heart Failure in Patients with Acute Dyspnea: Comparison with Boston Criteria and N-terminal Pro-hormone Brain Natriuretic Peptide	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=145 age= (HF) 81(8)y, (non HF) 75(1y) %males=NR HF Prev=44%	≤300	98	22	1.26	0.09	NR
					≥2200	83	70	2.77	0.24	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
O'Donoghue,[67] 2007 USA	Cross-Sectional (PRIDE); Ethnicity: NR African-American (n=8), Comorbidities: Diabetes (n=157) Prior hypertension (n=294), Prior MI (n=80), Previous cardiomyopathy (n=63), Previous chronic obstructive Pulmonary disease (n=214); Reference standard: 2 Cardiologists	Diagnosis of acute HF 1 year mortality	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=NR %males=50.58 HF Prev=35%	NR	NR	NR	NR	NR	NR
				With DM n=NR age=NR %males=NR HF Prev=56%	optimal diagnostic cutpoints of 450 pg/mL (age <50 years), 900 pg/mL (age 50 to 75 years) and 1800 pg/mL (age >75 years)	92	90	9.20	0.09	0.94
				No DM n=NR age=NR %males=NR HF Prev=27%	NR	NR	NR	NR	NR	NR
Oh,[68] 2009 Korea	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Dyslipidemia (n=5), hypertension (n=50), AF (n=28), Diabetes (n=33), Ischemic heart disease (n=44); Reference standard: ECHO - blinded analysis	Correlation between higher levels of RDW and elevated E/E' in patients with AHF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Clinical diagnosis of AHF n=100 age=64.3(13.y, %males=60 HF Prev=44%	NR	NR	NR	NR	NR	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Oh,[68] 2009 Korea (cont'd)	(repeated data) Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Dyslipidemia (n=5), hypertension (n=50), AF (n=28), Diabetes (n=33), Ischemic heart disease (n=44); Reference standard: ECHO - blinded analysis	(repeated data) Correlation between higher levels of RDW and elevated E/E' in patients with AHF	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	RDW tertile 1 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	NR	NR	NR
				RDW tertile 2 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	NR	NR	NR
				RDW tertile 3 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	NR	NR	NR
Potocki,[40] 2010 Germany	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=195), CAD (n=80), COPD (n=98), diabetes (n=52), Previous HF (n=69), Chronic kidney disease (n=80); Reference standard: 2 Cardiologists	Accuracy of MR-proANP with that of NT-proBNP to diagnose HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=287 age=77y*, %males=5 HF Prev=54%	1560	85	85	5.67	0.18	0.92

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Prosen,[69] 2011 Slovenia	Cohort (Independent study); Ethnicity: NR Comorbidities: Arrhythmia (n=59), COPD (n=78), Historical MI (n=22), Troponin T>0.03 ng/ml (n=57), Previous CHF (n=40), Previous asthma/COPD (n=25); Reference standard: Cardiologists, ICU physicians, Boston, Framingham	To determine the diagnostic accuracy of bedside lung ultrasound, NT-proBNP and clinical assessment in differentiating heart failure related acute dyspnea from pulmonary (COPD/asthma)-related acute dyspnea in the pre-hospital setting	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=218 age=(HF) 70.9(11.7)y; (Pulmonary edema) 52.3(15.3)y, %males=70 HF Prev=NR%	1,000	92	89	8.36	0.09	0.9
Ray,[41] 2005 France	Cross-Sectional (EPIDASA TRIAL); Ethnicity: NR Comorbidities: Chronic respiratory failure (n=35), Cardiac disease (n=64); Reference standard: Pulmonologist, cardiologist, emergency physician, or geriatric or internal medicine	Compare the usefulness of two rapid analytical methods for BNP and proBNP in the diagnosis of CPE in patients aged 65 and older with acute dyspnea	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=202 age=80(9)y, %males=49.5 HF Prev=44%; Echo done in only 45%, population selected for age 65 and over	≥1,500	75	76	3.13	0.33	0.8
Robaei,[70] 2011 Australia	RCT (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=47), Diabetes (n=12), Historical MI (n=25), Respiratory disease (n=32), Prior congestive cardiac failure (n=26), History of HF (n=24); Reference standard: 1 cardiologist	Diagnostic uncertainty and accuracy of NT-proBNP in patients presenting with dyspnea .	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=68 age=73(16)y, %males=44.1; HF Prev=40%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75;1800pg/mL in >75 years	81	66	2.38	0.29	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Sakhuja,[71] 2005 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Prior AMI/angina (n=13), AF (n=16), Left bundle branch block (n=10), QRS duration >=120 ms (n=23), LV hypertrophy (n=6), Median LVEF (n=15); Reference standard: 2 Cardiologists	Evaluating usefulness of combining NT-proBNP and prolonged QRS complex for noninvasive prediction of impaired LV function	NT-proBNP (ELECSYS -proBNP Immunoassay)	Shortness of breath n=135 age=(LVEF<50) 70y*; (LVEF>50)73y*, %males=48.89 HF Prev=36%	Optimal cutpoint	96	44	1.71	0.09	NR
Sanz,[46] 2006 Spain	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: (n=5), AF (n=8), COPD (n=11), Ischemic heart disease (n=5), Cardiomyopathy hypertensive (n=9), valvar (n=7); Reference standard: Clinicians	To evaluate the value of NT-proBNP and BNP in patients with acute dyspnea in the emergency room, Diagnostic accuracy of different assays.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=75 age=75(14.8)y, %males=67 HF Prev=60%	817	97.7	93.5	15.03	0.02	0.979
					300	100	50	2.00	0.00	NR
Shah,[48] 2009a USA	Cohort (Shah, 2009b); Ethnicity: Caucasian (n=136), African-American (n=264), Other (n=12); Comorbidities: Hypertension=(n=268), CAD (n=177), Diabetes (n=124), Historical MI (n=99), Renal disease (n=140), Heart failure (n=148); Reference standard: Panel of physicians	1 year all-cause mortality	NT-proBNP (DIMENSION -NT-proBNP (PBNP) Flex® reagent cartridge method)	Acute dyspnea n=412 age=58(14)y, %males=6 HF Prev=36%	NR	NR	NR	NR	NR	0.86

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Shah,[47] 2009b	Cohort (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=267), CAD (n=178), Atrial Fibrillation (n=81), Diabetes (n=121), CHF or Cardiomyopathy (n=147); Reference standard: Panel of physicians	Mortality after one year	NT-proBNP (DIMENSION - EXLTm N-terminal Pro-Brain Natriuretic Peptide (NTP) Flex® Reagent Cartridge (RF623))	diagnosis of LVEF ≤40% n=NR age=NR %males=NR HF Prev=37%	300	NR	NR	NR	NR	0.86
				diagnosis of diastolic dysfunction n=NR age=NR %males=NR HF Prev=NR%	300	NR	NR	NR	NR	0.67
				diagnosis of diastolic dysfunction in patients with preserved systolic function (LVEF≥50%) n=NR age=NR %males=NR HF Prev=NR%	300	NR	NR	NR	NR	0.6
Shaikh,[72] 2011 Karachi	Cohort; Ethnicity (Independent Study)=NR Comorbidities=hypertension (n=82), AF (n=12); COPD (n=21), DM (n=51), paroxysmal nocturnal dyspnea (n=58), edema (n=61); Reference Standard=NR	To determine the diagnostic significance of NT-proBNP estimation in patients presented with acute dyspnea in emergency department.	NT-proBNP (rule out) (ELECSY-proBNP Immunoassay)	dyspnea (all patients) (n=100, age=61±14y, %males=48); HF prevalance=79%	300	100	42.85	1.75	0.00	NR
			NT-proBNP (ELECSY-proBNP Immunoassay)		900	96.2	80.95	5.05	0.05	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Shaikh, [72] 2011 Karachi (cont'd)	(repeated data) Cohort (Independent Study); Ethnicity=NR Comorbidities=hypertension (n=82), AF (n=12); COPD (n=21), DM (n=51), paroxysmal nocturnal dyspnea (n=58), edema (n=61); Reference Standard=NR	(repeated data) To determine the diagnostic significance of NT-proBNP estimation in patients presented with acute dyspnea in emergency department.	NT-proBNP (ELECSY-proBNP Immunoassay)	age <50 (n=22, age=NR %males=NR HF prevalence=NR	450	100	33.33	1.50	0.00	NR
			NT-proBNP (rule in) (ELECSY-proBNP Immunoassay)	age>50 (n=78,age=NRy, %males= NR); HF prevalence=NR	900	96.82	86.66	7.26	0.04	NR
			NT-proBNP (rule out) (ELECSY-proBNP Immunoassay)	age <75 (n=NR age=NR %males=NR); HF prevalence=NR	125	99	NR	NR	NR	NR
			NT-proBNP (rule out) (ELECSY-proBNP Immunoassay)	age >75 (n=NR age=NR %males=NR); HF prevalence=NR	450	99	NR	NR	NR	NR
Steinhart,[73] 2009 Canada	Cohort (IMPROVE-CHF); Ethnicity: NR Comorbidities: NR Reference standard: 2 Cardiologists, Framingham, NHANES	Diagnosis of AHF (to derive and validate a prediction model by using N-terminal pro,ÄìB-type natriuretic peptide NT-proBNP) and clinical variables to improve the diagnosis of acute AHF)	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=483 age=70y, %males=NR HF Prev=NR%	<300	NR	NR	NR	NR	NR
					300-899	NR	NR	NR	NR	NR
					900	NR	NR	NR	NR	NR
					<300	NR	NR	NR	NR	NR
					300-899	NR	NR	NR	NR	NR
					900-2699	NR	NR	NR	NR	NR
					2700-8099	NR	NR	NR	NR	NR
					>8100	NR	NR	NR	NR	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Tung,[74] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: Caucasian (n=192); Comorbidities: Arrhythmia (n=35), Hypertension (n=101), CAD (n=47), Historical MI (n=18); Reference standard: 2 Cardiologists	To evaluate results from amino-terminal pro-brain natriuretic peptide (NT-proBNP) testing with or without those of clinical judgment for the evaluation of dyspneic patients with previous chronic obstructive pulmonary disease or asthma.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=216 age=(HF) 69(1y; no HF) 59(16)y, %males=44.9 HF Prev=25%; Only 140 echo was taken in whole of PRIDE study; this is a subset analysis	450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	87	84	5.44	0.15	0.9
					300	94	61	2.41	0.10	NR
				COPD, No h/o HF n=NR age=NR %males=NR HF Prev=13%	>450	82	90	8.20	0.20	0.88
				COPD, HF n=NR age=NR %males=NR HF Prev=63%	>450	91	47	1.72	0.19	0.85
				COPD, No h/o HF n=NR age=NR %males=NR HF Prev=13%	300	90	66	2.65	0.15	NR
				COPD, HF n=NR age=NR %males=NR HF Prev=63%	300	97	21	1.23	0.14	NR

Table H-2. Evidence Table: Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (cont'd)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
van Kimmenade,[75] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Arrhythmia (n=102), Hypertension (n=294), CAD (n=166), Acute MI (n=79), COPD (n=216), Diabetes (n=158), Cardiomyopathy (n=65), Congestive Heart failure (n=148); Reference standard: Study physician	60 day follow up survival, diagnostic accuracy	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=(AHF) 72(13.6)y, %males= no AHF) 56.9(16.3)y HF Prev=35%	NR	NR	NR	NR	NR	0.94
Zaninotto ,[76] 2005 Italy	Case-control (Independent study); Ethnicity: NR Comorbidities: CARD (n=56), Pulmonary Disease (n=23), Pulmonary And Concomitant Cardiac Disease (n=17), Other Disease (n=7), Pulmonary Embolism (n=8), AMI (n=11); Reference standard: European society of cardiology guideline	To verify the usefulness of NT-proBNP in the differential diagnosis of dyspnea in a population of patients presenting in the ER with breathlessness.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Continuous ER patients (Acute-severe dyspnea) n=122 age=78*y, %males=47.5 HF Prev=46%	1,760 ng/L	80	76	3.33	0.26	0.815

Abbreviations: AUC = Area Under the Curve; BACH = Biomarkers in Acute Heart Failure; BASEL = B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation; BMI = Body Mass Index; BNP = B-Type Natriuretic Peptide; CHF = Congestive Heart Failure; CI = Confidence Interval; ECG = Electrocardiogram; eGFR = Estimated glomerular filtration rate; EPIDASA = Epidemiological study of acute dyspnea in elderly patients; GFR = Glomerular filtration rate; glow = Lower gray zone; gup = Upper gray zone; HEARD-IT = Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment; HF = Heart Failure; KD = Kidney disease; kg/m2 = Kilograms per meter squared; LR- = Negative Likelihood Ratio; LR+ = Positive Likelihood Ratio; LVEF = Left Ventricular Ejection Fraction; mg/dL = Milligram per deciliter; mL/min/1.73m2 = Milliliter per minute per 1.73 meters squared; NA = Not applicable; ng/L = Nanogram per liter; NHANES = National Health and Nutrition Examination Survey; NR = Not reported ; pg/mL = Picograms per milliliter; RCT = Randomized controlled trial; SOB = Shortness of breath; yrs = years

Figure H-19. Summary Sensitivity (ED NT-proBNP, lowest cutpoints [pg/ml]), random effect

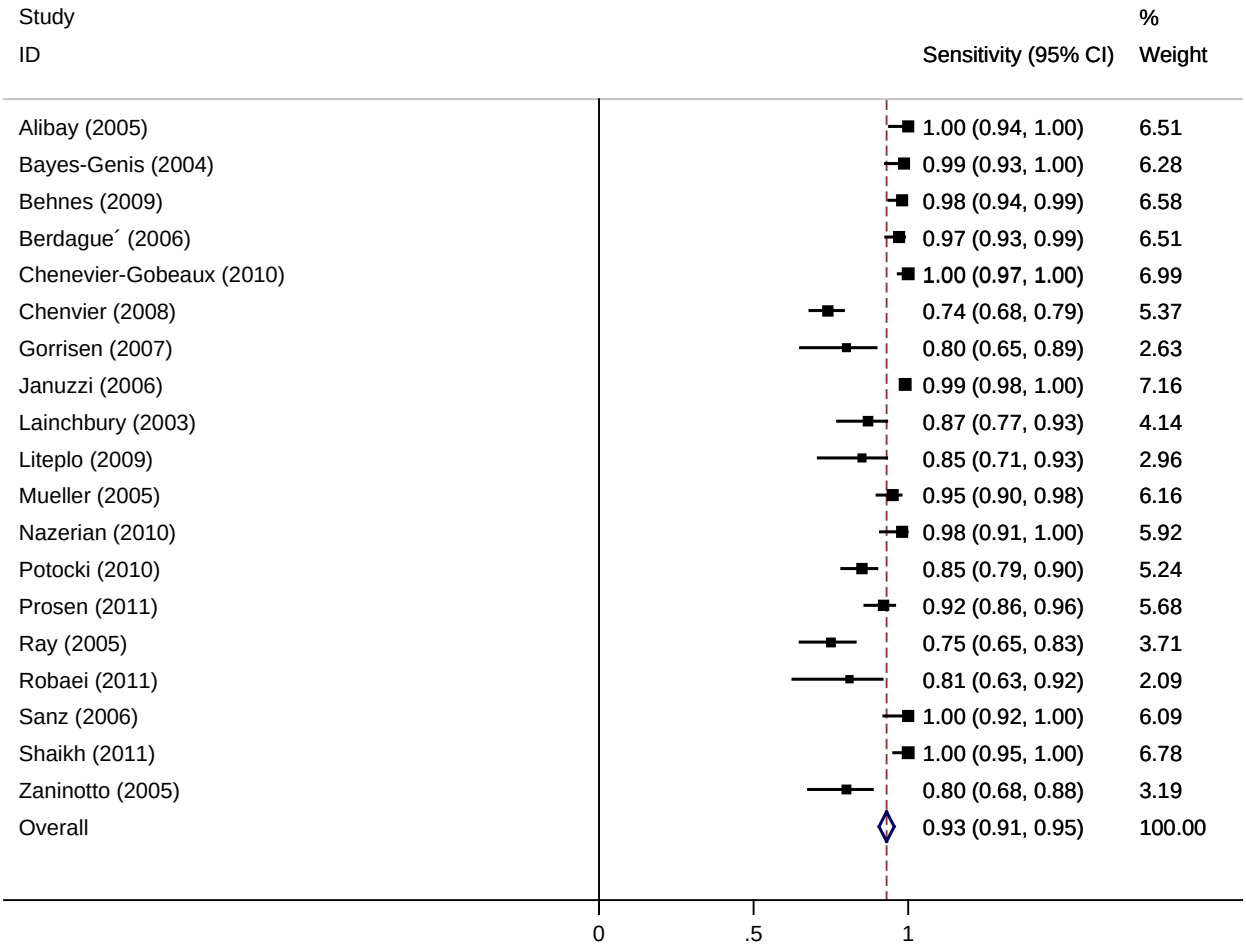


Figure H-20. Summary Sensitivity (ED NT-proBNP, optimal cutpoints [pg/ml]), random effect

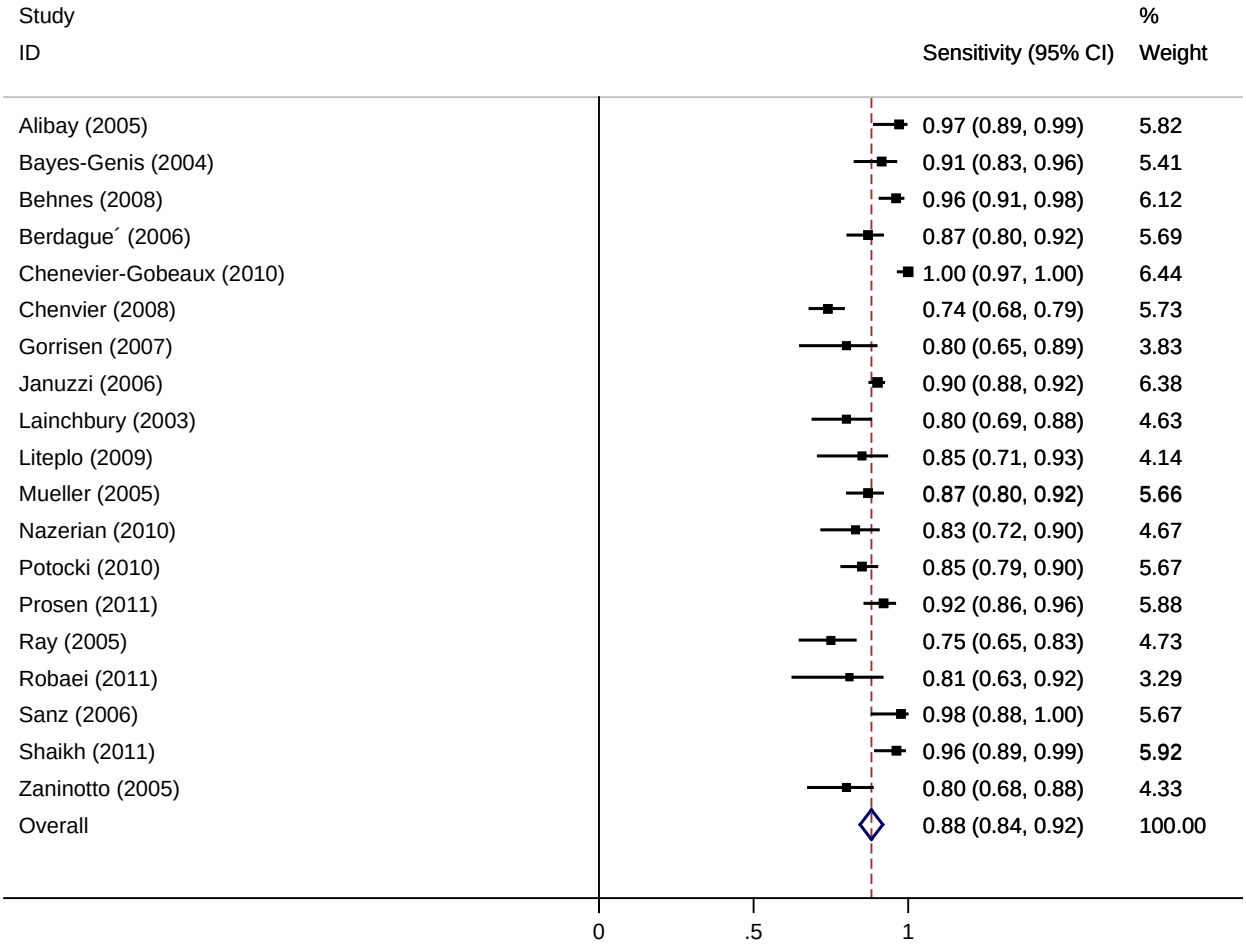


Figure H-21. Summary Specificity (ED NT-proBNP, lowest cutpoints [pg/ml]), random effect

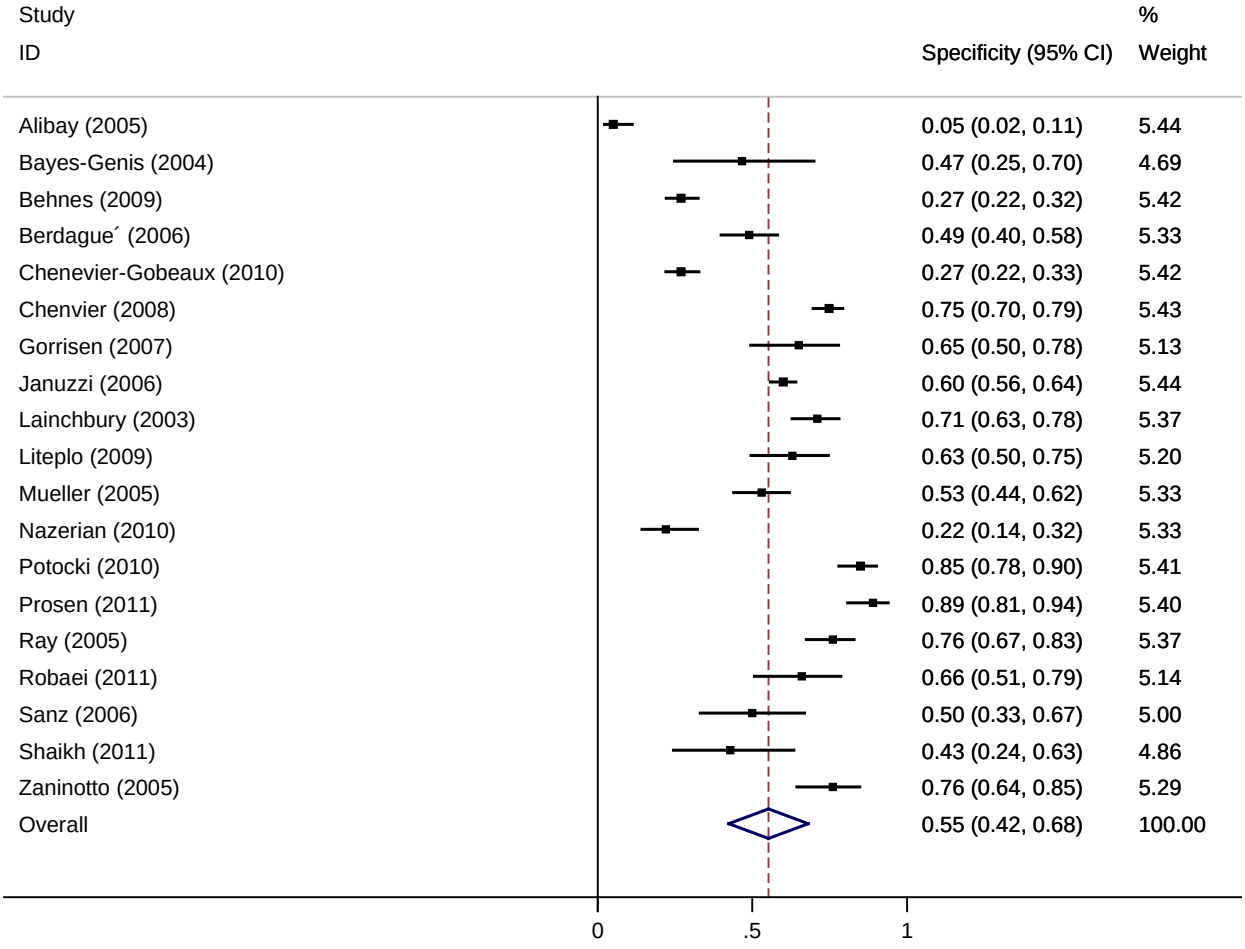


Figure H-22. Summary Specificity (ED NT-proBNP, optimal cutpoints [pg/ml]), random effect

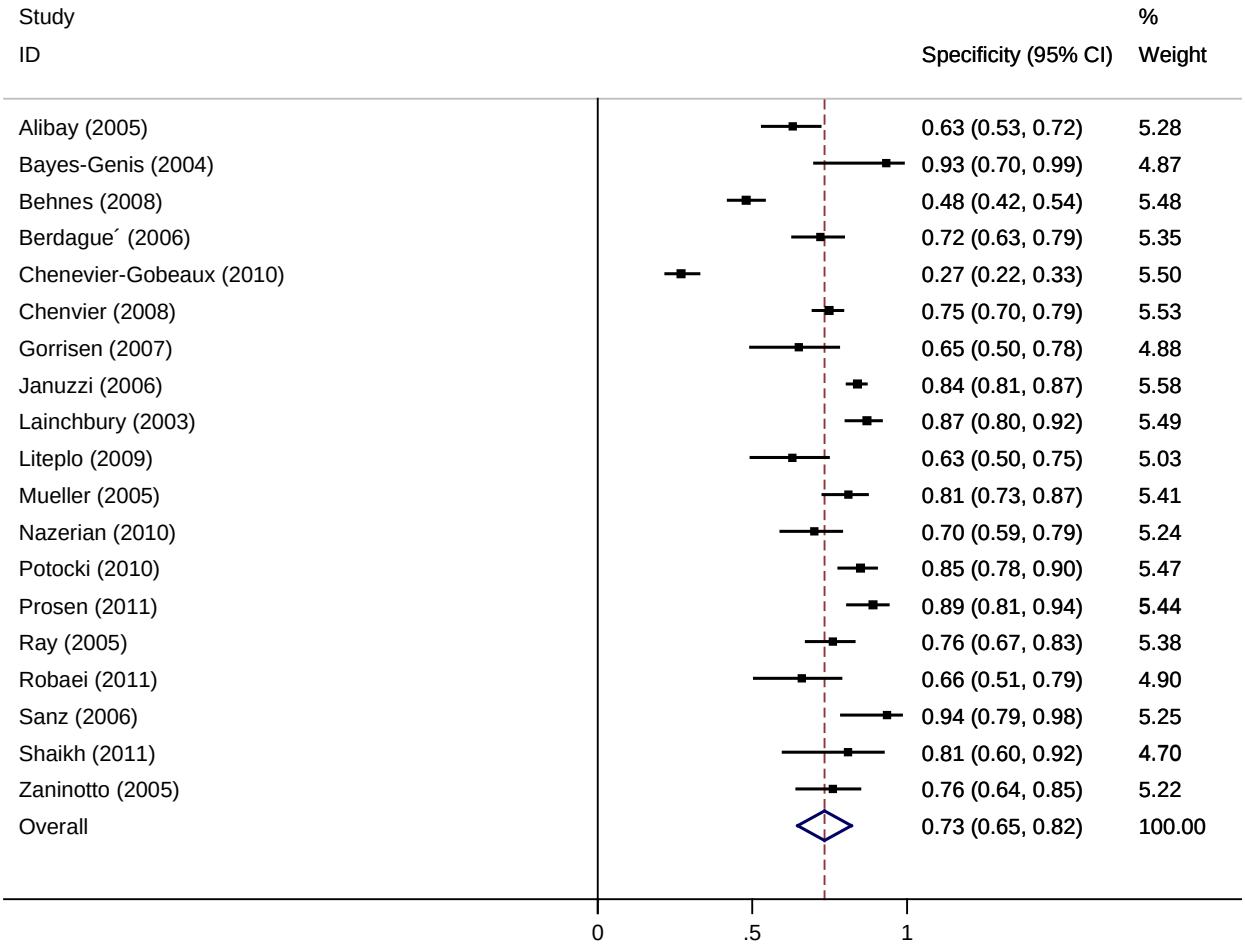


Figure H-23. Summary LR+ (ED NT-proBNP, lowest cutpoints [pg/ml]), random effect

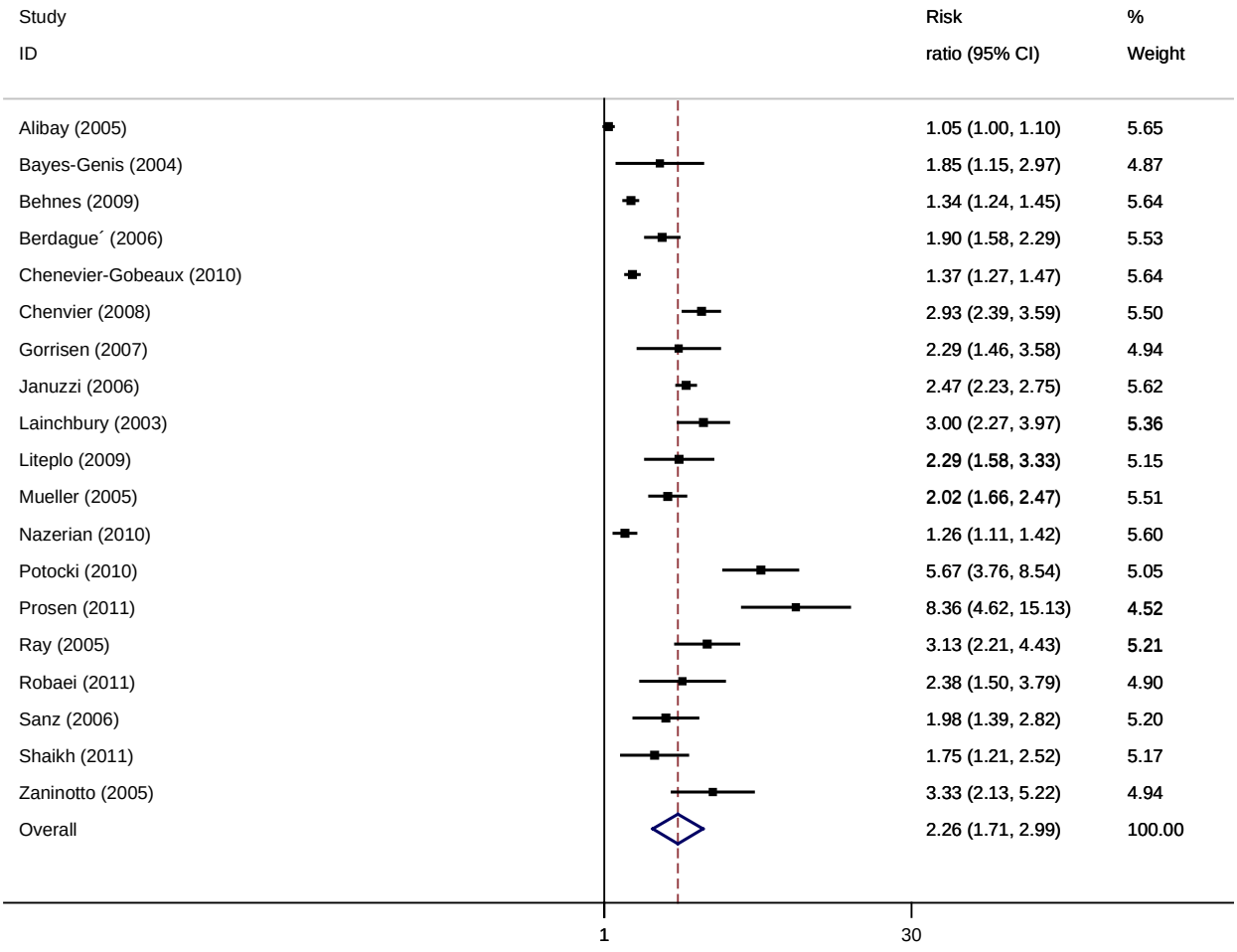


Figure H-24. Summary LR+ (ED NT-proBNP, optimal cutpoints [pg/ml]), random effect

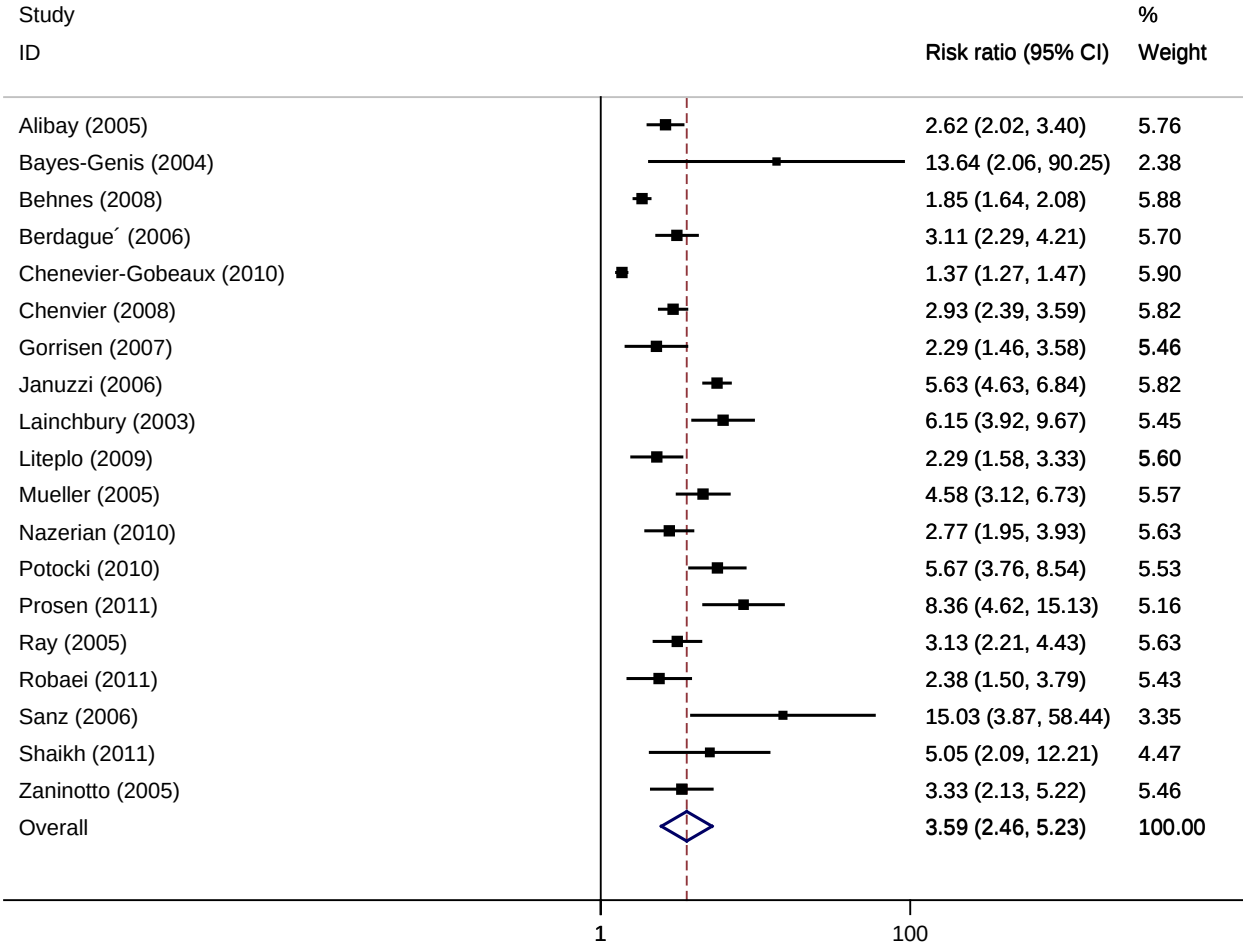


Figure H-25. Summary LR- (ED NT-proBNP, lowest cutpoints [pg/ml]), random effect

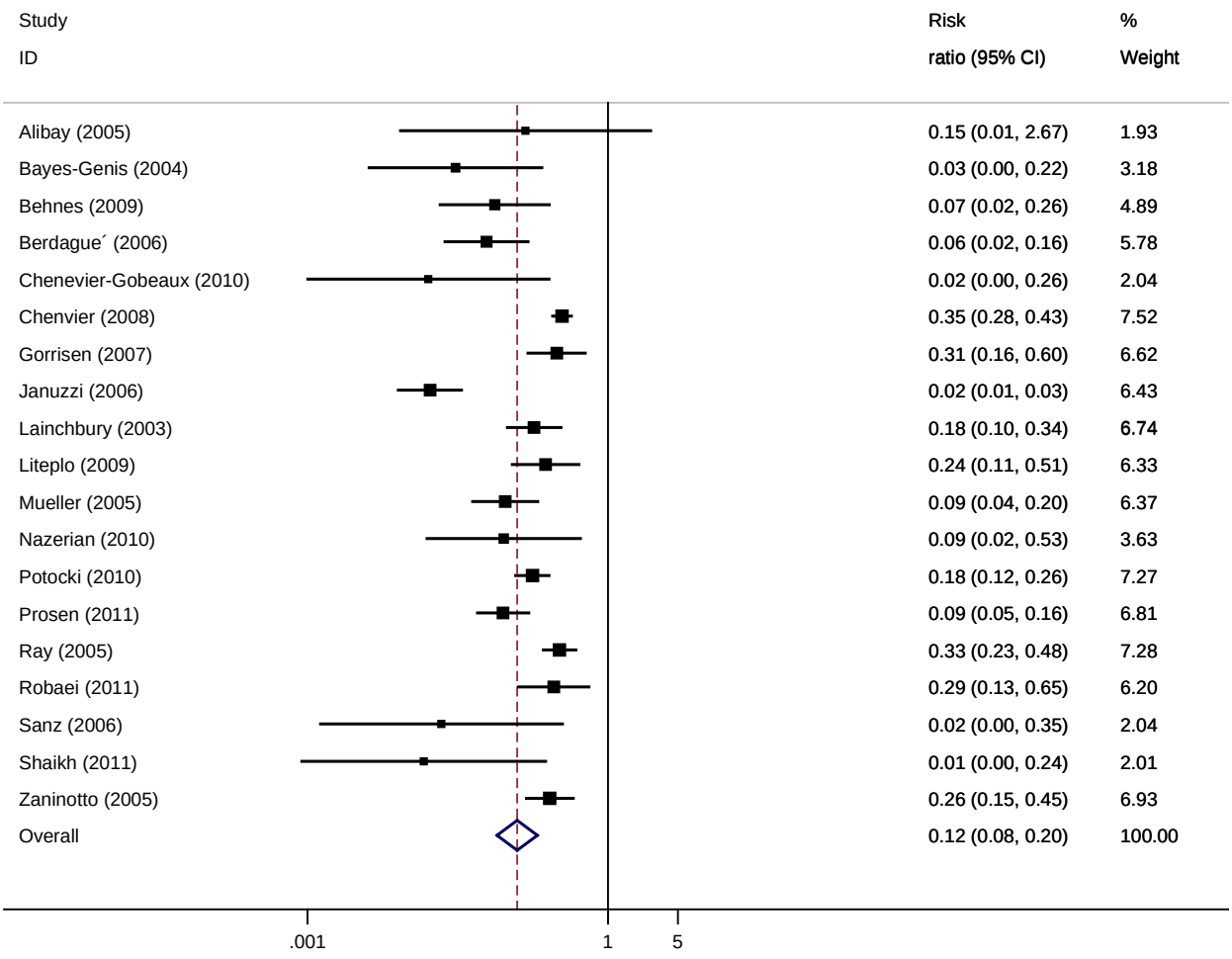


Figure H-26. Summary LR- (ED NT-proBNP, optimal cutpoints [pg/ml]), random effect

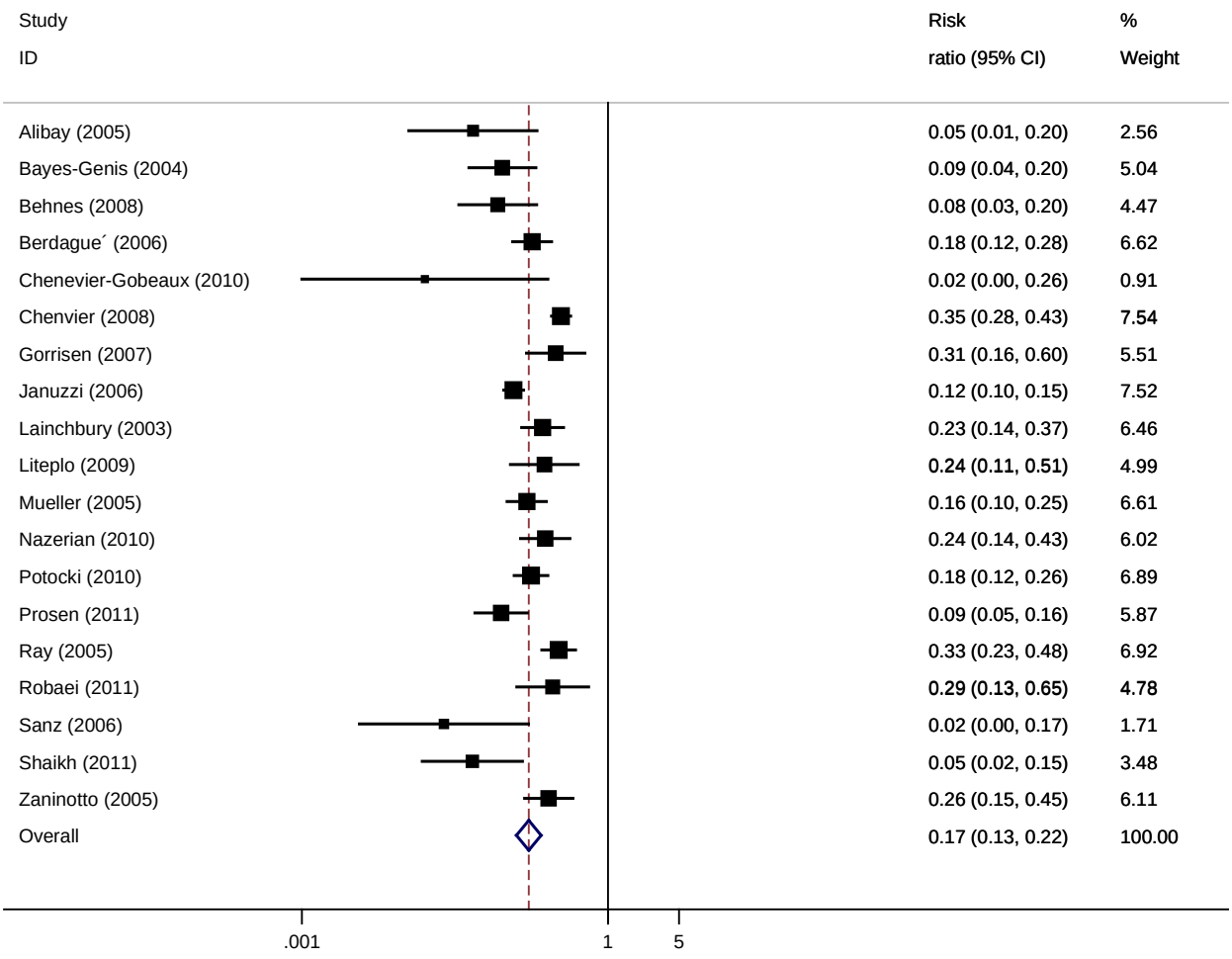


Figure H-27. Summary log DOR (ED NT-proBNP, lowest cutpoints [pg/ml]), random effect

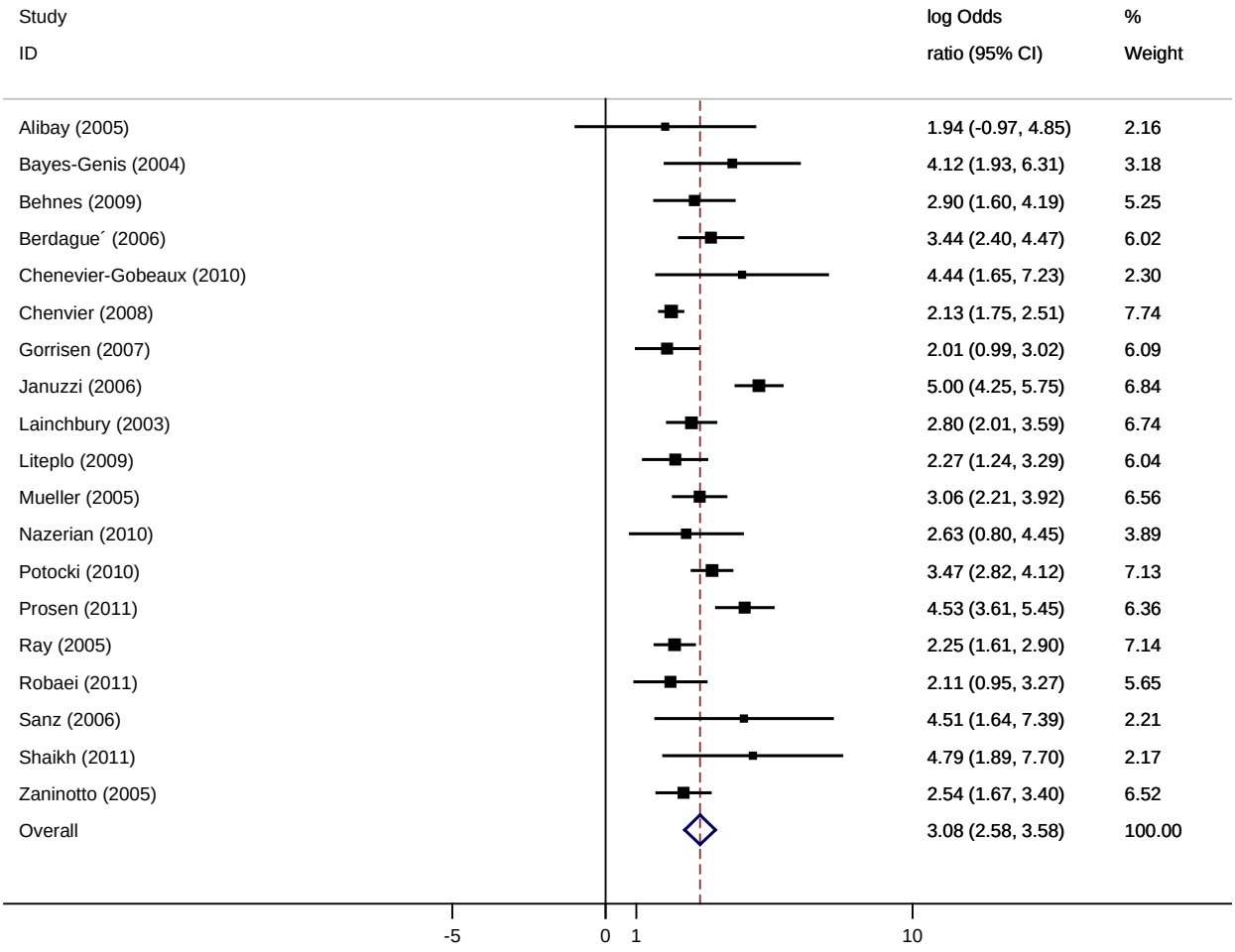


Figure H-28. Summary log DOR (ED NT-proBNP, optimal cutpoints [pg/ml]), random effect

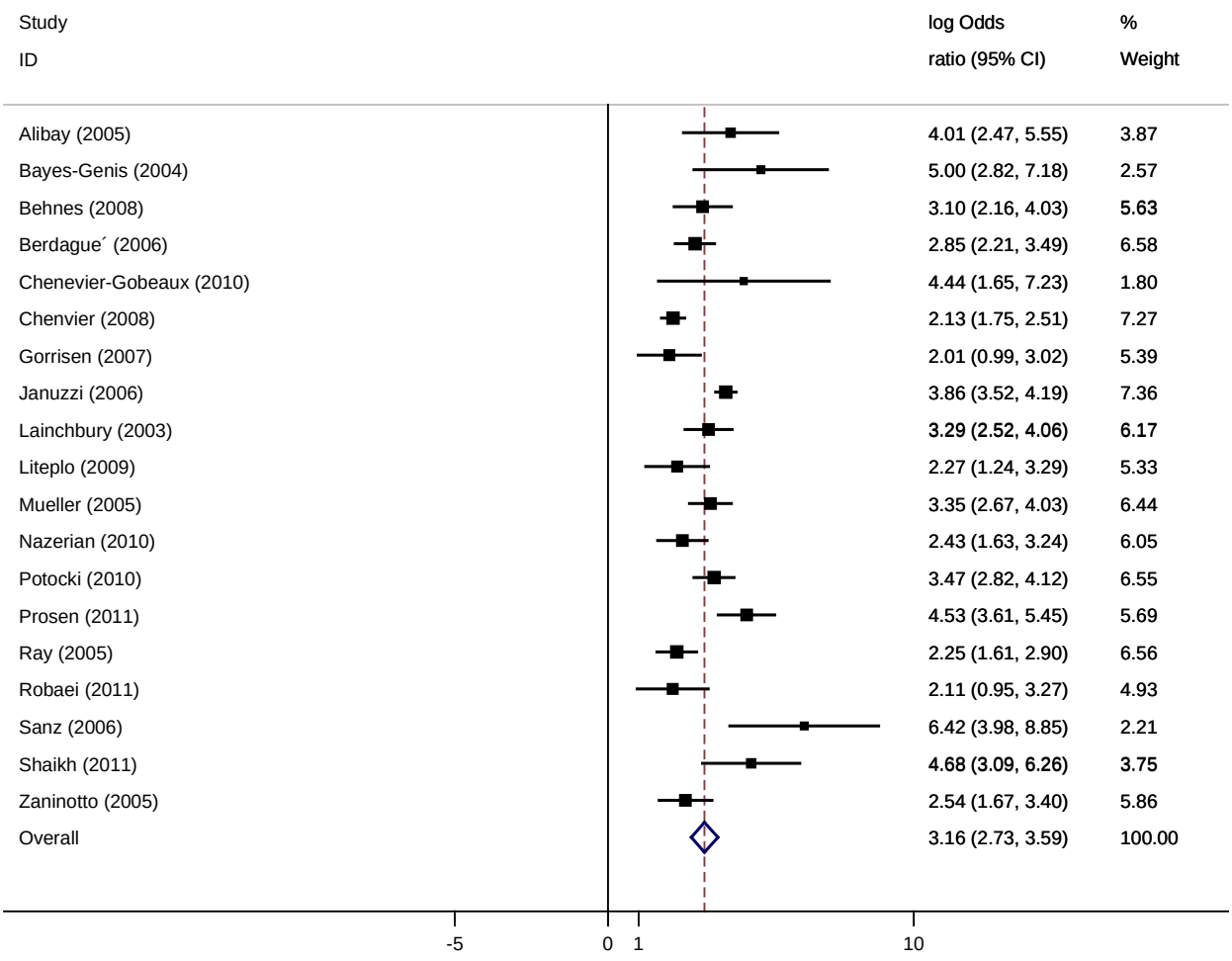


Figure H-29. Summary ROC-curve (ED NT-proBNP, lowest cutpoints [pg/ml]), random effect

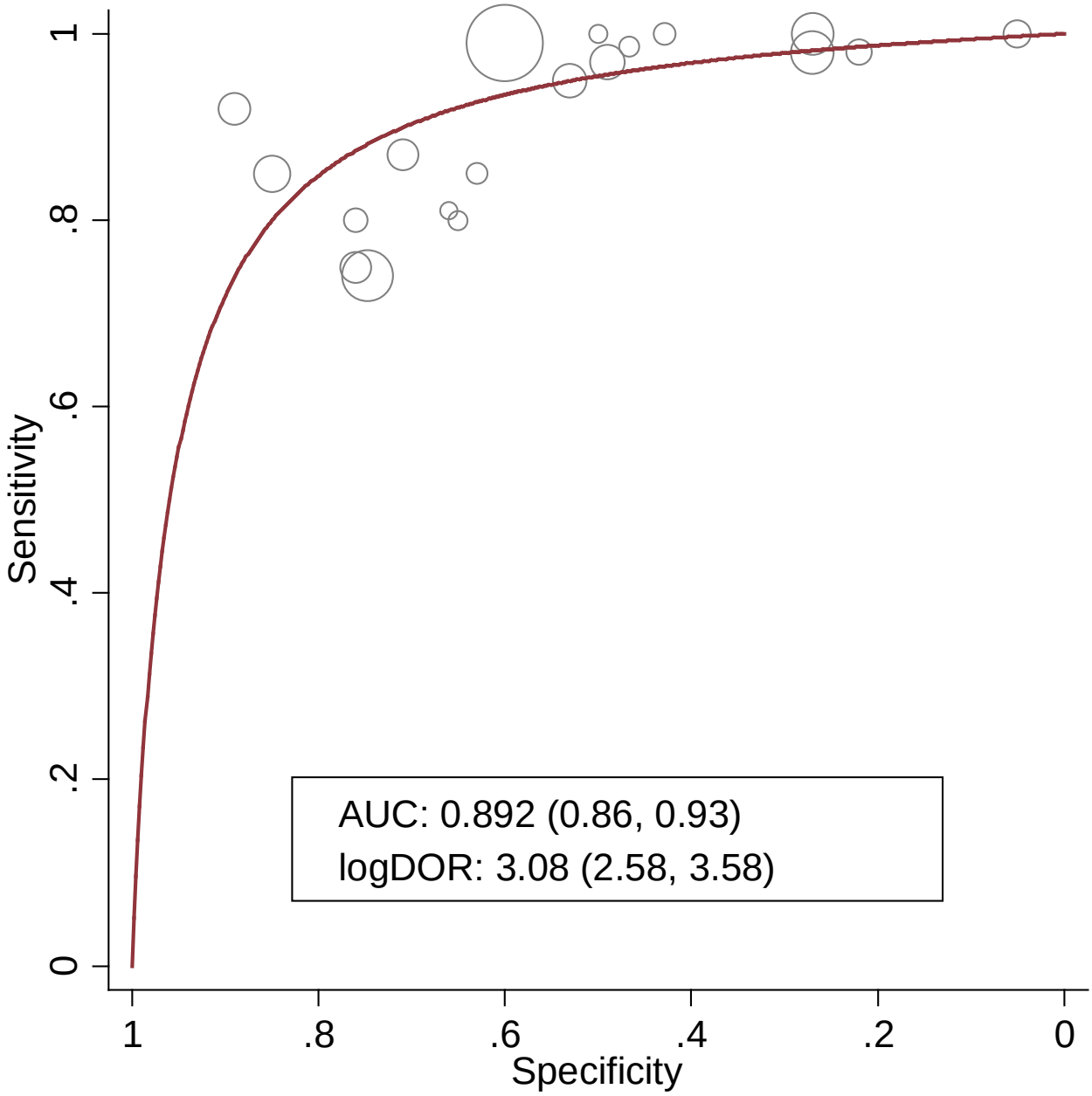


Figure H-30. Summary ROC-curve (ED NT-proBNP, optimal cutpoints [pg/ml]), random effect

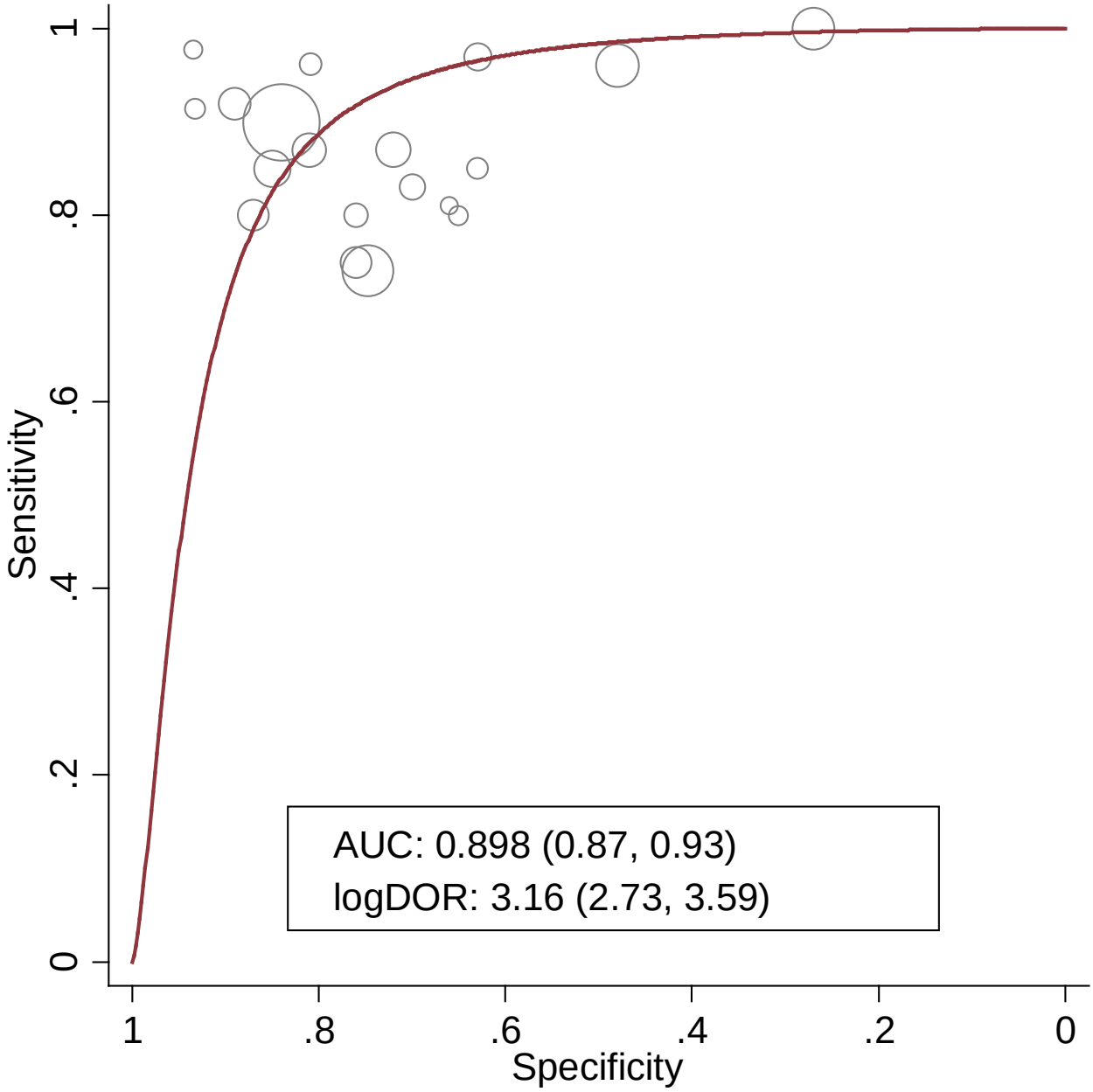


Table H-3. Risk of Bias and Applicability in all Diagnostic Studies using BNP in emergency department, results of QUADAS 2 quality assessment

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Alibay,[1] 2005	?	✓	✓	✓	✓	✓	✓
Arenja, [2] 2012	?	?	✓	?	✓	✓	✓
Arques,[3] 2007	✓	✓	✓	✓	✓	✓	✓
Barcarse,[4] 2004	✗	✓	✓	✓	✗	✓	✓
Boldanova,[5] 2010	✓	✓	✓	✓	✓	✓	✓
Chenevier-Gobeaux,[7] 2008	✗	✓	✓	?	✗	✓	✓
Chenevier-Gobeaux,[6] 2005	✗	✓	✓	✓	✓	✓	✓
Chenevier-Gobeaux,[8] 2010	✗	✓	✓	✗	✓	✓	✓
Choi,[9] 2007	?	✓	✓	✓	✗	✓	✓
Chung,[10] 2006	?	✓	✗	✓	✗	✗	✗
Collins,[11] 2006	✗	✓	✓	✗	✓	✓	✓
Coste,[12] 2006	✓	✓	✓	✓	✗	✗	✗
Daniels,[13] 2006	?	✓	✓	✓	✓	✓	✓
Dao,[14] 2001	✗	✓	✓	✓	✗	✓	✓
Defilippi,[15] 2007	✓	✓	✓	✓	✓	✓	✓
Dieplinger,[16] 2009	?	✓	✓	✓	✓	✓	✓
Gorissen,[17] 2007	✓	✓	✓	✗	✓	✓	✓
Gruson,[19] 2009	✓	✓	?	✓	✗	✗	✗
Gruson,[18] 2008	?	✓	✓	?	✓	✓	✓
Gruson, [20] 2012	✓	✗	✓	?	✓	✓	✓
Havelka,[21] 2011	✗	✓	✗	✓	✓	✓	✓
Kevin,[44] 2009	✗	✓	✓	✗	✓	✓	✓
Knudsen,[22] 2004	✓	✓	✓	✓	✓	✓	✓
Knudsen,[24] 2005	?	✓	✓	✓	✓	✓	✓
Knudsen,[23] 2004	?	✓	✓	✗	✓	✓	✓
Lainchbury,[25] 2003	?	✓	✓	✓	?	✓	✓
Logeart,[26] 2002	✓	✓	✓	✓	✓	✓	✓

Table H-3. Risk of Bias and Applicability in all Diagnostic Studies using BNP in emergency department, results of QUADAS 2 quality assessment (cont'd)

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Lokuge,[27] 2010	?	?	✔	✔	✔	✔	✔
Maisel,[30] 2004	?	✔	✔	✔	✔	✔	✔
Maisel,[31] 2010	✔	✔	✔	✔	✔	✔	✔
Maisel,[29] 2003	?	✔	✔	✔	?	✔	✔
Maisel,[28] 2002	?	✔	✔	✔	✔	✔	✔
McCullough,[32] 2003	?	✔	✔	✔	?	✔	✔
McCullough,[33] 2002	?	✔	✔	✕	✔	✔	✔
Morrison,[34] 2002	✕	✔	✔	✔	✕	✔	✔
Mueller,[35] 2005	?	✔	✔	✕	✕	✕	✕
Noveanu,[37] 2009	?	?	✔	✔	✔	?	✔
Pahle,[38] 2009	?	✔	✔	✕	✕	✕	✕
Parrinello,[39] 2008	?	✔	✔	✔	✔	✔	✔
Potocki,[40] 2010	✔	✔	✔	✔	✔	✔	✔
Ray,[42] 2004	?	✔	✔	✕	✕	✔	✔
Ray,[41] 2005	?	✔	✔	✔	✕	✕	✕
Ro, [43] 2011	✔	✔	✔	?	✔	✔	✔
Rogers,[45] 2009	?	✔	✔	✔	✕	✕	✕
Sanz,[46] 2006	?	✔	✔	?	✕	✕	✕
Shah,[47] 2009	?	✔	✔	✔	✕	✕	✕
Shah,[48] 2009	✕	✔	✔	✔	✕	✕	✕
Steg,[49] 2005	?	✔	✔	✔	✕	✕	✕
Villacorta,[50] 2002	✔	✔	✔	✔	✔	✔	✔
Wang,[51] 2010	?	✔	✔	✕	?	✔	✔
Wu,[52] 2004	?	✔	✔	✔	?	✔	✔

✔ = Low Risk ✕ = High Risk ? = unclear

Figure H-31. Proportion (%) of diagnostic studies used BNP with low, high, or unclear concerns regarding risk of Bias in emergency department

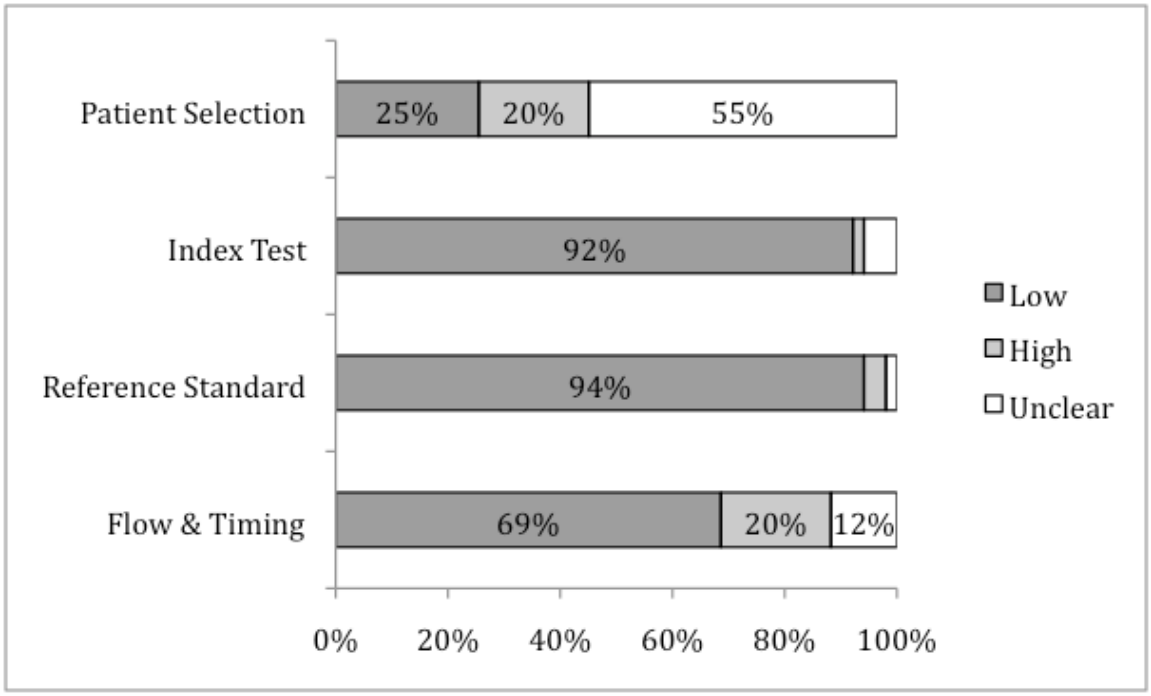


Figure H-32. Proportion (%) of diagnostic studies used BNP with low, high, or unclear concerns regarding applicability in emergency department

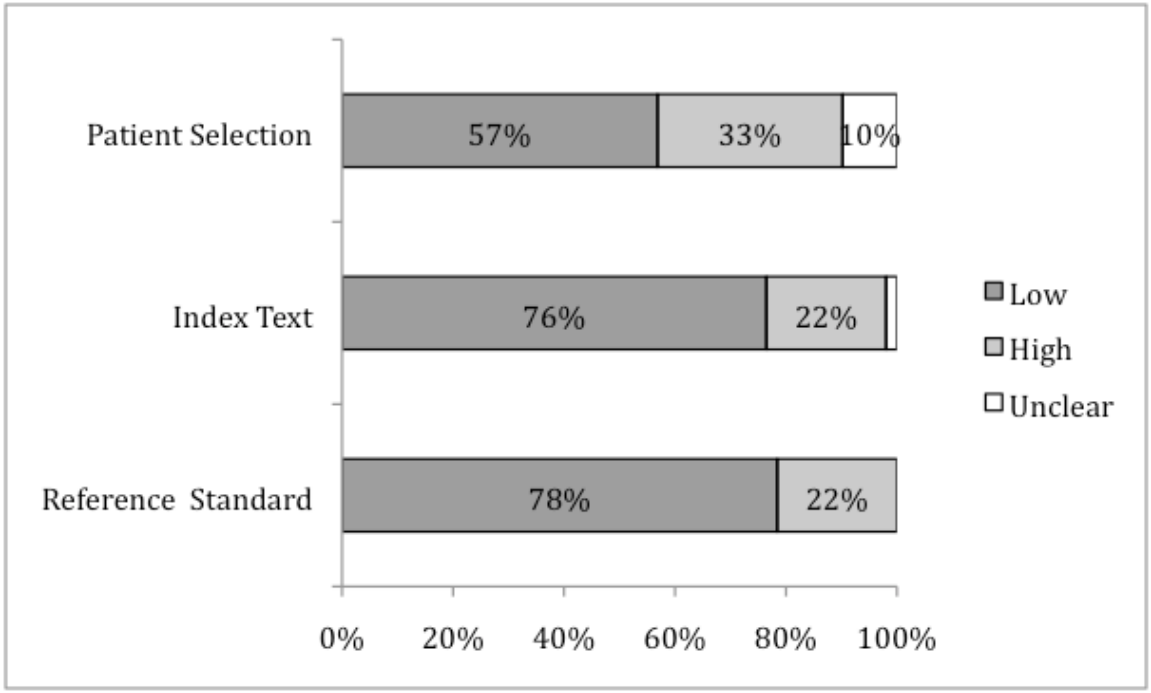


Table H-4. Risk of bias and applicability in all diagnostic studies using NT-ProBNP in emergency department, results of QUADAS 2 quality assessment

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Alibay,[1] 2005	?	✓	✓	✓	✓	✓	✓
Anwaruddin,[53] 2006	✗	✓	✓	✓	✓	✓	✓
Bayes-Genis,[55] 2007	✗	✓	✗	✓	✓	✓	✓
Bayes-Genis,[54] 2004	✓	✓	✗	✓	✓	✓	✓
Behnes,[57] 2011	✓	✓	✓	✓	✓	✓	✓
Behnes,[56] 2009	✓	✓	✓	✓	✗	✗	✗
Berdague,[58] 2006	?	✓	✗	✓	✗	✓	✓
Chenevier-Gobeaux,[7] 2008	✗	✓	?	✓	✗	✓	✓
Chenevier-Gobeaux,[6] 2005	✗	✓	✓	✓	✓	✓	✓
Chenevier-Gobeaux,[8] 2010	✗	✓	✗	✓	✓	✓	✓
Defilippi,[15] 2007	✓	✓	✓	✓	✓	✓	✓
Gorissen,[17] 2007	✓	✓	✗	✓	✓	✓	✓
Green,[59] 2008	✗	✓	✓	✓	✓	✓	✓
Gruson,[18] 2008	?	✓	?	✓	✓	✓	✓
Gruson, [20] 2012	✓	✗	✓	?	✓	✓	✓
Januzzi,[61] 2006	?	✓	✗	✓	✓	✓	✓
Januzzi,[60] 2005	✗	✓	✓	✓	✓	✓	✓
Krauser,[62] 2006	✗	✓	✓	✓	✗	✗	✗
Lainchbury,[25] 2003	?	✓	✓	✓	?	✓	✓
Liteplo,[63] 2009	✗	✓	✓	✓	✗	✗	✗
Martinez-Rumayor,[64] 2010	✗	✓	✓	✓	✓	✓	✓
Moe,[65] 2007	✗	✓	✗	✓	✓	✓	✓
Mueller,[35] 2005	?	✓	✗	✓	✗	✗	✗
Nazerian,[66] 2010	✗	✓	✓	✓	✗	✓	✓
O'Donoghue,[67] 2007	✗	✓	✓	✓	✓	✓	✓
Oh,[68] 2009	?	✓	✓	✓	✓	✓	✓
Potocki,[40] 2010	✓	✓	✓	✓	✓	✓	✓

Table H-4. Risk of bias and applicability in all diagnostic studies using NT-ProBNP in emergency department, results of QUADAS 2 quality assessment (cont'd)

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Prosen,[69] 2011	✓	✓	✓	✓	✓	✓	✓
Ray,[41] 2005	?	✓	✓	✓	✕	✕	✕
Robaei,[70] 2011	✓	✓	?	✓	✓	✓	✓
Sakhuja,[71] 2005	✕	✓	✓	✓	✓	✓	✓
Shaikh, [72] 2011	✓	?	?	?	✓	?	?
Sanz,[46] 2006	?	✓	?	✓	✕	✕	✕
Shah,[47] 2009	?	✓	✓	✓	✕	✕	✕
Shah,[48] 2009	✕	✓	✓	✓	✕	✕	✕
Steinhart,[73] 2009	✕	✓	✕	✓	✕	✕	✕
Tung,[74] 2006	✕	✓	✓	✓	✓	✓	✓
van Kimmenade,[75] 2006	✕	✓	✓	✓	✕	✕	✕
Zaninotto,[76] 2005	✓	✓	?	✓	✓	✓	✓

✓ = Low Risk ✕ = High Risk ? = unclear

Figure H-33. Proportion (%) of diagnostic studies used NT-ProBNP with low, high, or unclear concerns regarding risk of Bias in emergency department

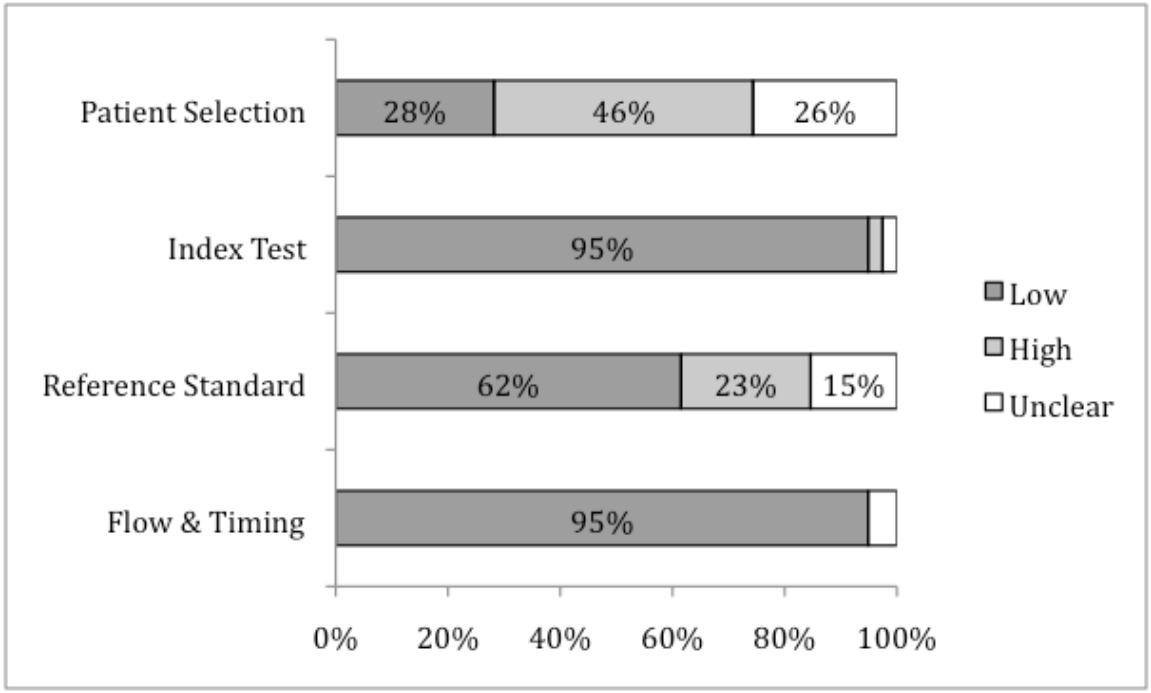


Figure H-34. Proportion (%) of diagnostic studies used NT-ProBNP with low, high, or unclear concerns regarding applicability in emergency department

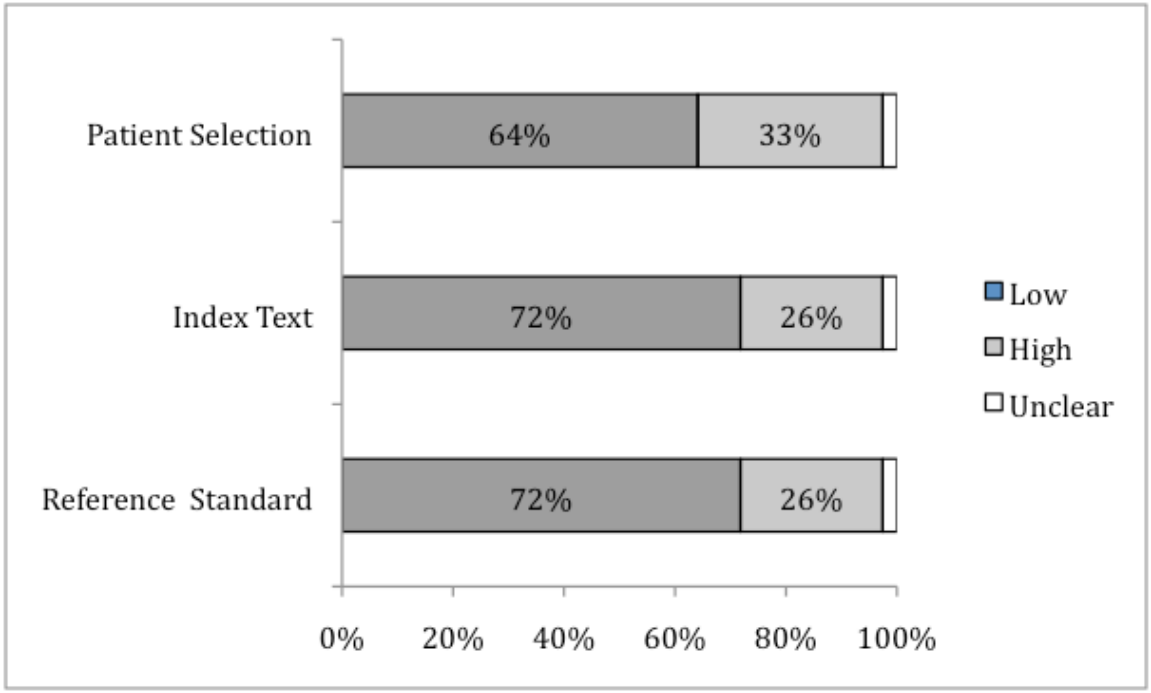


Table H-5a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing BNP in emergency department settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Arques,[3] 2007 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Chenevier-Gobeaux,[7] 2008 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Defilippi,[15] 2007 Dieplinger,[16] 2009 Gorissen,[17] 2007 Gorissen,[17] 2007 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ray,[41] 2005 Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Villacorta,[50] 2002 Wang,[51] 2010	Sensitivity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=11,459	0.9 (0.88-0.92)	High	High

Table H-5a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing BNP in emergency department settings (cont'd)

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay[1] 2005 Arques[3] 2007 Boldanova[5] 2010 Chenevier-Gobeaux[8] 2010 Chenevier-Gobeaux[7] 2008 Choi[9] 2007 Chung[10] 2006 Dao[14] 2001 Defilippi[15] 2007 Dieplinger[16] 2009 Gorissen[17] 2007 Gorissen[17] 2007 Knudsen[22] 2004 Lainchbury[25] 2003 Logeart[26] 2002 Lokuge[27] 2010 Maisel[28] 2002 Maisel[31] 2010 Morrison[34] 2002 Mueller[35] 2004 Parrinelo[39] 2008 Ray[42] 2006 Ray[41] 2005 Rogers[45] 2009 Sanz[46] 2006 Sanz[46] 2006 Steg[49] 2005 Villacorta[50] 2002 Wang[51] 2010	Specificity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=11,459	0.77 (0.72-0.83)	Moderate	Moderate

Table H-5b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing BNP in emergency department settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Arques,[3] 2007 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Chenevier-Gobeaux,[7] 2008 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Defilippi,[15] 2007 Dieplinger,[16] 2009 Gorissen,[17] 2007 Gorissen,[17] 2007 Gruson,[19] 2009 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ray,[41] 2005 Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Villacorta,[50] 2002 Wang,[51] 2010	Sensitivity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	Consistent – range of estimates is small	n=11,556	0.94 (0.93-0.96)	High	High

Table H-5b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing BNP in emergency department settings (cont'd)

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Arques,[3] 2007 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Chenevier-Gobeaux,[7] 2008 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Defilippi,[15] 2007 Dieplinger,[16] 2009 Gorissen,[17] 2007 Gorissen,[17] 2007 Gruson,[19] 2009 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ray,[41] 2005 Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Villacorta,[50] 2002 Wang,[51] 2010	Specificity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=11,556	0.64 (0.57-0.72)	Moderate	Moderate

Table H-5c. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on manufacturer cutpoints for diagnostic studies utilizing BNP in emergency department settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ro,[43] Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Wang,[51] 2010	Sensitivity	Cross-sectional (n=21), RCT (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	Consistent – range of estimates is small	n=9,584	0.95 (0.93-0.96)	High	High

Table H-5c. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on manufacturer cutpoints for diagnostic studies utilizing BNP in emergency department settings (cont'd)

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ro,[43] Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Wang,[51] 2010	Specificity	Cross-sectional (n=21), RCT (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=9,584	0.64 (0.57-0.71)	Moderate	Moderate

Abbreviations: CI = confidence interval; RCT = randomized controlled trial

Table H-6**. Summary test statistics of publication bias using diagnostic odds ratios (DOR), for emergency department, stratified by assay and presented separately for different cutpoints**

Assay	Groups	n study	Begg z	Begg p	Egger t	Egger p
BNP	Manufacturer cutpoint	22	0.99	0.324	1.19	0.247
	Optimum cutpoint	29	**2.03**	**0.043**	**2.14**	**0.041**
	Publication year < 2006	11	**2.57**	**0.010**	2.02	0.052
	Publication year ≥ 2006	18	1.17	0.240	1.44	0.250
	Optimum cutpoint = lowest cutpoint	14	**2.03**	**0.043**	**2.26**	**0.032**
	Optimum cutpoint > lowest cutpoint	15	1.24	0.216	1.13	0.378
	Lowest cutpoint	31	**2.29**	**0.022**	**2.35**	**0.026**
	Lowest cutpoint = optimum cutpoint	14	**2.03**	**0.043**	**2.26**	**0.032**
	Lowest cutpoint < optimum cutpoint	17	0.74	0.458	0.66	0.524
NT-proBNP	Manufacturer cutpoint	4	-1.36	0.174	**-11.4**	**0.008**
	Optimum cutpoint	19	1.08	0.278	0.71	0.489
	Lowest cutpoint	19	0.94	0.345	1.45	0.165

Background. Sensitivity and specificity are inversely related with each other in different cutpoints,[78] therefore Song and coworker suggested the utilization of DOR for estimating publication bias because it contains both sensitivity and specificity.[79] Due to higher degree of random variation, studies with small sample size will have wider distribution of results than studies of larger sample.[80] The possibility of publication is high for larger studies with positive results, and small/negative studies may not be published and often lead to asymmetry in the funnel.[79] In the meta-analysis of screening and diagnostic data, commonly acceptable measures of test accuracy are not yet established.[81] Precision of the asymmetry of funnel plots can be measured using Begg's adjusted rank correlation method and Egger statistical approach.[82,83] Begg's test assesses the correlation between test accuracy estimates and their variance,[82] but Egger's test determines whether there is an association between test accuracy estimates and their precision using regression analysis.[83] In our current analysis, we consider publication bias if Begg's and Egger's test reveals publication bias. The tests for publication bias exposed significant bias in the following conditions in the meta-analysis: 1) optimum cutpoint; 2) lowest cutpoint; and 3) publication year for BNP at emergency department, but not for the Primary Care Settings.

Figure H-35. Emergency department publication bias: BNP

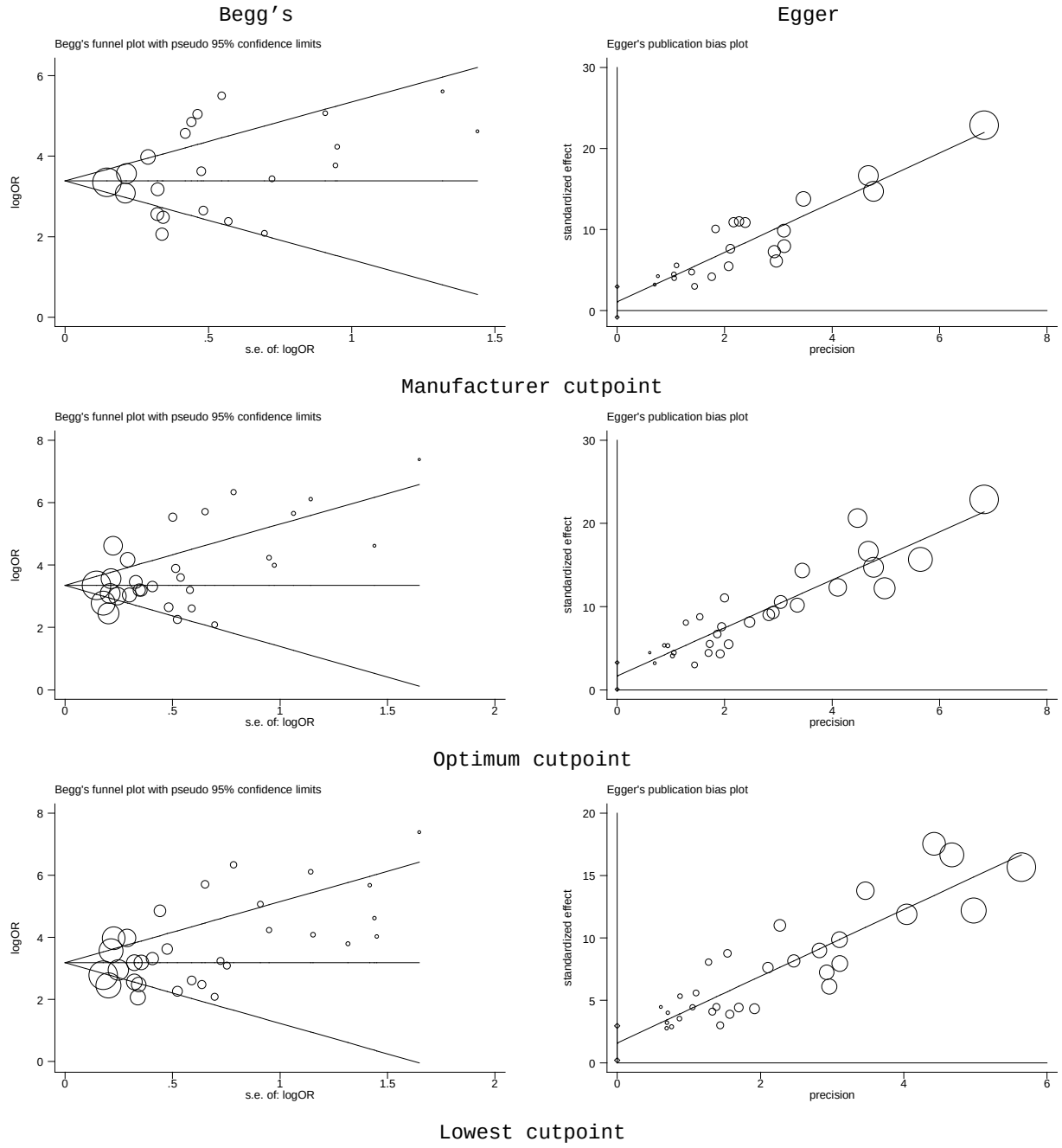
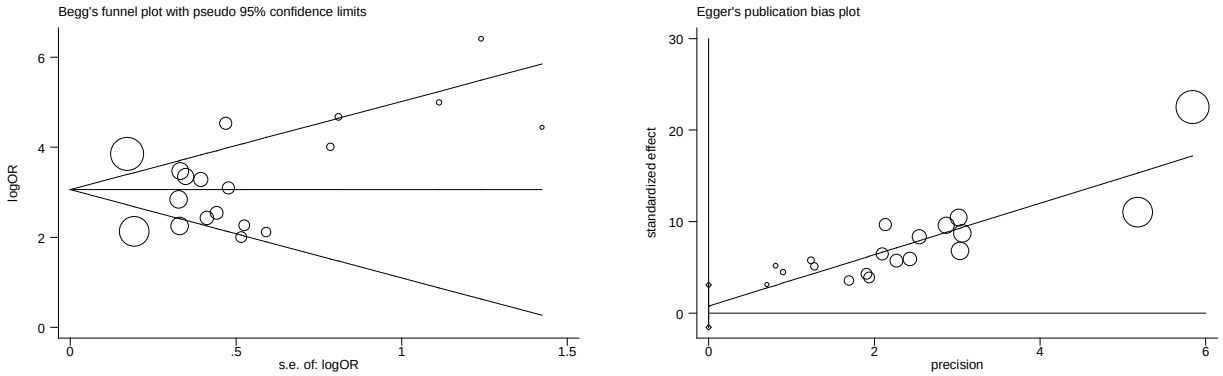


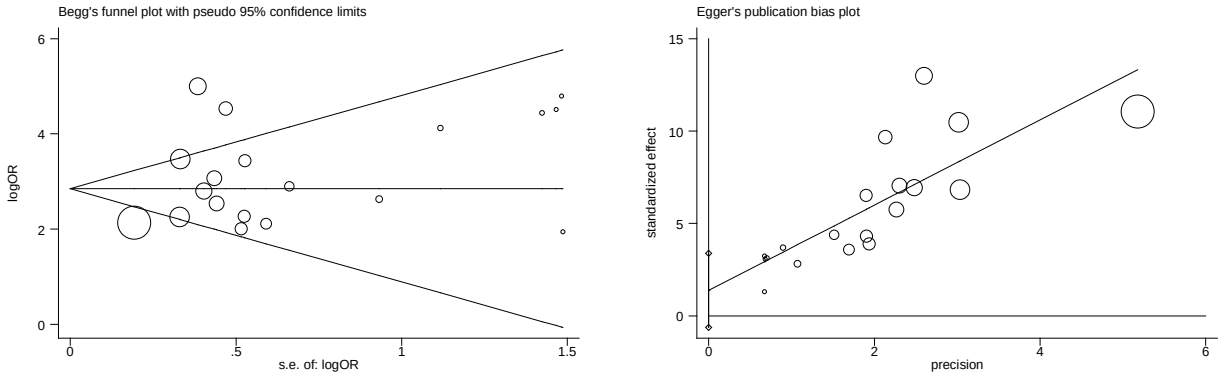
Figure H-36. Emergency department publication bias: NT-proBNP

Begg's

Egger



Optimum cutpoint



Lowest cutpoint

Table H-7a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Shaikh,[72] Zaninotto,[76] 2005	Sensitivity	Cross-sectional (n=14), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=4,955	0.9 (0.87-0.94)	High	High

Table H-7a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings (cont'd)

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Zaninotto,[76] 2005	Specificity	Cross-sectional (n=13), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=4,855	0.95 (0.44-0.86)	Moderate	Moderate

Table H-7b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Zaninotto,[76] 2005	Sensitivity	Cross-sectional (n=13), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=4,855	0.92 (0.90-0.95)	High	High

Table H-7b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings (cont'd)

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Zaninotto,[76] 2005 Shaikh,[72] 2011	Specificity	Cross-sectional (n=14), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=4,955	0.56 (0.43-0.96)	Moderate	Moderate

Appendix H. Reference List

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APPENDIX I.

KQ2 Evidence Set

Appendix I. KQ2 Evidence Set – Table of Contents

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Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Arques,[1] 2005 (country unreported)	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=36), CAD (n=23), COPD (n=36), Diabetes (n=18), HF (n=12), Reference standards: 2 Cardiologists, 1 Chest physician, Framingham criteria	Diagnosis of either decompensated HF or respiratory disease as the primary cause of SOB	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Acute/recently aggravated dyspnea n=70 mean age= HF: 77y (12); noHF: 74y (12) %males=50 HF Prev=45.7%	>100	97	63	2.63	0.05	NR
					>146	91	76	3.82	0.12	0.875
					>402	59	90	5.66	0.45	NR
Aspromonte,[2] 2006 Italy	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=91), AF(n=36), COPD (n=28), Diabetes (n=17),IHD (n=60), Renal disease (n=13) Reference standards: Cardiologists, Framingham	Diagnostic accuracy and cost analysis for HF	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected CHF referred by GPs (all) n=357 mean age= (HF) 76y (10); (no HF) 71y (11) %males=50 HF Prev=67%	30	99	71	3.41	0.01	NR
					50	93	85	6.20	0.08	NR
					70	87	89	7.91	0.15	NR
					80	84	90	8.40	0.18	NR
					100	80	91	8.89	0.22	NR
					120	76	92	9.50	0.26	NR
					200	86	60	2.15	0.23	NR
					300	86	69	2.77	0.20	NR
					400	86	77	3.74	0.18	0.85
					470	86	81	4.53	0.17	NR
					500	86	81	4.53	0.17	NR
Barrios,[3] 2011 Spain	Cross-sectional (PANAMA) Ethnicity: NR Comorbidities: Dyslipidemia (n=39), HBP (n=54), Diabetes (n=21), IHD(n=15) Reference Standard: Framingham	Clinical applicability of BNP in suspected HF primary care patients	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Clinical diagnosis of HF≥18 n=72 mean age= 75.1y (8.7), %males=25.4 HF Prev=61%	>100	25	81	1.30	0.93	0.72

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Christenson,[4] 2010 United States	Cross-sectional (INDEPENDENT STUDY) Ethnicity: African-American (n=246) Comorbidities: HBP (n=209), CAD (n=227), AF(n=147), Diabetes (n=245), Prior HF (n=236) Reference standards: 1 Cardiologist	Adjudicated acute HF, all-cause mortality (evaluated the accuracy of NTproBNP and BNP across a range of BMIs for diagnosis of decompensated HF in a community based dyspneic patient population; also investigated whether the prognostic accuracies of NT-proBNP and BNP concentrations differed based on BMI for predicting 1-year all-cause mortality)	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Dyspnea, Suspected HF n=675 mean age= NR %males=48 HF Prev=35%	100	NR	NR	NA	NA	0.73
				Dyspnea (decompensated HF, Normal Weight, BMI <25 kg/m2) n=212 mean age= 69.8y (15.5) %males=52.4 HF Prev=36.3%	100	89	38	1.44	0.29	0.78
				Dyspnea (decompensated HF, Over Weight, BMI 25-30 kg/m2) n=193 mean age= 66.6y (13.8) %males=57.5 HF Prev=37.3%	100	85	38	1.37	0.39	0.62
				Dyspnea (decompensated HF, Obese, BMI >30 kg/m2) n=280 mean age= 62.5y (14.6) %males=37.8 HF Prev=32.2%	100	81	49	1.59	0.39	0.72

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Fuat,[5] 2006 United Kingdom	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=102), AF, (n=56), COPD (n=69), Diabetes (n=27), Historical MI (n=39),IHD (n=87) Reference standards: GPs,15% of ECHO verified by cardiologists	To test and compare the diagnostic accuracy and utility of B-type natriuretic peptide (BNP) and N-terminal B-type natriuretic peptide (NT proBNP) in diagnosing HF due to left ventricular systolic dysfunction	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GPs n=297, mean age= (patients with LVSD) 73.5y; (patients with no LVSD) 74y %males=37 HF Prevalence=38%	40	92	38	1.48	0.21	0.79
Jeyaseelan,[6] 2007 United Kingdom	Cross-sectional (INDEPENDENT STUDY); Ethnicity: NR Comorbidities: HBP (n= 218), Previous Revascularization (n=35), Prior AMI/Angina (n=176), AF(n=42), Myocardial Infarction (n=89), Valvular Disease (n=209), LVSD (n=37), Clinical HF (n=57), LV Hypertrophy (n=44) Reference Standards:1 Cardiologist, 1 Physician, 1 Cardiologist fellow	Diagnostic adequacy of ECG and BNP as screening for LVSD and HF	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GP (all) n=458 mean age= 72.6y %males=40.2 HF Prev=8%	>100	NR	NR	NA	NA	NR
				LVSD n=458 mean age= 72.6y %males=40.2 HF Prev=8.1%	>100	86	74	3.31	0.19	NR
				Clinical HF (LVSD + other) n=458 mean age= 72.6y %males=40.2 HF Prev=13%	>100	82	76	3.42	0.24	NR
				Left ventricular hypertrophy n=458 mean age= 72.6y %males=40.2 HF Prev=10%	>100	59	73	2.19	0.56	NR

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Jeyaseelan,[6] 2007 (cont'd)				Valvular disease n=458 mean age= 72.6y %males=40.2 HF Prev=46%	>100	48	84	3.00	0.62	NR
Kelder,[7] 2011 Netherlands	Cross-sectional (UHFO-IA) Ethnicity: NR Comorbidities: HBP (n=88), AF(n=8), COPD (n=47), Diabetes (n=29), Stroke Or TIA (n=15), MI/PCI/CABG (n=9) Reference Standard: 1 Cardiologist, 1 Pulmonologist, I GP	Data on the comparative performance of 3 popular automated assays in patients suspected of new slow onset HF	BNP (Abbott AxSYM® B-Type Natriuretic Peptide Microparticle Enzyme Immunoassay (MEIA), ADIVA -Centaur® B - Type Natriuretic Peptide Assay)	Suspected HF referred by GPs n=172 mean age=70.2y (11.3) %males=34.3 HF Prev=29.7%	NR	NR	NR	NA	NA	NR
				Intermediate risk of HF n=111 mean age=74.4y (8.3) %males=36 HF Prev=34.2%	NR	NR	NR	NA	NA	0.85
Macabasco-O'Connell,[8] 2010 United States	Cross-sectional (INDEPENDENT STUDY) Ethnicity: Caucasian (n=9), African-American (n=4), Hispanic (n=34), Asian= (n=4), Other (n=2) Comorbidities: Dyslipidemia (n=12), HBP (n=39), Diabetes (n=27), Obesity (n=48), Metabolic syndrome (n=25); Reference Standard: ECHO	to describe BNP levels in asymptomatic low-income, uninsured individuals with multiple CRFs and determine the correlation between BNP levels and echocardiography for identifying ALVD)	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Low-Income, uninsured Patients. age ≥30 years and a history of three or more CRFs with no prior history of HF or LVSD n=53 mean age= 55y (10) %males=36 HF Prev=57%	50	88	67	2.67	0.18	0.82
Mak,[9] 2008 United Kingdom	Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=174), AF(n=71), COPD (n=44), Diabetes (n=41),IHD (n=55) Reference standards: 1 Cardiologist, Framingham	To determine the diagnostic value of BNP in HF referrals by GPs	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GPs n=327 mean age= 75y(10) %males=49 HF Prev=39%	100	84	23	1.09	0.70	NR

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Murtagh,[10] 2012 Finland	Cross-Sectional Design (STOP-HF); Ethnicity: NR; Comorbidities: dyslibide (n=563), hypertension (n=539), CAD (n=159), vascular disease/claudication/perpheral arterial anloplastry (n=21), diabetes melitus (n=121); Reference Standard: NR	Using the STOP-HF population (ClinicalTrials.gov identifier: NCT00921960), we assessed the significance of ALVDD in explaining the false-positive burden when using brain natriuretic peptide (BNP) to screen for ALVSD. Secondly, we determined the effectiveness of BNP as a screen in defining PCVD. Both assessments were made with or without the addition of electrocardiogram (ECG) to the screening strategy, as it is well described that this investigation can be an effective rule-out for ALVSD.	BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	patients over 40 with at least one risk factor for venticular dysfuncton (n= 814, age= 67±10y, %males= 48); HF prevalance= 4.05%	>20	88	46	1.63	0.26	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>50	70	77	3.04	0.39	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>100	45	90	4.50	0.61	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>50	70	77	3.04	0.39	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>100	45	90	4.50	0.61	NR

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 Korea	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259),IHD (n=664), Valvular Disease (n=22), Hypothyroidism (n=155), Cardiomyopathy (n=90) Reference standards: 1 Cardiologist	Detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	BNP (ADIVA - Centaur® B -Type Natriuretic Peptide Assay)	Dyspnea or chest discomfort (0verall) n=1032 mean age= 62y(13) %males=53.8 HF Prev=NR%	NR	NR	NR	NA	NA	NR
				Men, LVSD n=555 mean age=NR %males=100 HF Prev=9.5%	111	81	79	3.84	0.24	0.892
				Men, advanced DD n=555, mean age= NR %males=100 HF Prev=7.2%	99	80	80	4.08	0.25	0.89
				Women, LVSD n=477, mean age= NR, %males=100); HF Prev=9.8%	209	85	85	5.67	0.18	0.929
				Women, advanced DD n=477 mean age=NR %males=100 HF Prev=6.9%	166	85	85	5.51	0.18	0.907
				Age ≥ 65, LVSD n=NR mean age=NR %males= NR HF Prev=NR%	250	84	84	5.15	0.19	0.903
				Age ≥ 65, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	236	84	84	5.28	0.19	0.9

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259),IHD (n=664), Valvular Disease (n=22), Hypothyroidism (n=155), Cardiomyopathy (n=90) Reference standards: 1 Cardiologist	(repeated data) Detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) BNP (ADIVA - Centaur® B -Type Natriuretic Peptide Assay)	Age < 65, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	82	84	84	5.32	0.19	0.916
				Age < 65, advanced DD n=NR mean age= NR, %males= NR HF Prev=NR%	70	83	83	4.99	0.20	0.912
				BMI ≥ 25, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	151	85	85	5.67	0.18	0.933
				BMI ≥ 25, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	82	80	80	4.02	0.25	0.841
				BMI < 25, LVSD n=NR, mean age= NR, %males= NR); HF Prev=NR%	154	81	81	4.35	0.23	0.897
				BMI<25, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	140	83	83	4.91	0.20	0.916
				Hb ≥ 12, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	110	82	82	4.49	0.22	0.909

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259),IHD (n=664), Valvular Disease (n=22), Hypothyroidism (n=155), Cardiomyopathy (n=90) Reference standards: 1 Cardiologist	(repeated data) Detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) BNP (ADIVA - Centaur® B -Type Natriuretic Peptide Assay)	Hb ≥ 12, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	80	81	81	4.24	0.24	0.901
				Hb < 12, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	345	80	81	4.15	0.25	0.882
				Hb < 12, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	338	81	79	3.87	0.24	0.872
				eGFR ≥ 60, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	89	82	82	4.62	0.22	0.915
				eGFR ≥ 60, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	70	83	82	4.50	0.20	0.894
				eGFR < 60, LVSD n=NR mean age= NR, %males= NR HF Prev=NR%	264	78	78	3.55	0.28	0.866
				eGFR < 60, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	247	78	78	3.60	0.28	0.876

Table I-1. Diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (cont'd)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Zaphiriou,[12] 2005 United Kingdom	Cross-sectional (INDEPENDENT STUDY); Ethnicity: NR Comorbidities: Dyslipidemia (n=67), HBP (n=168), Stroke (n=35), COPD (n=58), Diabetes (n=58), MI(n=42), PVD (n=20), Angina (n=80), CABG(n=18) Percutaneous Coronary Intervention (n=7) Reference standards: 1 Cardiologist	Sensitivity, specificity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios for BNP, NTproBNP and the ECG for the diagnosis of HF. Area under the receiver operating characteristics (ROC) curves for the two natriuretic peptides	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GPs (all) n=306, mean age= 74y (52-87)* %males=42 HF Prev=34%	100	79	72	2.82	0.29	0.84
					65	87	57	2.02	0.23	NR
					30	95	35	1.46	0.14	NR

Abbreviations: AF = Atrial Fibrillation; AMI = Acute myocardial infarction; AUC = Area Under the Curve; AVLD = Asymptomatic Left Ventricular Dysfunction; BMI = Body Mass Index; BNP = B-Type Natriuretic Peptide; CAD = Coronary Artery Disease; CABG = Coronary Artery Bypass Graft; CHF = Congestive Heart Failure; COPD = Chronic obstructive pulmonary disease; CRF = Chronic renal failure; DD = Diastolic dysfunction; ECHO = Echocardiogram; ECG = Electrocardiogram; eGFR = Estimated glomerular filtration rate; GP = General practitioner; Hb = Hemoglobin; HF = Heart Failure; IHD = Ischemic Heart Disease; kg/m2 = Kilograms per metre squared; LR- = Negative Likelihood Ratio; LR+ = Positive Likelihood Ratio; LV = Left ventricle; LVSD = Left ventricular systolic dysfunction ; LVDD = Left ventricular diastolic dysfunction ; MI = Myocardial Infarction; NA = Not applicable; NPV = Negative predictive value; NR = Not reported ; NT-proBNP = N-Terminal proBNP; PANAMA = Patients with suspected heart failure in primary care; PCI = Percutaneous coronary intervention; pg/mL = Picograms per millilitre; PPV = Positive predictive value ; ROC = Receiver operating characteristic ; SD = standard deviation; SOB = shortness of breath;TIA = Transient ischemic attack; UHFO-IA = Utrecht Heart Failure Organisation – Initial Assessment; USA = United States of America; y = years

Figure I-1. Summary sensitivity (PC BNP, 100±5 pg/ml cutpoint), random effect

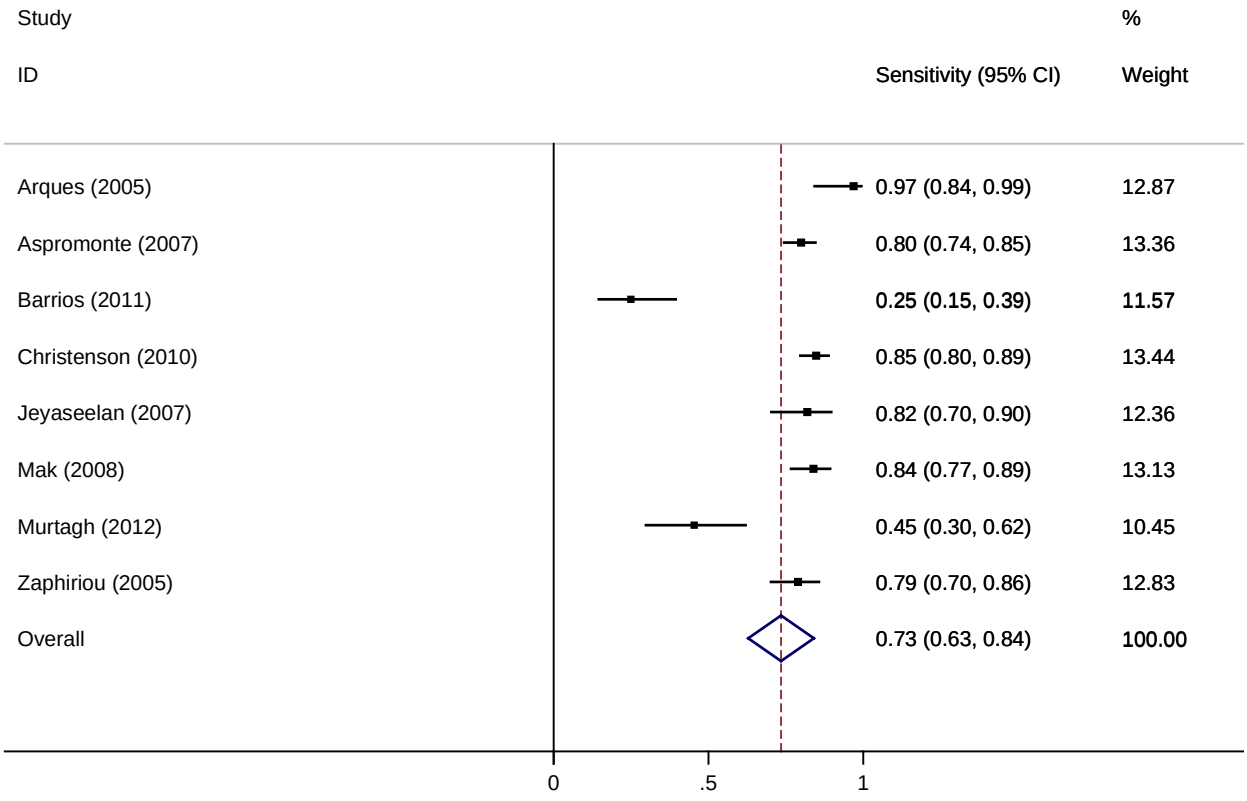

Figure I-2. Summary sensitivity (PC BNP, lowest cutpoint [pg/ml]), random effect

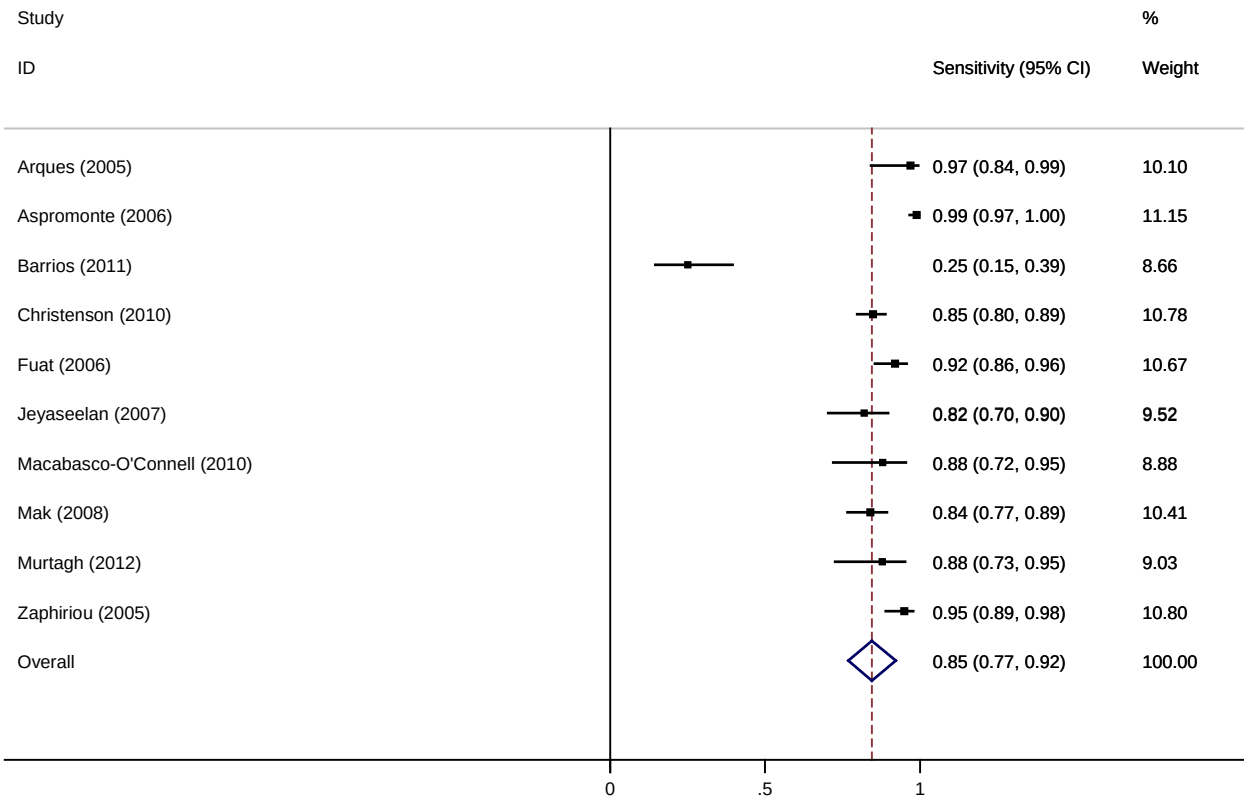

Figure I-3. Summary sensitivity (PC BNP, optimum cutpoint [pg/ml]), random effect

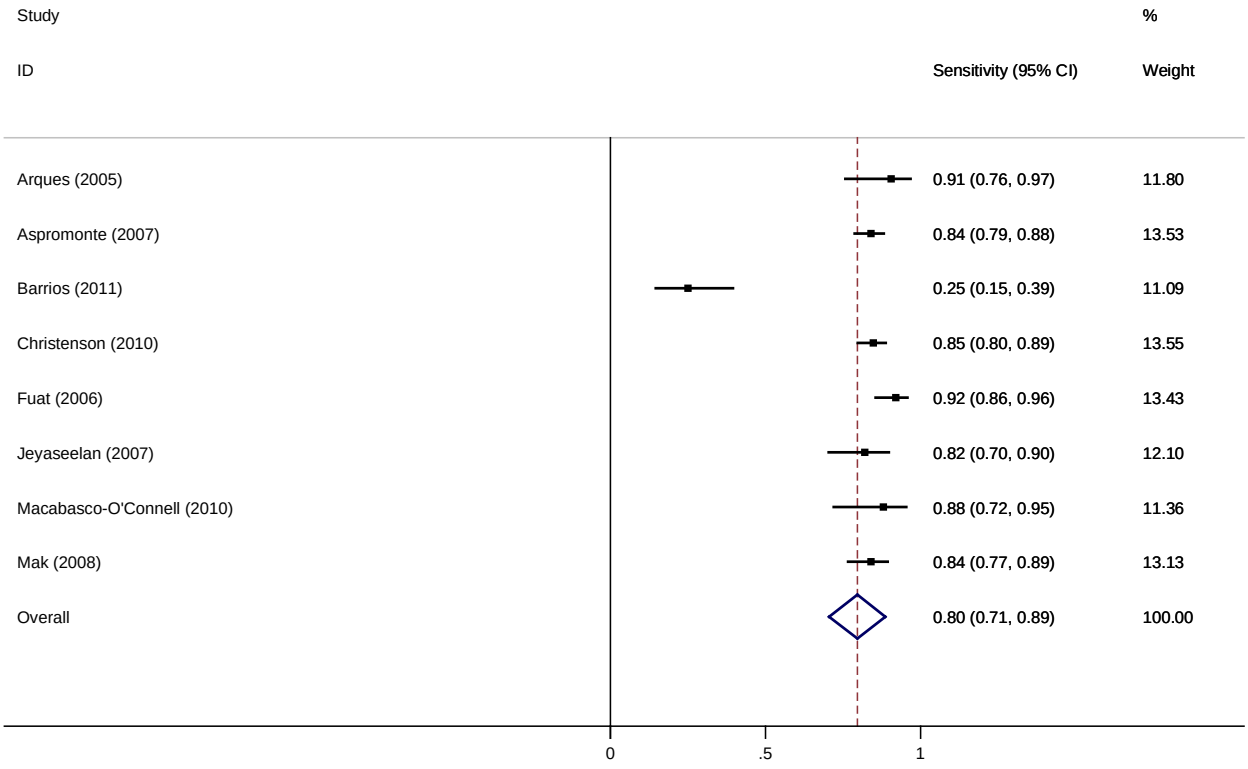

Figure I-4. Summary specificity (PC BNP, 100±5 pg/ml cutpoint), random effect

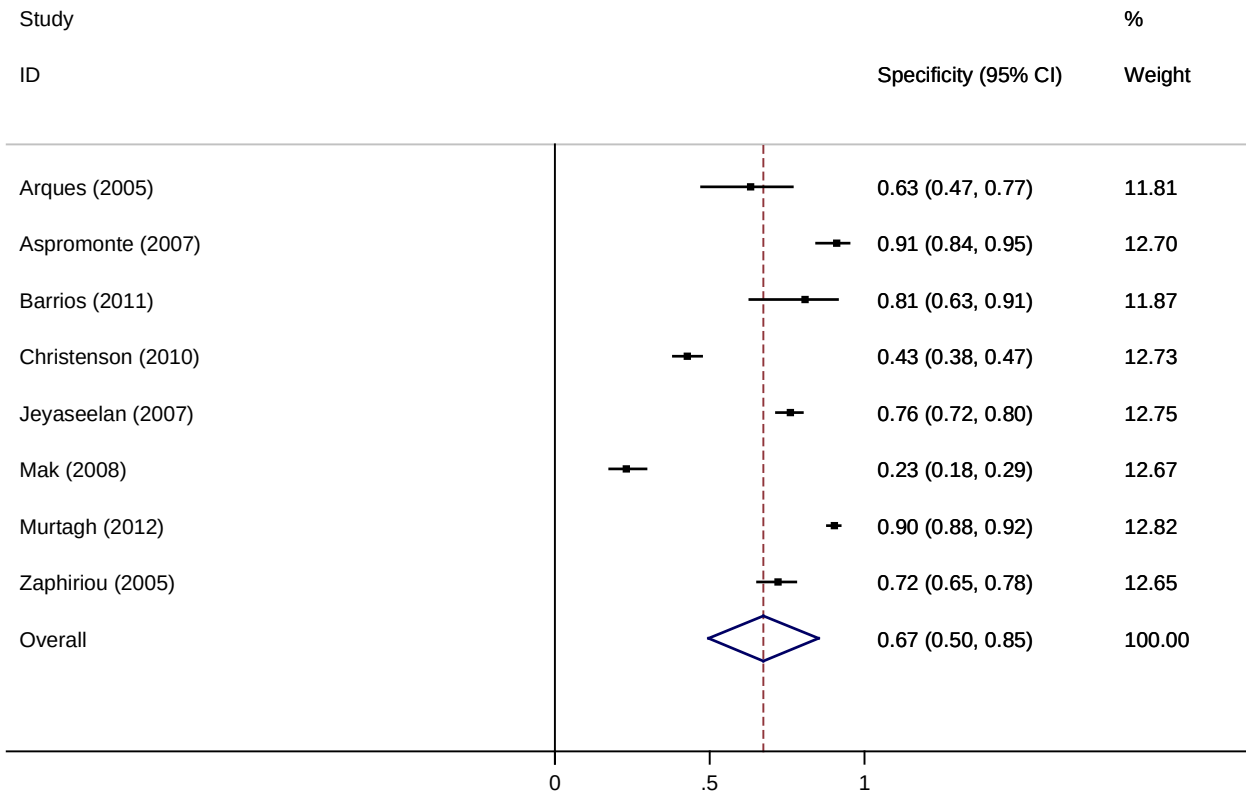

Figure I-5. Summary specificity (PC BNP, lowest cutpoint [pg/ml]), random effect

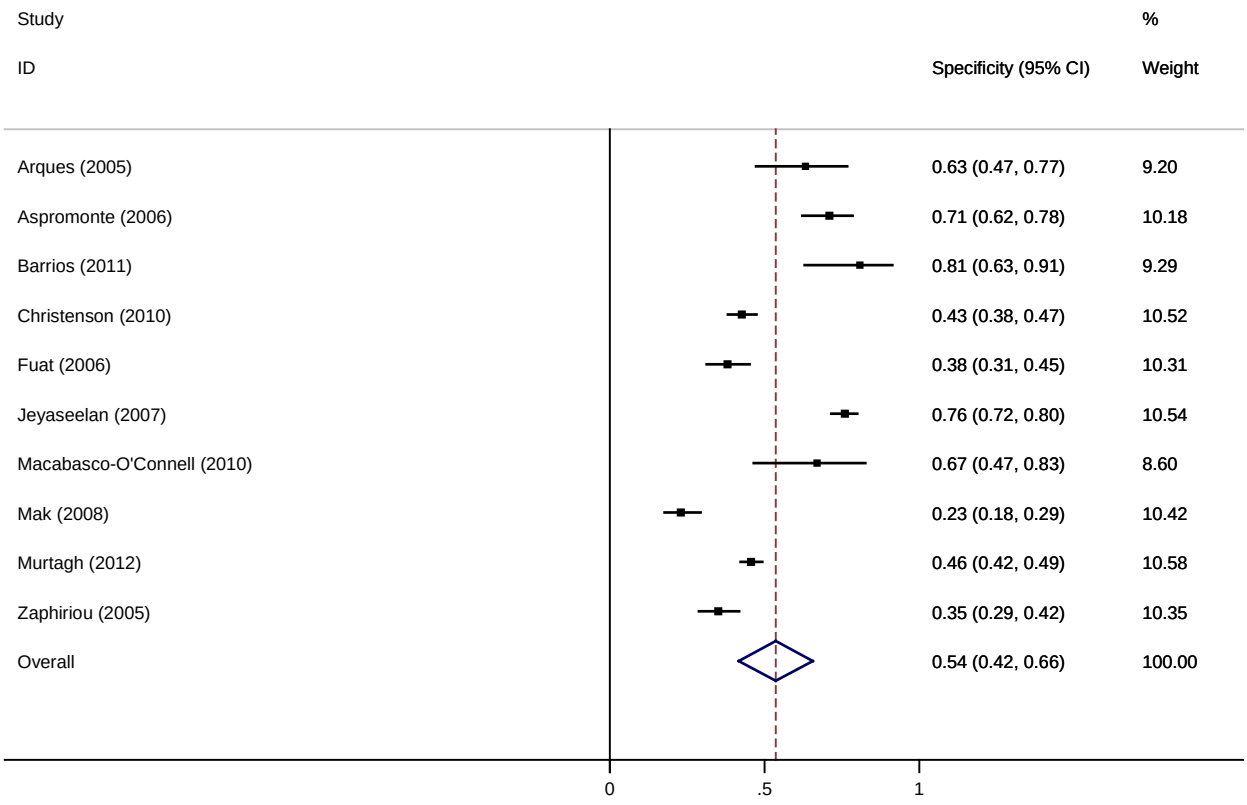

Figure I-6. Summary specificity (PC BNP, optimum cutpoint [pg/ml]), random effect

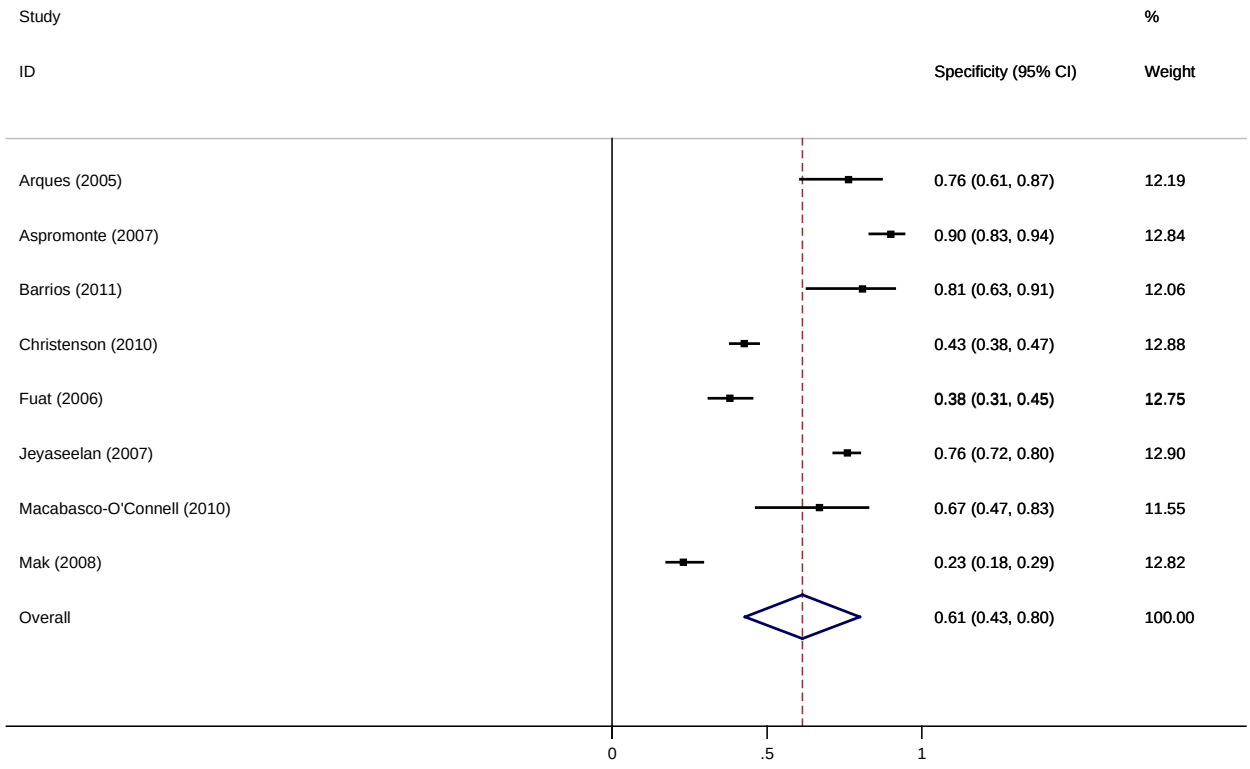

Figure I-7. Summary LR+ (PC BNP, 100±5 pg/ml cutpoint), random effect

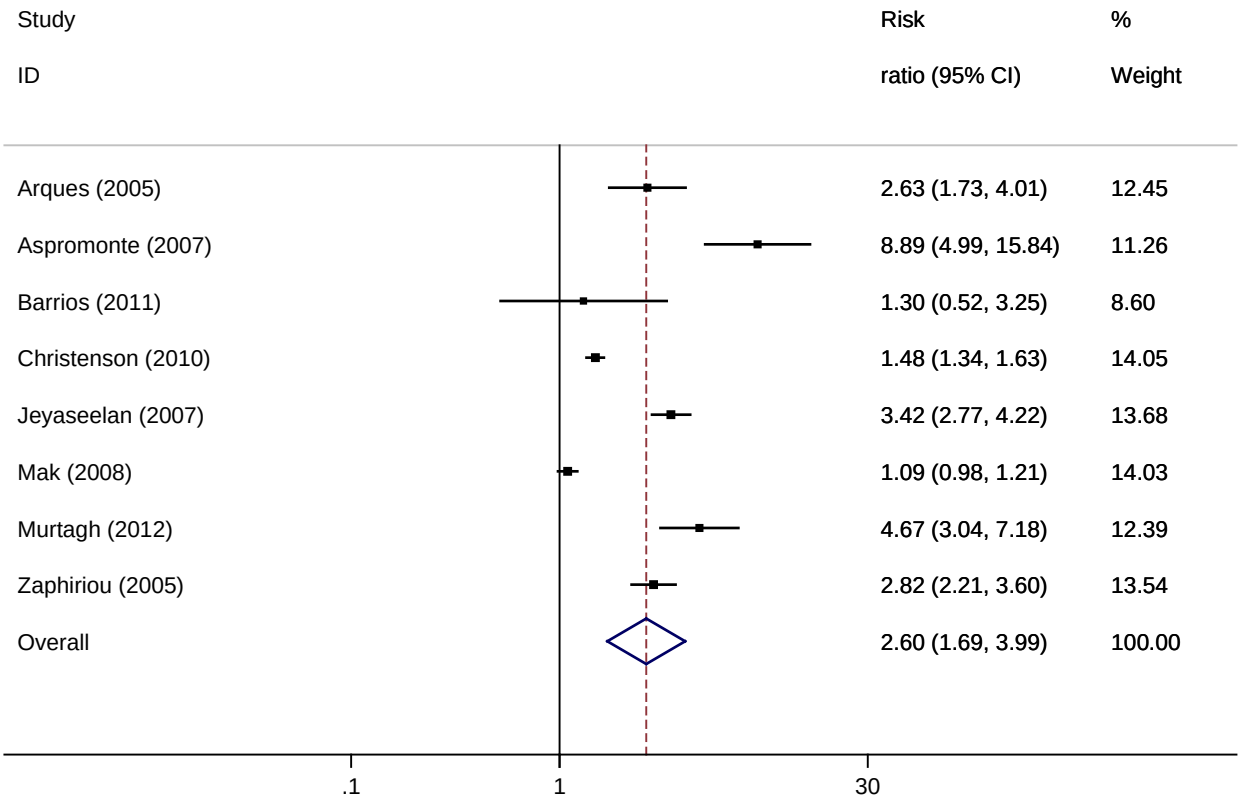

Figure I-8. Summary LR+ (PC BNP, lowest cutpoint [pg/ml]), random effect

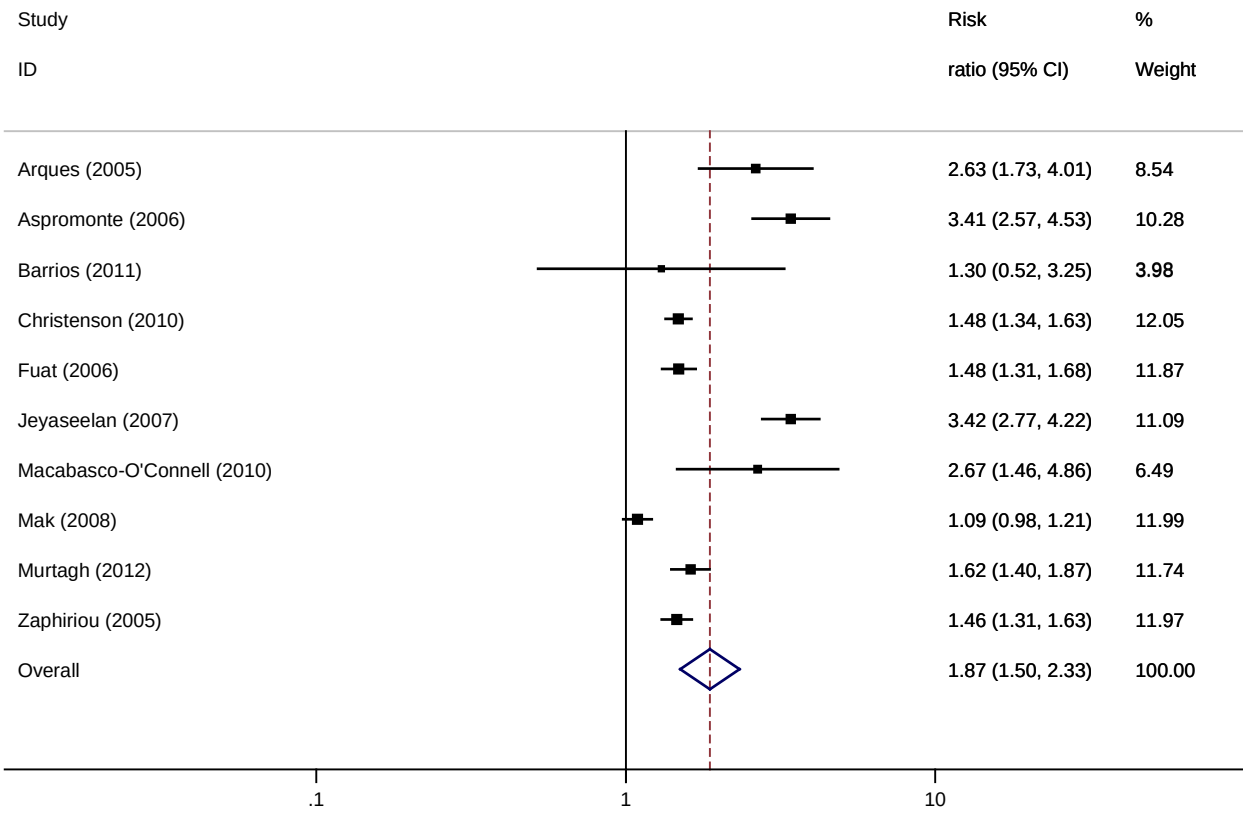

Figure I-9. Summary LR+ (PC BNP, optimum cutpoint [pg/ml]), random effect

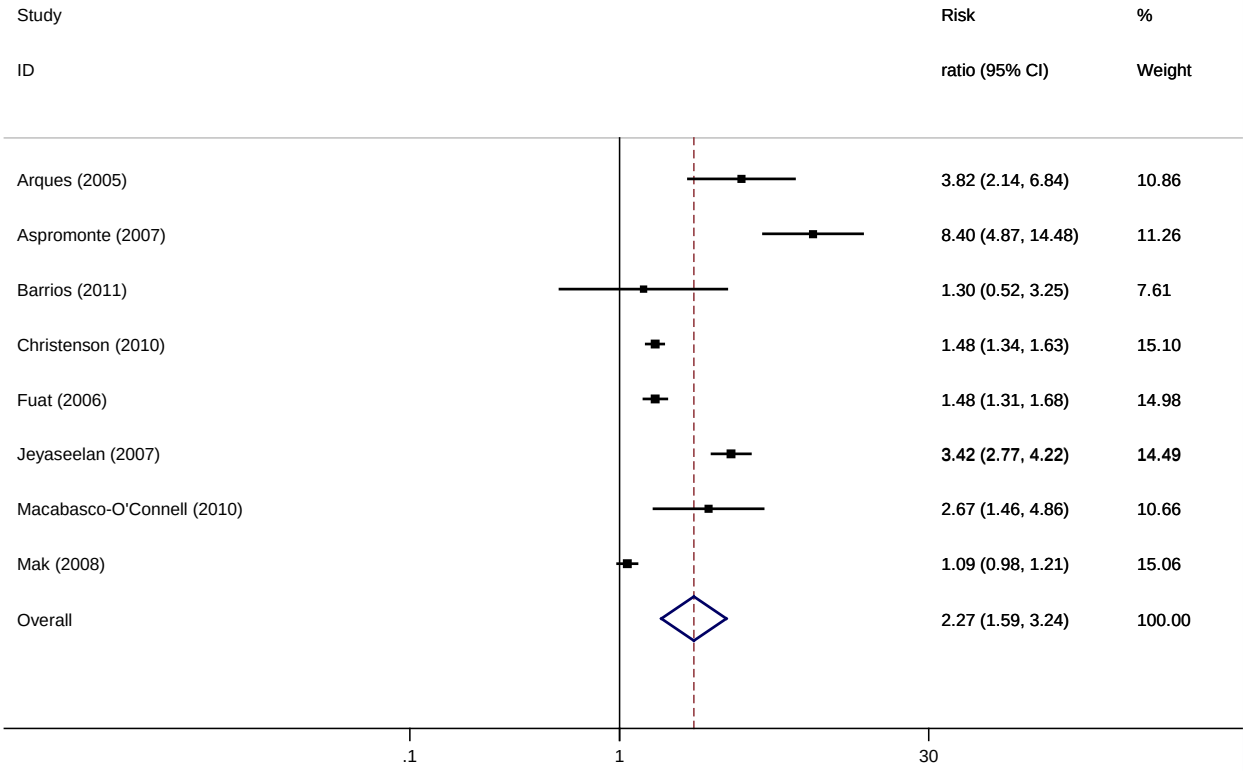

Figure I-10. Summary LR- (PC BNP, 100±5 pg/ml cutpoint), random effect

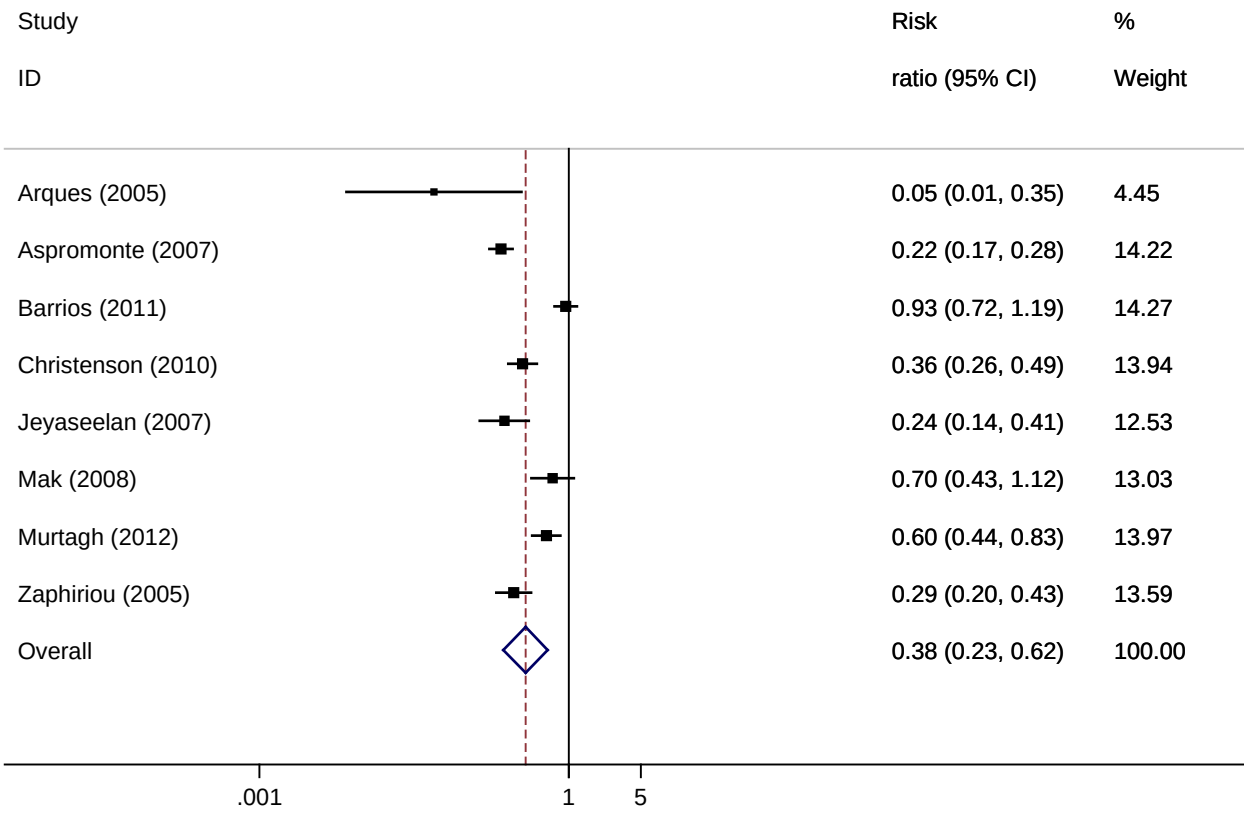

Figure I-11. Summary LR- (PC BNP, lowest cutpoint [pg/ml]), random effect

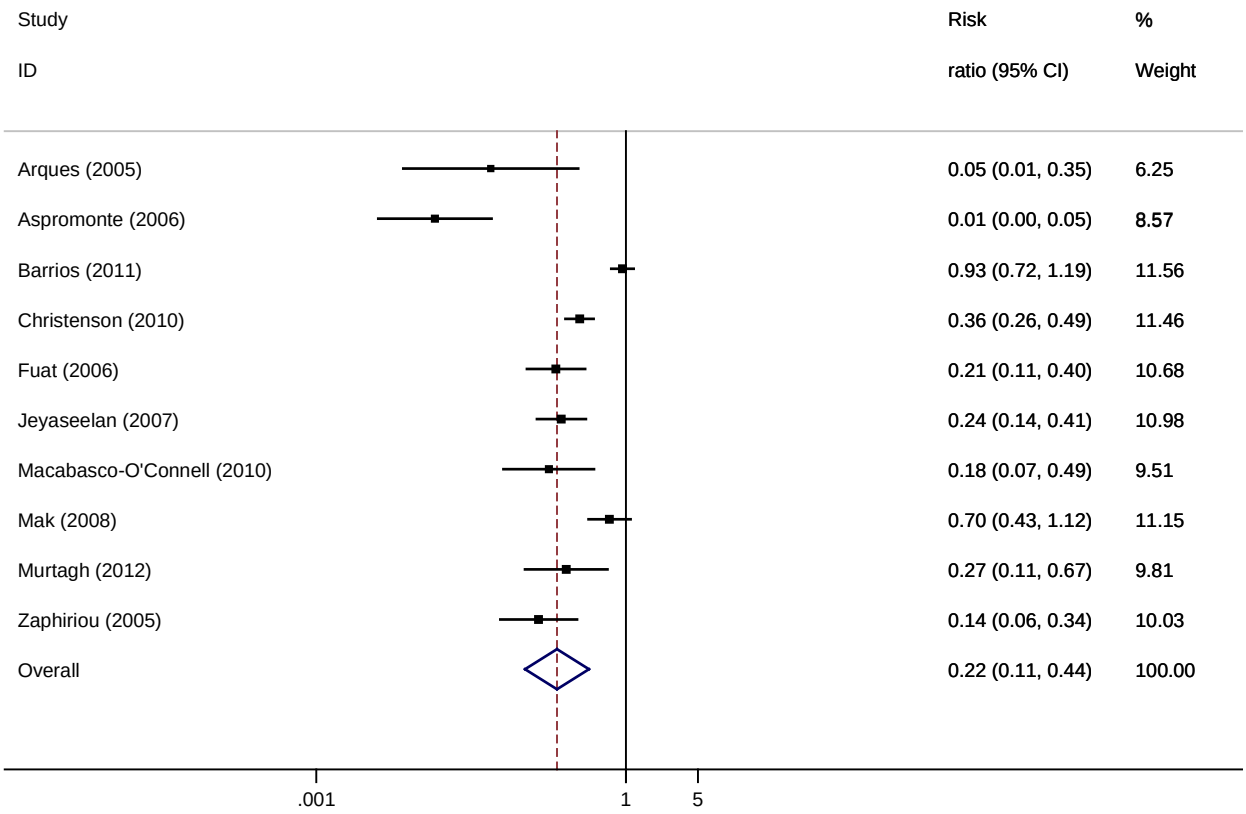

Figure I-12. Summary LR- (PC BNP, optimum cutpoint [pg/ml]), random effect

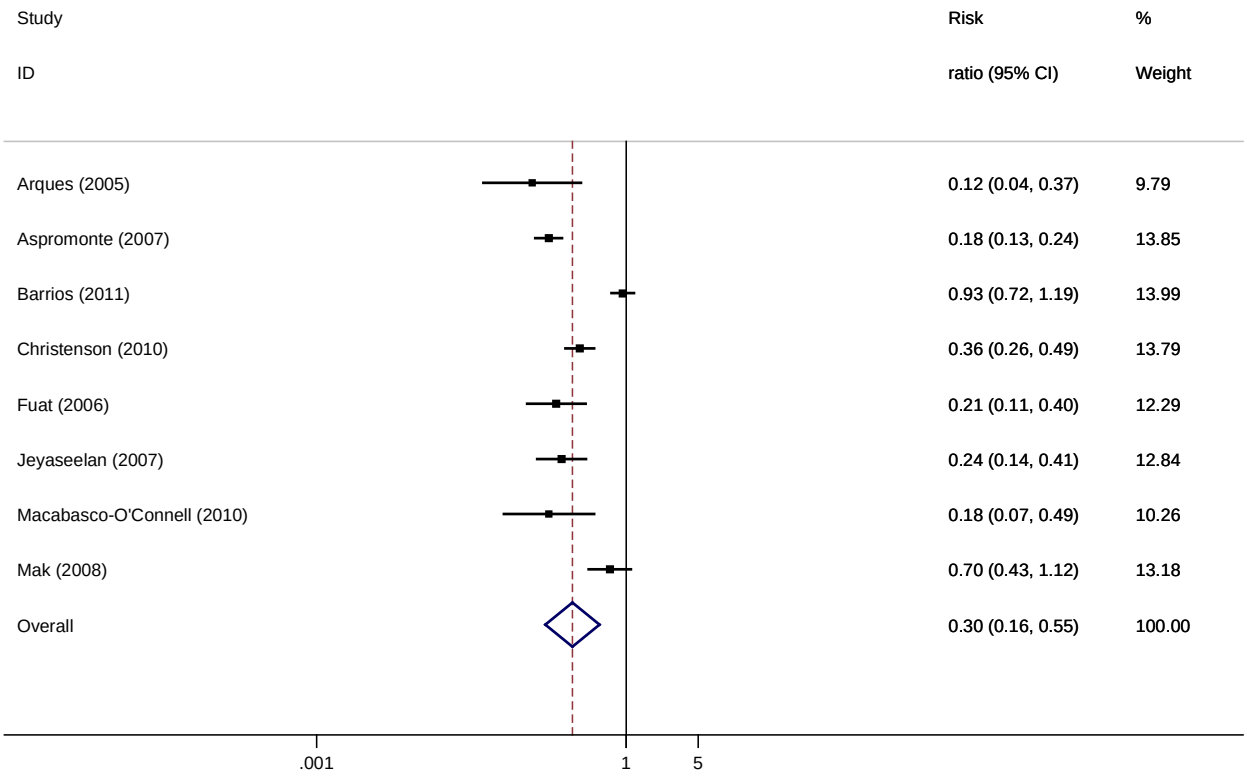

Figure I-13. Summary log DOR (PC BNP, 100±5 pg/ml cutpoint), random effect

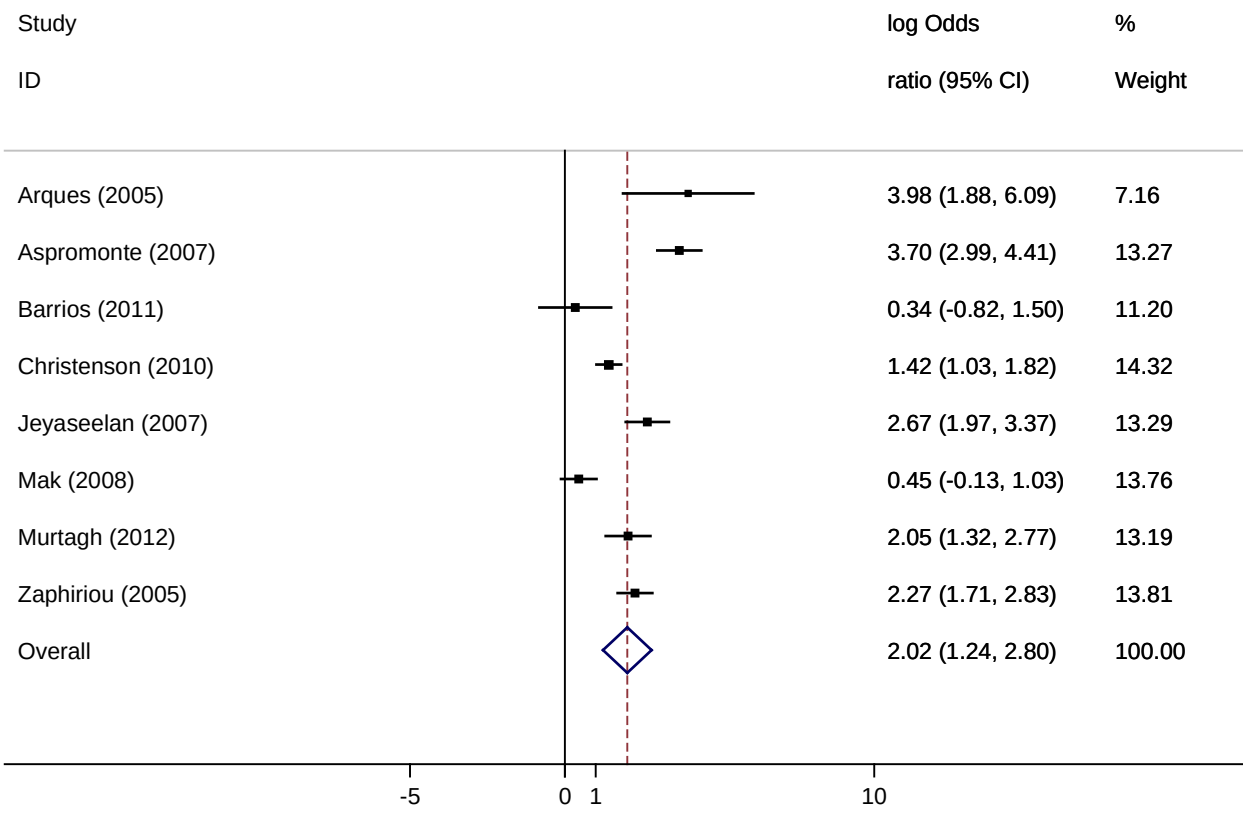

Figure I-14. Summary log DOR (PC BNP, lowest cutpoint [pg/ml]), random effect

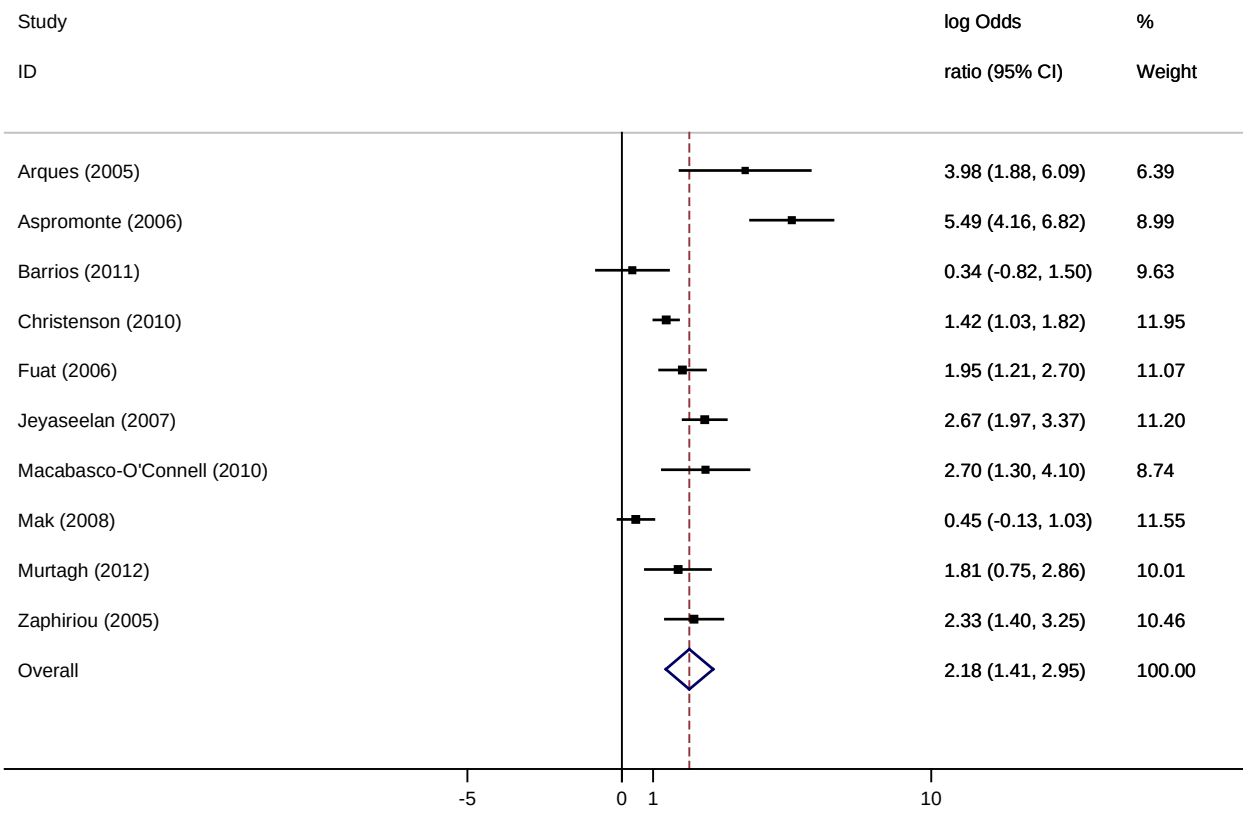

Figure I-15. Summary log DOR (PC BNP, optimum cutpoint [pg/ml]), random effect

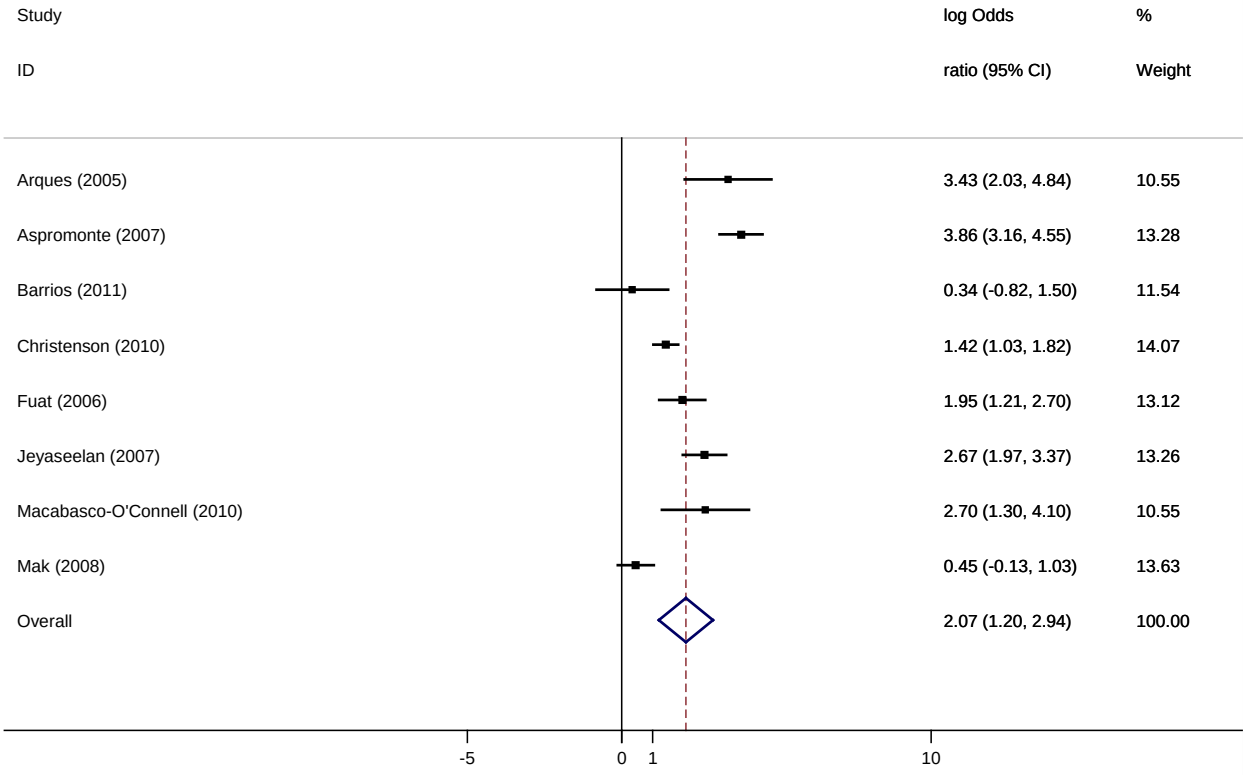

Figure I-16. Summary ROC-curve (PC BNP, 100±5 pg/ml cutpoint), random effect

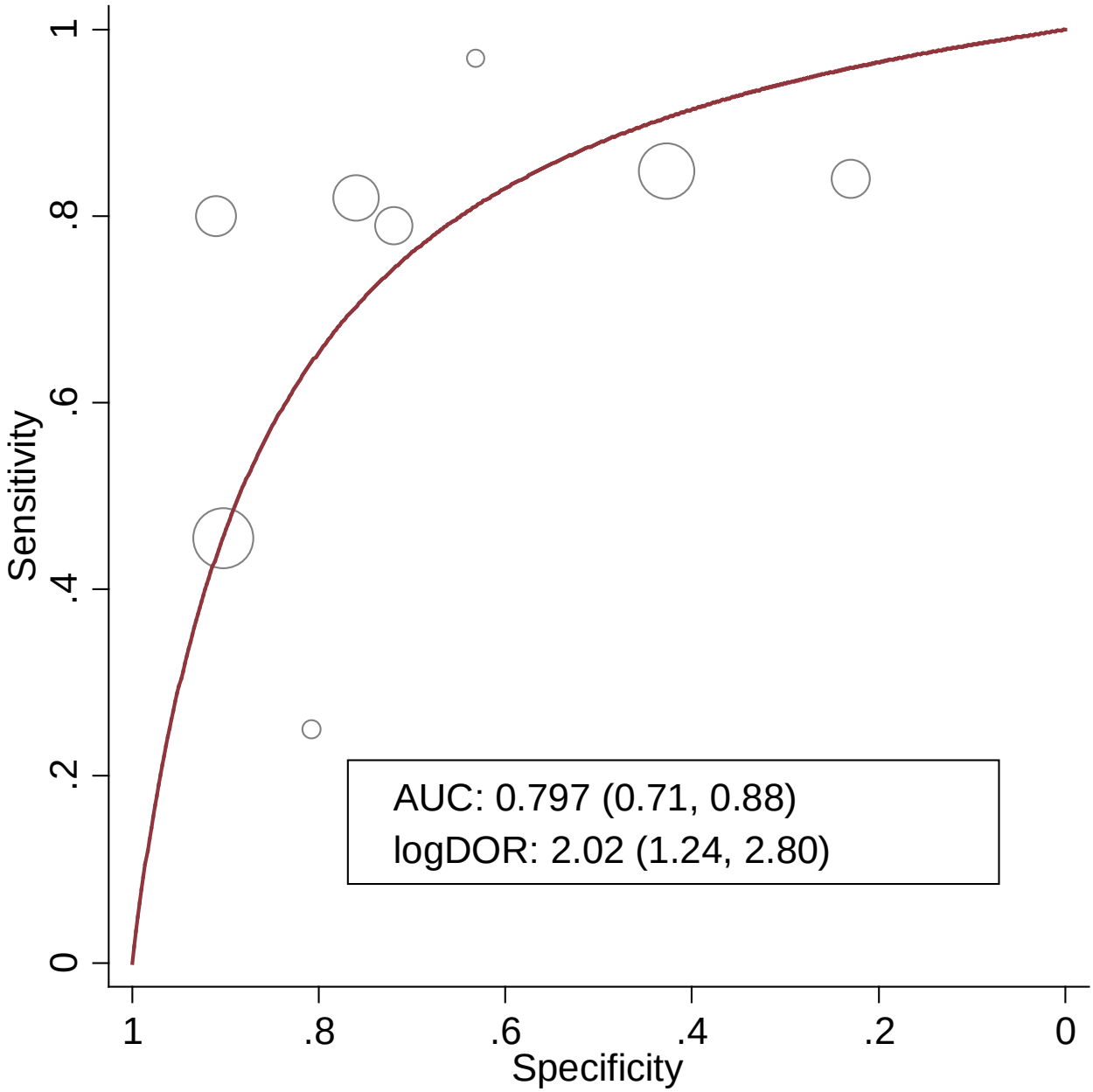

Figure I-17. Summary ROC-curve (PC BNP, lowest cutpoint [pg/ml]), random effect

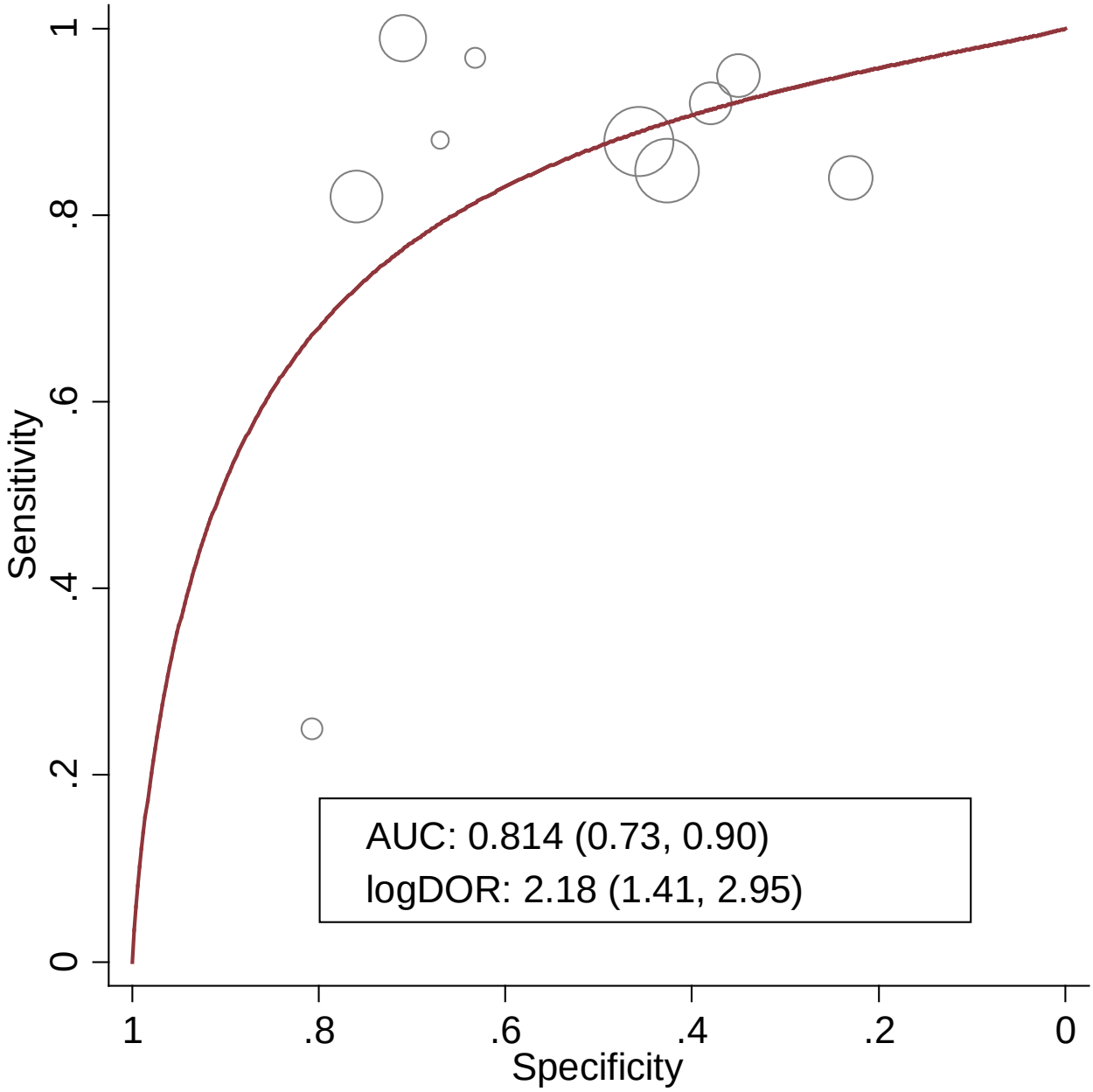

Figure I-18. Summary ROC-curve (PC BNP, optimum cutpoint [pg/ml]), random effect

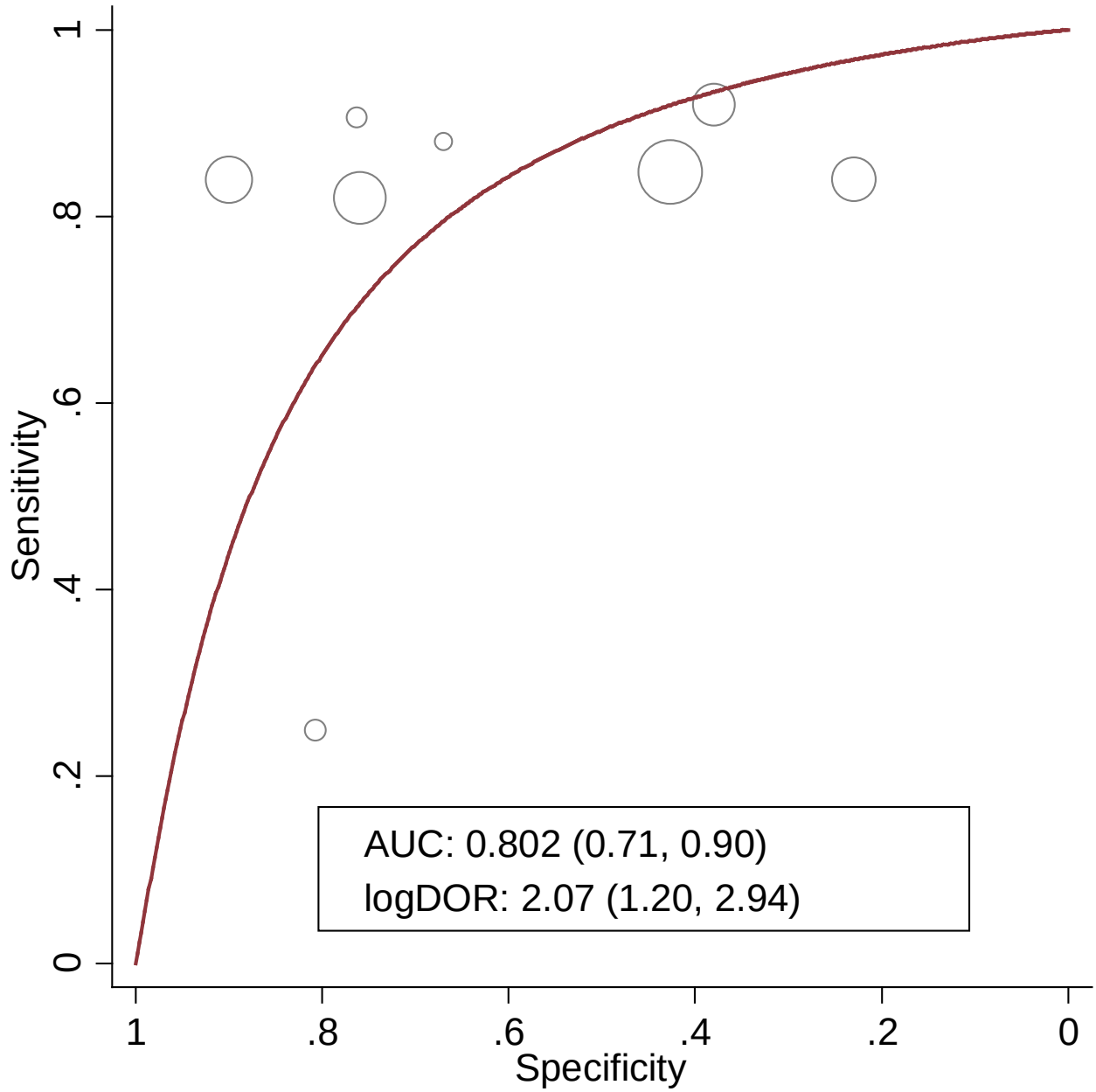
Sensitivity
0
.2
.4
.6
.8
1
Specificity
1
.8
.6
.4
.2
0
AUC: 0.802 (0.71, 0.90)
logDOR: 2.07 (1.20, 2.94)

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Christenson,[4] 2010 United States	Cross-Sectional (Independent Study) Ethnicity: African-American (n=246) Comorbidities: HBP (n=209), CAD (n=227), AF (n=147), Diabetes (n=245), Prior HF (n=236) Reference Standard: 1 Cardiologist	Adjudicated acute HF, all-cause mortality (evaluated the accuracy of NTproBNP and BNP across a range of BMIs for diagnosis of decompensated HF in a community-based dyspneic patient population; also investigated whether the prognostic accuracies of NT-proBNP and BNP concentrations differed based on BMI for predicting 1-year all-cause mortality)	NT-proBNP (ELECSYS - proBNP Immunoassay)	Dyspnea (decompensated HF, overall) n=675 mean age= NR %males= NR HF Prev=NR%; Age specific cutoffs, 450 pg/ml for age <50yrs, 900 pg/ml for 50-75yrs and 1800 pg/ml for >75yrs	Age specific	NR	NR	NA	NA	0.72
				Dyspnea (decompensated HF, Normal Weight, BMI <25 kg/m n=211 mean age= 69.8y (15.5) %males=5 HF Prev=36%; Age specific cutoffs, 450 pg/ml for age <50yrs, 900 pg/ml for 50-75yrs and 1800 pg/ml for >75yrs	Age specific	88	50	1.76	0.24	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Christenson,[4] 2010 United States (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: African-American (n=246) Comorbidities: HBP (n=209), CAD (n=227), AF (n=147), Diabetes (n=245), Prior HF (n=236) Reference Standard: 1 Cardiologist	(repeated data) Adjudicated acute HF, all-cause mortality (evaluated the accuracy of NTproBNP and BNP across a range of BMIs for diagnosis of decompensated HF in a community-based dyspneic patient population; also investigated whether the prognostic accuracies of NT-proBNP and BNP concentrations differed based on BMI for predicting 1-year all-cause mortality)	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	Dyspnea (decompensated HF, Over Weight, BMI 25-30 kg/m n=193 mean age= 66.6y (13.8) %males=58 HF Prev=37%; Age specific cutoffs, 450 pg/ml for age <50yrs, 900 pg/ml for 50-75yrs and 1800 pg/ml for >75yrs	Age specific	68	51	1.39	0.63	NR
				Dyspnea (decompensated HF, Obese, BMI >30 kg/m n=280 mean age= 62.5y (14.6) %males=38 HF Prev=32%; Age specific cut offs, 450pg/ml for age <50yrs, 900pg/ml for 50-75yrs and 1,800pg/ml for >75yrs	Age specific	69	64	1.92	0.48	NR
Fuat,[5] 2006 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=102), AF(n=56), COPD (n=69), Diabetes (n=27), Historical Mi (n=39), Ischemic (n=87) Reference Standard: Gps,15% Of Echo Verified By Cardiologists	To test and compare the diagnostic accuracy and utility of B-type natriuretic peptide (BNP) and N-terminal B-type natriuretic peptide (NT proBNP) in diagnosing HF due to left ventricular systolic dysfunction	NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected HF referred by GPs n=297 mean age= (patients with LVSD) 73.5y; (patients with no LVSD) 74y, %males=37 HF Prev=38%	150	94	40	1.57	0.15	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Goode,[13] 2007 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=283), Diabetes (n=82),IHD (n=140), Ankle Oedema Or Worse (n=31), Previous MI (n=144), Angina (n=65), Reference Standard: 1 Cardiologist	LVSD (to assess the univariate and multivariable utility of NT-proBNP, QRS duration, symptoms and evidence of myocardial infarction (MI) to detect LVSD)	NT-proBNP (ELECSYS - proBNP Immunoassay)	HF (LVSD) n=427 mean age= 70y (8) %males=57 HF Prev=8%	150	84	45	1.52	0.35	NR
				Using upper 97.5th centile of normal population after Galasko et al; men <60yrs (100pg/ml);women <60yrs (164pg/ml); men ≥60yrs (172pg/ml); Women ≥60yrs (255pg/ml)	Age/Sex specific	84	53	1.79	0.29	NR
					NR	NR	NR	NA	NA	0.72
Goode,[14] 2008 United Kingdom	Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=52), AF(n=14), COPD (n=9), Diabetes (n=12), Historical MI (n=17), IHD (n=31), Angina (n=9), Anemia (n=17), GFR<30 Ml/Min/1.73 ^2 (n=3) Reference Standard: 1 Cardiologist	To assess the diagnostic utility of NT-proBNP and QRS width (independently and in combination) as the initial investigation for patients in whom the primary-care physician suspected HF	NT-proBNP (ELECSYS - proBNP Immunoassay)	HF (Overall) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=19%	NR	NR	NR	NA	NA	NR
				HF (Major LVSD) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=19%; Prevalence of HF and threshold for NT-proBNP based on Original Echo Scoring	<178	NR	47	NA	NA	0.88

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Goode,[14] 2008 United Kingdom (cont'd)	(repeated data) Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=52), AF(n=14), COPD (n=9), Diabetes (n=12), Historical MI (n=17), IHD (n=31), Angina (n=9), Anemia (n=17), GFR<30 Ml/Min/1.73 ^2 (n=3) Reference Standard: 1 Cardiologist	(repeated data) To assess the diagnostic utility of NT-proBNP and QRS width (independently and in combination) as the initial investigation for patients in whom the primary-care physician suspected HF	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	HF (Major LVSD) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=16%; Prevalence of HF and threshold for NT-proBNP changed due to revised Echo scoring	<464	NR	72	NA	NA	0.91
				HF (Any LVSD) n=94, mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=32%; Prevalence of HF and threshold for NT-proBNP based on Original Echo Scoring	<25	NR	3	NA	NA	0.82
				HF (Any LVSD) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=30%; Prevalence of HF and threshold for NT-proBNP changed due to revised Echo scoring	<76	NR	24	NA	NA	0.79

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Goode,[14] 2008 United Kingdom (cont'd)	(repeated data) Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=52), AF(n=14), COPD (n=9), Diabetes (n=12), Historical MI (n=17), IHD (n=31), Angina (n=9), Anemia (n=17), GFR<30 Ml/Min/1.73 ^2 (n=3) Reference Standard: 1 Cardiologist	(repeated data) To assess the diagnostic utility of NT-proBNP and QRS width (independently and in combination) as the initial investigation for patients in whom the primary-care physician suspected HF	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	HF (Major Structural heart disease) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=36%; Prevalence of HF and threshold for NT-proBNP based on Original Echo Scoring	<93	NR	35	NA	NA	0.91
				HF (Major Structural heart disease) n=94, mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=35%; Prevalence of HF changed due to revised Echo scoring	<93	NR	35	NA	NA	0.91
Gustafsson,[15] 2003 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), AF(n=15), COPD (n=25), Diabetes (n=7), Ischemic (n=47) Reference Standard: NR	Diagnosis of LVSD	NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected HF (All) n=367, mean age= 68.8y* (39.0-84.0) %males=0 HF Prev=9%	NR	NR	NR	NA	NA	NR
				Suspected HF (LVEF > 40%) n=334 mean age= 68.0y* (38.0-84.5) %males=43 HF Prev=NR%	NR	NR	NR	NA	NA	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Gustafsson,[15] 2003 Denmark (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), AF(n=15), COPD (n=25), Diabetes (n=7), Ischemic (n=47) Reference Standard: NR	(repeated data) Diagnosis of LVSD	(repeated data) NT-proBNP (ELECSYS-proBNP Immunoassay)	Suspected HF (LVEF ≤ 40%) n=33 mean age= 70.3y* (38.4-84.0) %males=76 HF Prev=NR%	125	97	46	1.80	0.07	NR
				Suspected HF (LVEF ≤ 40%) n=33 mean age= 70.3y* (38.4-84.0) %males=76 HF Prev=NR%; Age specific cutoffs, 125 pg/ml for age <75yrs or 450 pg/ml for age ≥ 75yrs	Age specific	91	60	2.28	0.15	NR
				Suspected HF (LVEF ≤ 40%) n=33 mean age= 70.3y* (38.4-84.0) %males=76 HF Prev=NR%; Sex specific cut offs, 144pg/ml for Females and 93pg/ml for males	Sex specific	91	60	2.28	0.15	NR
				Suspected HF (LVEF ≤ 30%) n=14 mean age= 67.0y* (51.0-84.0) %males=86 HF Prev=NR%	125	100	56	2.27	0.00	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Gustafsson,[15] 2003 Denmark (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), AF(n=15), COPD (n=25), Diabetes (n=7), Ischemic (n=47) Reference Standard: NR	(repeated data) Diagnosis of LVSD	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected HF (LVEF ≤ 30%) n=14 mean age= 67.0y* (51.0-84.0) %males=86 HF Prev=NR%; Age specific cut offs, 125pg/ml for age <75yrs or 450pg/ml for age ≥ 75yrs	Age specific	100	58	2.38	0.00	NR
				Suspected HF (LVEF ≤ 30%) n=14 mean age= 67.0y* (51.0-84.0) %males=86 HF Prev=NR%; Sex specific cut offs, 144 pg/ml for Females and 93 pg/ml for males	Sex specific	100	44	1.79	0.00	NR
Gustaffson,[16] 2005 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), Obstructive Lung Disease (n=25), AF(n=15), Diabetes (n=7),IHD (n=47) Reference Standard: Blinded Investigator	Mortality and diagnosis	NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected CHF (LVSD) n=367 mean age= 68.8y %males=46 HF Prev=9%	125	97	46	1.80	0.07	0.87
				LVSD (Age specific) n=367 mean age= 68.8y %males=46 HF Prev=9%; Age specific cut off values , 125pg/ml for Age <75yrs and 450pg/ml for Age ≥ 75yrs	Age specific	91	60	2.28	0.15	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Gustaffson,[16] 2005 Denmark (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), Obstructive Lung Disease (n=25), AF(n=15), Diabetes (n=7),IHD (n=47) Reference Standard: Blinded Investigator	(repeated data) Mortality and diagnosis	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	Severe LVSD (LVEF ≤ 30 %) n=367 mean age= 68.8y %males=46 HF Prev=4%	125	100	56	2.27	0.00	0.93
				Severe LVSD (Age specific) n=367 mean age= 68.8y %males=46 HF Prev=4%; Age specific cut off values , 125pg/ml for Age <75yrs and 45pg/ml for Age ≥ 75yrs	Age specific	100	58	2.38	0.00	NR
Hobbs,[17] 2004 United Kingdom	Cross-Sectional (Echoes) Ethnicity: Caucasian (n=573), Other (n=98) Comorbidities: HBP (n=232), Prior Ami/Angina (n=127), Diabetes (n=68), Historical Mi (n=87) Reference Standard: NR	no specified endpoint, diagnostic study	NT-proBNP (ELECSYS - proBNP Immunoassay)	All n=591 mean age= 65.8y (10.7) %males=54 HF Prev=6%. Prevalence for HF (LVSD, n=33) reported in overall population n=59 but not for individual groups	NR	NR	NR	NR	NR	NR
				General population over 45yrs n=307 mean age= NR %males= NR HF Prev=NR%	40 pmol/L	80	73	2.96	0.27	0.76

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Hobbs,[17] 2004 United Kingdom (cont'd)	(repeated data) Cross-Sectional (Echoes) Ethnicity: Caucasian (n=573), Other (n=98) Comorbidities: HBP (n=232), Prior Ami/Angina (n=127), Diabetes (n=68), Historical Mi (n=87) Reference Standard: NR	(repeated data) no specified endpoint, diagnostic study	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	Pts with previous HF diagnosis n=103 mean age= NR %males=NR HF Prev=NR%	40 pmol/L	100	18	1.22	0.00	0.7
				Pts on diuretics n=87 mean age= NR %males= NR HF Prev=NR%	40 pmol/L	86	40	1.43	0.35	0.81
				Pts at high risk for HF n=133 mean age= NR %males= NR HF Prev=NR%	40 pmol/L	100	46	1.85	0.00	0.73
Kelder,[7] 2011 Netherlands	Cross-Sectional (Uhfo-Ia) Ethnicity: NR Comorbidities: HBP (n=88), AF(n=8), COPD (n=47), Diabetes (n=29), Stroke , TIA (n=15), MI, PCI, CABG (n=9) Reference Standard: Expert Panel (1 Cardiologist, 1 Pulmonologist, And 1 Gp	Data on the comparative performance of 3 popular automated assays in patients suspected of new slow-onset HF	NT-proBNP (ELECSYS - proBNP Immunoassay)	HF n=172 mean age= 70.2y (11.3) %males=34 HF Prev=30%	NR	NR	NR	NA	NA	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Koschack,[18] 2008 Germany	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Dyslipidemia (n=282), HBP (n=468), Cad (n=166), Diabetes (n=170), Historical Mi (n=41), Family History Heart Disease (n=231) Reference Standard: 1 Cardiologist	Diagnostic power of the NT-proBNP assessment in ruling out left ventricular systolic dysfunction and compared it to a risk score derived from a logistic regression model of easily acquired clinical information	NT-proBNP (ELECSYS - proBNP Immunoassay)	HF (LVSD) n=542 mean age= (noLVSD) 63y (62-63); (LVSD) 69y (66-73) %males=57.55 HF Prev=4%	<98.5	91	46	1.69	0.20	0.83
Lim,[19] 2007 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=78), AF(n=19), Diabetes (n=24), History HID/MI (n=32) Reference Standard: Echo (Physician)	Determine cost effectiveness assessment of patients suspected HF	NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected HF (overall) n=137 mean age= 71y (13) %males=50 HF Prev=24%	20 pmol/L	91	62	2.39	0.15	NR
				LVSD n=137, mean age= 71y (13) %males=50 HF Prev=14%	20 pmol/L	100	57	2.33	0.00	NR
				LVDD n=137, mean age= 71y (13) %males=50 HF Prev=9%	20 pmol/L	75	69	2.42	0.36	NR
				LVSD + LVDD n=137 mean age= 71y (13) %males=50 HF Prev=23%	20 pmol/L	90	60	2.25	0.17	NR
				VHD or RVD n=137 mean age= 71y (13) %males=50 HF Prev=4%	20 pmol/L	100	51	2.04	0.00	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Mikkleson,[20] 2006 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=64), Diabetes (n=16),IHD (n=44) Reference Standard: History, Physical Exam, Chest Xray, Echo	Diagnosis of LVD	NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected cardiac dyspnea (Left ventricular dysfunction (LVD) = LVSD + IDD) n=150 mean age= (LVSD) 70y* %males= (IDD) 68y* HF Prev=53%	≥87	95	76	3.96	0.07	0.95
				LVD (male) n=82 mean age= NR %males= NR HF Prev=NR%	≥85	95	71	3.28	0.07	NR
				LVD (female) n=68 mean age= NR %males= NR HF Prev=NR%	≥110	98	88	8.17	0.02	NR
				LVSD n=150 mean age= 70y* %males=54.6 HF Prev=15%	≥270	100	85	6.67	0.00	0.98
				LVSD (male) n=82 mean age= NR %males= NR HF Prev=NR%	≥270	100	85	6.67	0.00	NR
				LVSD (female) n=68 mean age= NR %males= NR HF Prev=NR%	≥595	100	96	25.00	0.00	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Nielson,[21] 2004 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: COPD (n=166) Reference Standard: Combination Of History, Physical Exam, ECG Chest X-Ray Exam, Lung Spirometry, Echocardiography And Blood Tests (Blood-Haemoglobin, Thyroid Hormones, Creatinine, Sodium, Potassium And Glucose).	Diagnosis of HF	NT-proBNP (not stated)	Patients with dyspnoea, all n=345 mean age= 65y (18-89) %males=5 HF Prev=24%	NR	NR	NR	NR	NR	NR
				male patients ≥50 years n=146 mean age= NR %males= NR HF Prev=NR%	9 pmol/L	100	60	NR	NA	NR
					11 pmol/L	96	67	NA	NA	0.93
					18 pmol/L	89	79	NA	NA	NR
					8 pmol/L	100	27	NA	NA	NR
					17 pmol/L	94	69	NA	NA	0.9
					26 pmol/L	91	84	NA	NA	NR
Olofsson,[22] 2010 Sweden	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=43), AF(n=19), Historical MI (n=22), Valvular Heart Disease (n=18), Angina (n=37) Reference Standard: 1 Cardiologist	"Main outcome measures. NPV, PPV, sensitivity, specificity, and cut off levels. To explore the negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity of natriuretic peptides, cut-off levels, and the impact of sex and age in elderly patients with systolic HF	NT-proBNP (ELECSYS - proBNP Immunoassay)	Dyspnoea (HF) n=109 mean age= (HF) 79y (6.4); (noHF) 76y (8.6), %males=32 HF Prev=44%	100 ng/L	96	18	1.17	0.22	NR
					200 ng/L	92	46	1.70	0.17	NR
					300 ng/L	81	69	2.61	0.28	NR
					400 ng/L	75	82	4.17	0.30	NR
					500 ng/L	73	87	5.62	0.31	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Park,[11] 2010 Korea	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), Ischemic (n=664), Valvular Heart Disease (n=22), Hypothyroidism (n=155), Hyperthyroidism (n=34), Cardiomyopathy (n=90) Reference Standard: 2 Cardiologists	The detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	NT-proBNP (ELECSYS - proBNP Immunoassay)	Dyspnea or chest discomfort (Overall) n=1,032 mean age= 62.0y (13.0) %males=54 HF Prev=10%	NR	NR	NR	NA	NA	NR
				Men, LVSD n=555 mean age= NR %males=100 HF Prev=10%	510	81	81	4.22	0.23	0.867
				Men, advanced DD n=555 mean age= NR %males=100 HF Prev=7%	1,678	83	81	4.41	0.22	0.879
				Women, LVSD n=477 mean age= NR %males=100 HF Prev=10%	431	87	87	6.87	0.15	0.925
				Women, advanced DD n=477 mean age= NR %males=100 HF Prev=7%	860	85	85	5.51	0.18	0.878
				Age ≥ 65, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	1,446	82	81	4.32	0.22	0.875
				Age ≥ 65,advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	1,356	84	83	4.91	0.19	0.894

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), Ischemic (n=664), Valvular Heart Disease (n=22), Hypothyroidism (n=155), Hyperthyroidism (n=34), Cardiomyopathy (n=90) Reference Standard: 2 Cardiologists	(repeated data) The detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	Age < 65, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	379	84	84	5.26	0.19	0.912
				Age < 65, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	276	83	82	4.73	0.20	0.893
				BMI ≥ 25, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	771	85	87	6.44	0.17	0.947
				BMI ≥ 25,advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	309	80	80	4.02	0.25	0.893
				BMI < 25, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	830	81	81	4.21	0.23	0.869
				BMI<25,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	682	81	81	4.29	0.23	0.885
				Hb ≥ 12, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	512	83	84	5.11	0.20	0.901

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), Ischemic (n=664), Valvular Heart Disease (n=22), Hypothyroidism (n=155), Hyperthyroidism (n=34), Cardiomyopathy (n=90) Reference Standard: 2 Cardiologists	(repeated data) The detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	Hb ≥ 12,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	389	83	84	5.03	0.20	0.906
				Hb < 12, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	2,464	83	82	4.63	0.21	0.856
				Hb < 12,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	1,912	77	77	3.27	0.30	0.82
				eGFR ≥ 60, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	418	84	84	5.41	0.18	0.915
				eGFR ≥ 60,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	276	83	82	4.65	0.20	0.889
				eGFR < 60, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	1,981	78	78	3.55	0.28	0.832
				eGFR < 60,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	1,733	78	76	3.32	0.28	0.836

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Shelton,[23] 2006 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Cerebrovascular (n=91), HBP (n=585), Diabetes (n=276), IHD (n=707) Reference Standard: Echo, MSHD Classification(No Mention Of Clinicians)	Diagnostic Accuracy	NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected HF / Dyspnea n=1321 mean age= (MSHD-AF) 74.5y; (No-MSHD with AF) 72.6y; (SR-MSHD) 69.7y; (SR-No MHSD) 69.1y, %males=58 HF Prev=60%	NR	NR	NR	NA	NA	NR
				MSHD with AF n=276 mean age=NR %males=6 HF Prev=40%	400	99	7	1.06	0.14	NR
					500	99	11	1.11	0.09	NR
					600	98	23	1.27	0.09	NR
					800	92	32	1.35	0.25	NR
					1,000	90	50	1.80	0.20	NR
					1,200	81	60	2.03	0.32	NR
					1,400	77	68	2.41	0.34	NR
					1,600	74	75	2.96	0.35	NR
					1,764	69	77	3.01	0.40	0.784
				MSHD with SR n=1,045 mean age=NR %males=57 HF Prev=57%	365	75	75	2.95	0.34	0.794
				MSHD with AF (Age > 75) n=140 mean age=NR %males=NR HF Prev=75%	757	100	3	1.03	0.00	NR
					1,764	69	61	1.75	0.51	NR
				MSHD with AF (Age ≤ 75) n=136, mean age=NR %males=NR HF Prev=72%	125	100	0	1.00	NR	NR
					1,758	70	90	7.12	0.33	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Shelton,[23] 2006 United Kingdom (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Cerebrovascular (n=91), HBP (n=585), Diabetes (n=276), IHD (n=707) Reference Standard: Echo, MSHD Classification(No Mention Of Clinicians)	(repeated data) Diagnostic Accuracy	(repeated data) NT-proBNP (ELECSYS - proBNP Immunoassay)	MSHD with SR (Age ≤ 75) n=725 mean age=NR, %males=NR HF Prev=56%	125	89	43	1.56	0.26	NR
					357	73	79	3.43	0.34	NR
				MSHD with SR (Age>75) n=320 mean age=NR %males=NR HF Prev=58%	450	75	68	2.34	0.37	NR
					652	69	79	3.23	0.39	NR
Sivakumar,[24] 2006 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: BP (n=35), AF (n=35), Diabetes (n=10), IHD (n=38) Reference Standard: 1 Clinician	Diagnosis: systolic dysfunction, diastolic dysfunction, AF, and valve HD	NT-proBNP (ELECSYS - proBNP Immunoassay)	suspected HF/valvular disease (LVSD) n=100 mean age=82.4y %males=40 HF Prev=25%	424	96	45	1.75	0.09	0.71
					1,226	68	68	2.13	0.47	NR
					1,689	60	76	2.50	0.53	NR
					6,180	44	96	11.00	0.58	NR
				Valvular disease only n=75 mean age= NR %males= NR HF Prev=29%	227	91	43	1.60	0.21	NR
					334	91	53	1.94	0.17	NR
					424	82	55	1.82	0.33	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Stahrenberg,[25] 2010 Germany	Cohort (DIAST/CHF) Ethnicity: NR Comorbidities: HBP (n=210), CAD (n=94), AF(n=58), Diabetes (n=75), Hyperlipidemia (n=122, HF Patients Only) Reference Standard: Physicians, Framingham	Investigated the clinical relevance of GDF-15 plasma levels in HFnEF. ROC curves were constructed for discrimination between controls and subjects with HFnEFESC or HFnEFNew and sensitivity, specificity, and odds ratios HFnEF were calculated.	NT-proBNP (ELECSYS - proBNP Immunoassay)	Chronic HF (HFnEFESC) n=416 mean age= (HFnEFESC Grp) 73y (66-78); (HFrEF Grp) 71y (66-75); (Controls) 56y (52-63) %males=44.7; HF Prev=34%; Discrimination of HFnEFESC (HF normal Ejection Fraction) from healthy controls, Prevalence NR in paper but calculated using info on N's	>220 ng/L	65	97	20.34	0.36	NR
				Discrimination of HFnEFESC (HF normal Ejection Fraction) from healthy controls, Prevalence NR in paper but calculated using info on N's	NR	NR	NR	NA	NA	0.88
				Specificity Fixed, Prevalence NR in paper but calculated using info on N's	120 ng/L	74	80	3.70	0.33	NR
				Sensitivity Fixed, Prevalence NR in paper but calculated using info on N's	220 ng/L	55	97	18.33	0.46	NR
				Prevalence NR in paper but calculated using info on N's	NR	NR	NR	NA	NA	0.859

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Valle,[26] 2005 Italy	Cohort Ethnicity: NR Comorbidities: HBP (n=27), AF(n=8), COPD (n=3), Diabetes (n=10), Ischemic (n=7), Renal Disease (n=2), Valve Disease (n=6) Reference Standard: Framingham	Diagnosis HF, Deaths, hospitalization for chronic HF and cases of acute HF without hospitalization.	NT-proBNP(ELECSYS -proBNP Immunoassay)	suspected HF in elderly n=101, mean age= 84(9)y, %males=20); HF HF Prev=13%	NR	NR	NR	NA	NA	NR
				LVD (LVSD + DDF) n=101 mean age= 84y (9) %males=20 HF Prev=42%; 230 is optimal to distinguish between patients with or without some kind of ventricular dysfunction	150	93	41	1.58	0.17	NR
					200	83	53	1.77	0.32	NR
					230*	80	60	2.00	0.33	0.78
					250	76	60	1.90	0.40	NR
					300	73	66	2.15	0.41	NR
					350	70	70	2.33	0.43	NR
				LVSD + restrictive diastolic pattern n=101 mean age= 84y (9) %males=20 HF Prev=NR%; 530 is optimal threshold distinguish between patients with serious systolic and /or diastolic ventricular dysfunction	350	100	65	2.86	0.00	NR
					400	95	70	3.17	0.07	NR
					500*	95	82	5.28	0.06	0.93
					550	90	84	5.63	0.12	NR
					600	85	84	5.31	0.18	NR

Table I-2. Diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (cont'd)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Zaphiriou,[12] 2005 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Dyslipidemia (n=67), HBP (n=168), Stroke (n=35), COPD (n=58), Diabetes (n=58), MI (n=42), PVD (n=20), Angina (n=80), CABG(n=18), PCI (n=7) Reference Standard: 1 Cardiologist	Sensitivity, specificity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios for BNP, NTproBNP and the ECG for the diagnosis of HF. Area under the ROC curves for the two natriuretic peptides	NT-proBNP (ELECSYS - proBNP Immunoassay)	Suspected HF referred by GPs (all) n=306 mean age= 74y* (52-87) %males=4 HF Prev=34%	≥125	98	35	1.51	0.06	0.85
					≥166	96	43	1.68	0.09	NR

Abbreviations: AF = Atrial Fibrillation; AMI = Acute myocardial infarction; AUC = Area Under the Curve; BMI = Body Mass Index; BNP = B-Type Natriuretic Peptide; CAD = Coronary Artery Disease; CAGB = Coronary Artery Bypass Graft; CHF = Congestive Heart Failure; COPD = Chronic obstructive pulmonary disease; DD = Diastolic dysfunction; DDF = Diastolic dysfunction; DIAST-CHF = Diastolic congestive heart failure; ECG = Electrocardiogram; ECHO = Echocardiogram; ECHOES = Echocardiographic Heart of England Screening; eGFR = Estimated glomerular filtration rate; GDF-15 = Growth differentiation factor 15; GFR = Glomerular filtration rate; GP = General practitioner; Hb = Hemoglobin; HBP = High Blood Pressure/Hypertension; HF = Heart Failure; HFnEF = Heart failure with normal ejection fraction; HFnEFESC = Heart failure with normal ejection fraction recommended by European Society of Cardiology; HFnEFNew = Heart failure with normal ejection fraction recommended by American Society of ; HFrEF Grp Heart failure with reduced ejection fraction group; echocardiography; IDD = Isolated diastolic dysfunction ; IHD = Ischemic Heart Disease; IQR = Interquartile range; kg/m2 = Kilograms per metre squared; LR- = Negative Likelihood Ratio; LR+ = Positive Likelihood Ratio; LVD = Left ventricular dysfunction; LVDD = Left ventricular diastolic dysfunction; LVEF = Left Ventricular Ejection Fraction; LVSD = Left ventricular systolic dysfunction ; MI = Myocardial Infarction; mL/min/1.73m2 = Millilitre per minute per 1.73 metres squared; MSHD = Major structural heart disease; NA = Not applicable; ng/L = Nanogram per litre; NPV = Negative predictive value; NR = Not reported; NT-proBNP = N-Terminal proBNP; PCI = Percutaneous coronary intervention; pg/mL = Picograms per millilitre; pmol/L = Picomol per litre; PPV = Positive predictive value ; Pts = Patients; QRS = QRS complex on electrocardiogram; ROC = Receiver operating characteristic ; RVD = Right ventricular dysplasia; SOB = shortness of breath; SR = Sinus rhythm; TIA = Transient ischemic attack; UHFO-IA = Utrecht Heart Failure Organisation – Initial Assessment; VHD = Valvular heart disease; yrs = Years

Figure I-19. Summary sensitivity (PC NT-proBNP, manufacturer cutpoints [pg/ml]), random effect

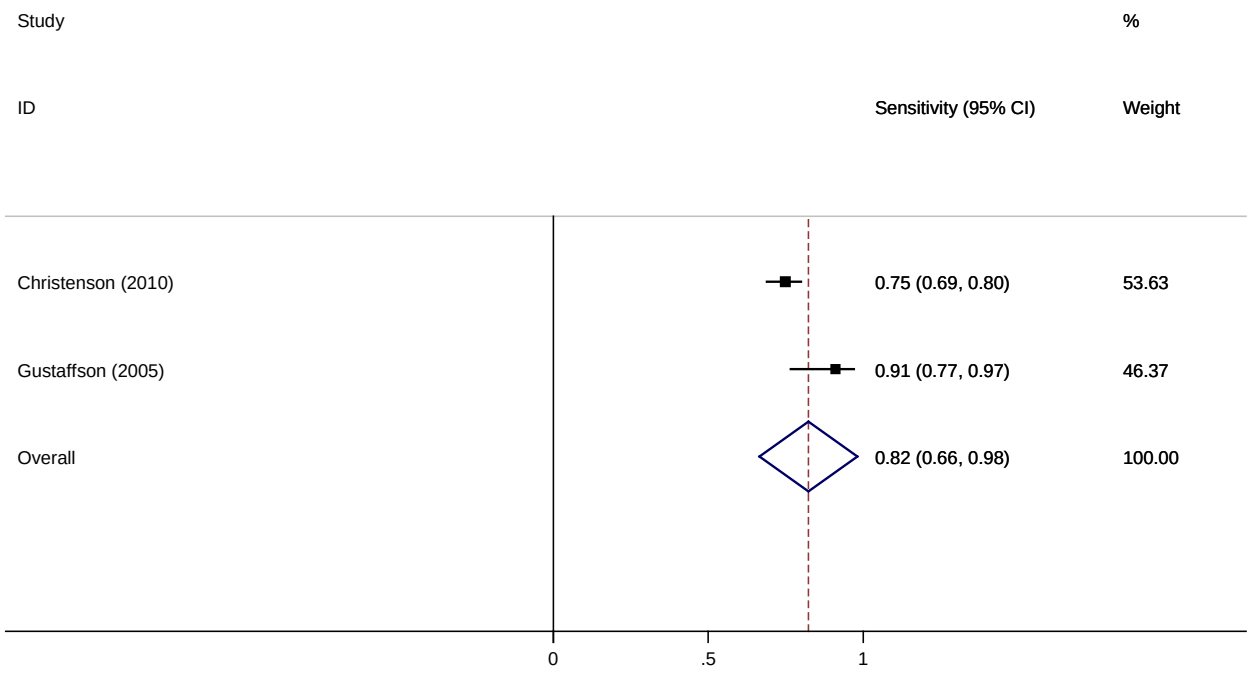

Figure I-20. Summary sensitivity (PC NT-proBNP, lowest cutpoints [pg/ml]), random effect

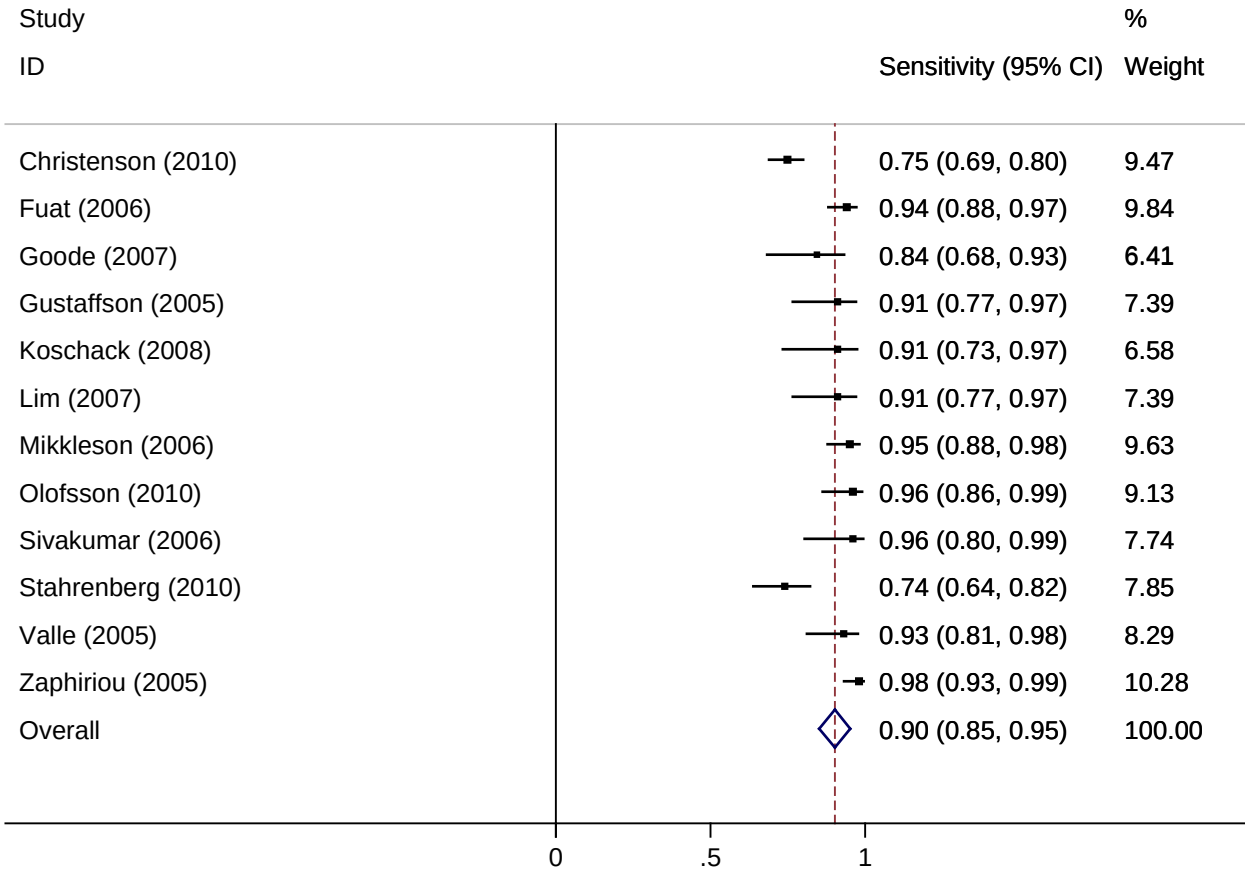

Figure I-21. Summary sensitivity (PC NT-proBNP, optimal cutpoints [pg/ml]), random effect

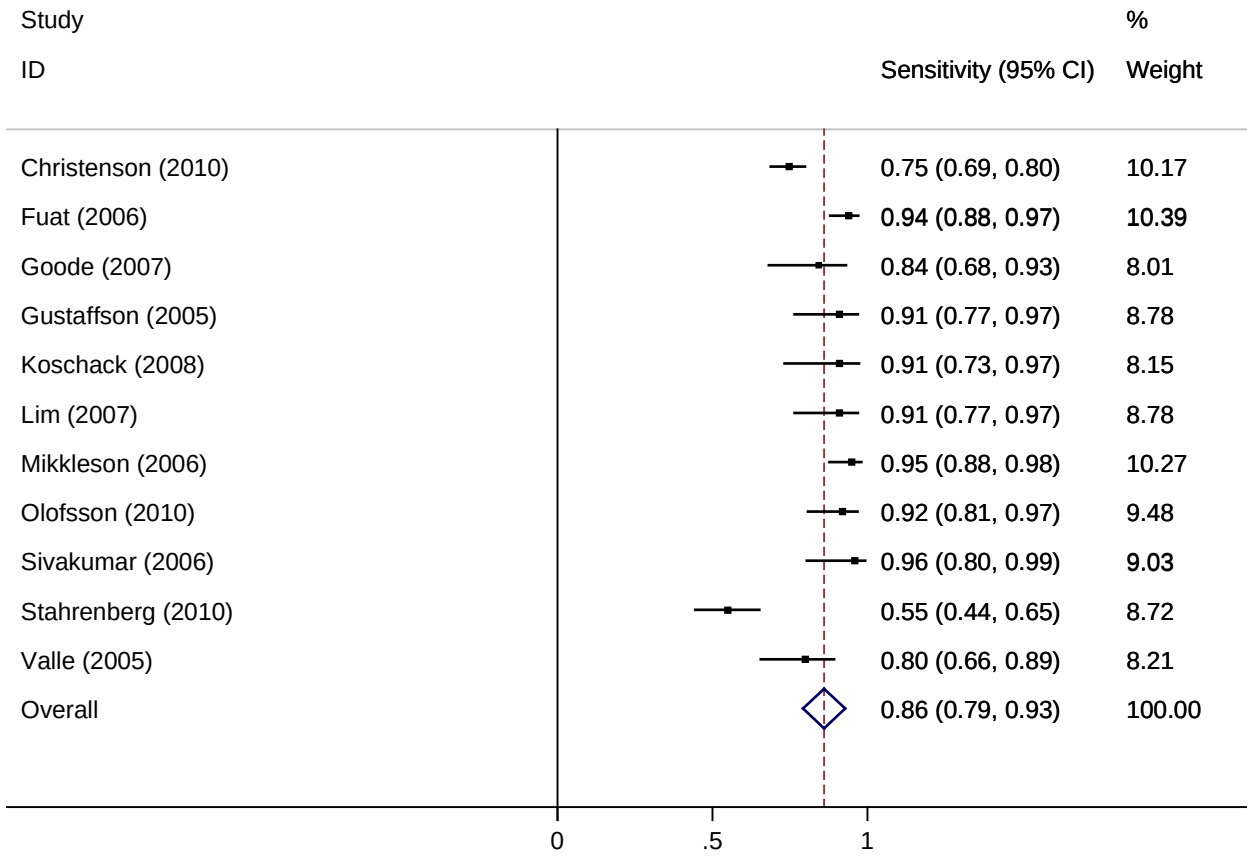

Figure I-22. Summary specificity (PC NT-proBNP, manufacturer cutpoints [pg/ml]), random effect

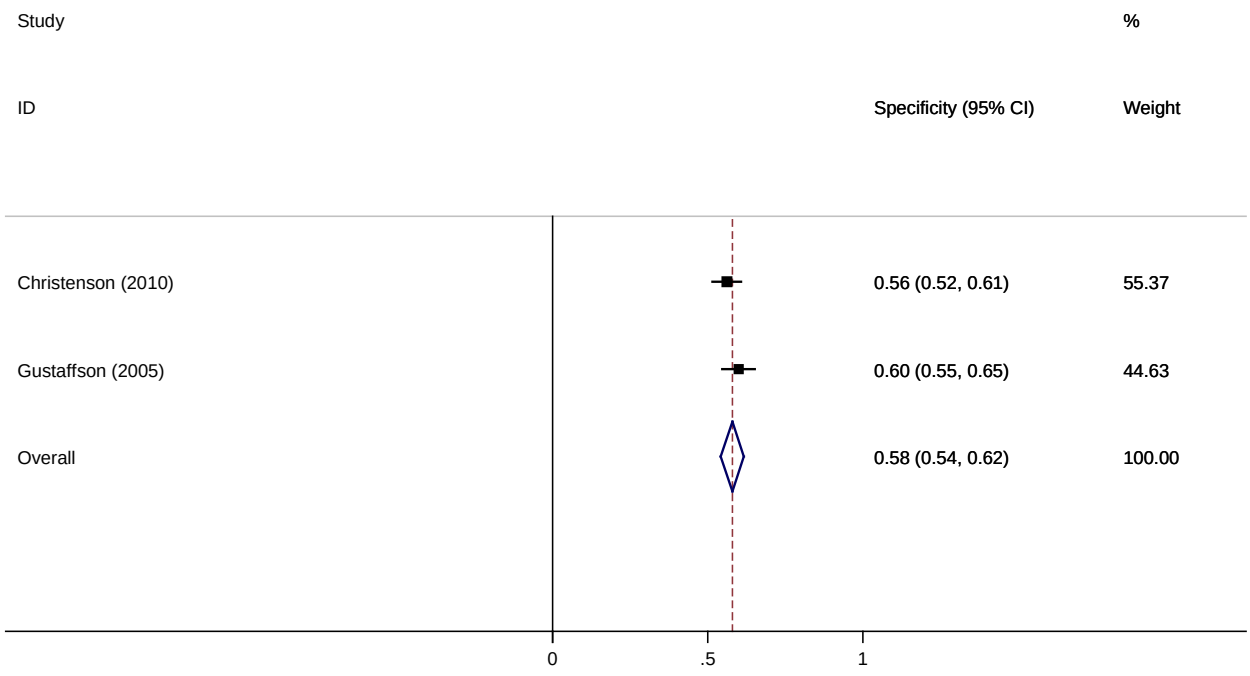

Figure I-23. Summary specificity (PC NT-proBNP, lowest cutpoints [pg/ml]), random effect

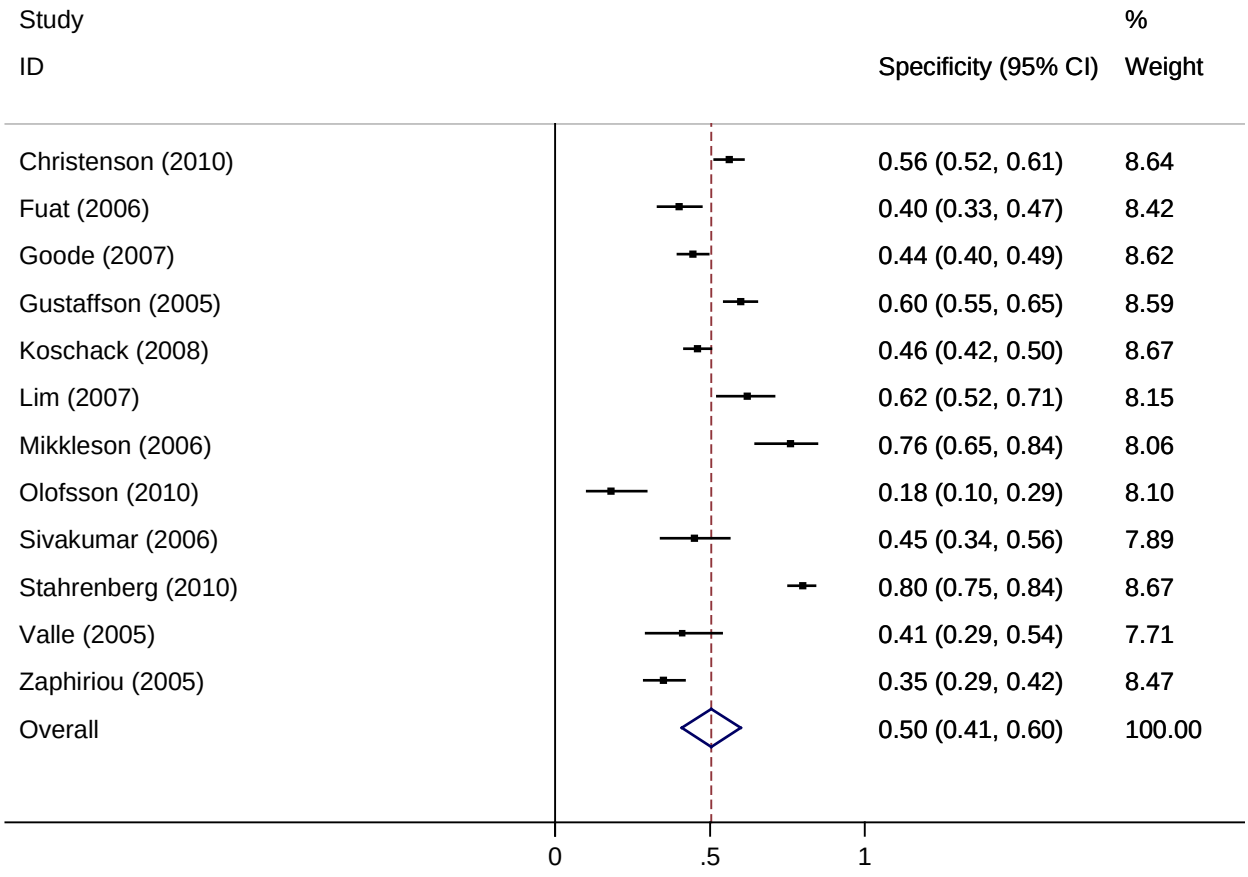

Figure I-24. Summary specificity (PC NT-proBNP, optimal cutpoints [pg/ml]), random effect

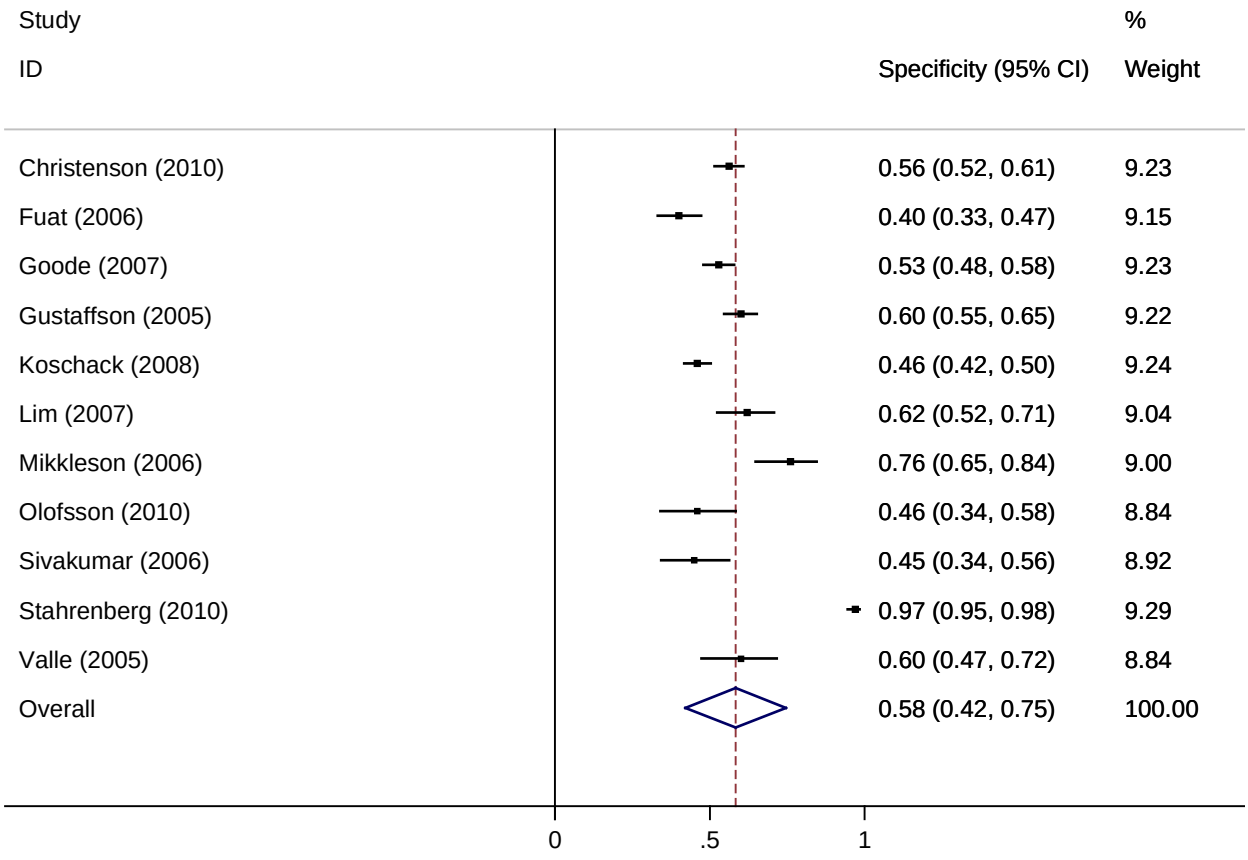

Figure I-25. Summary LR+ (PC NT-proBNP, manufacturer cutpoints [pg/ml]), random effect

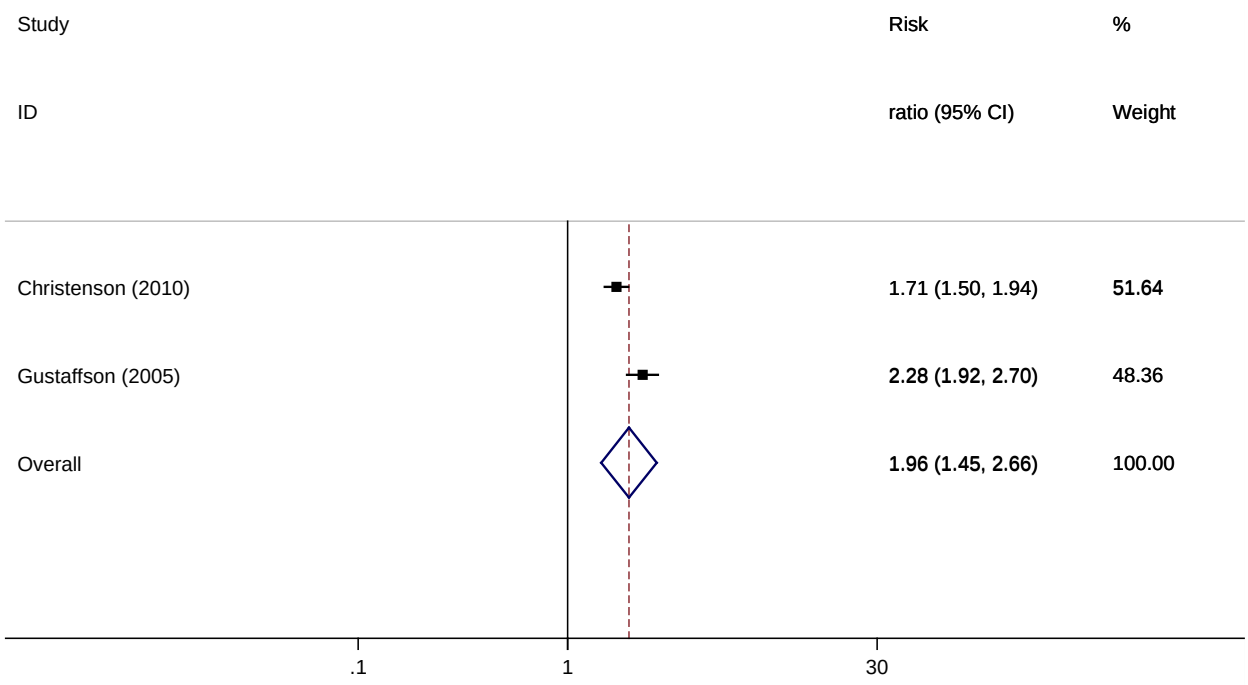

Figure I-26. Summary LR+ (PC NT-proBNP, lowest cutpoints [pg/ml]), random effect

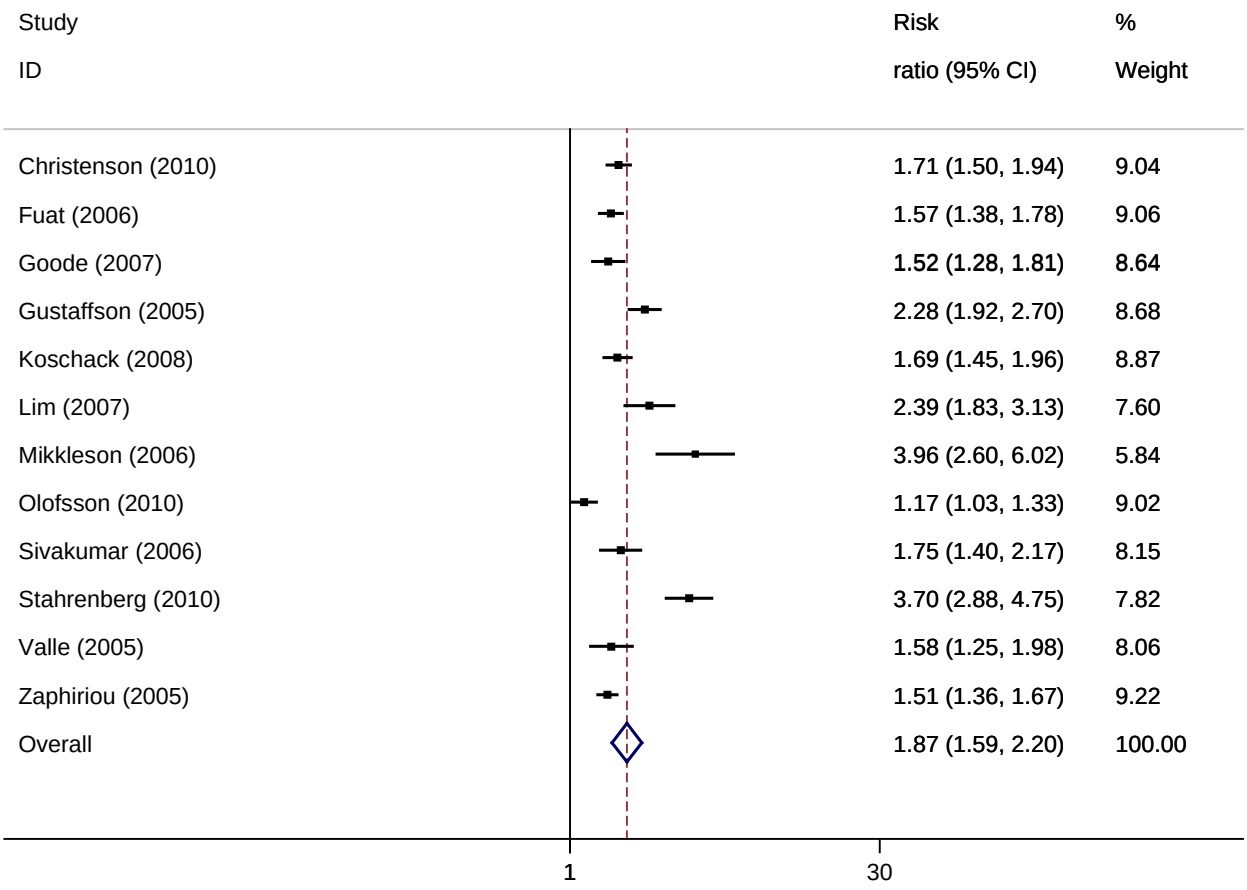

Figure I-27. Summary LR+ (PC NT-proBNP, optimal cutpoints [pg/ml]), random effect

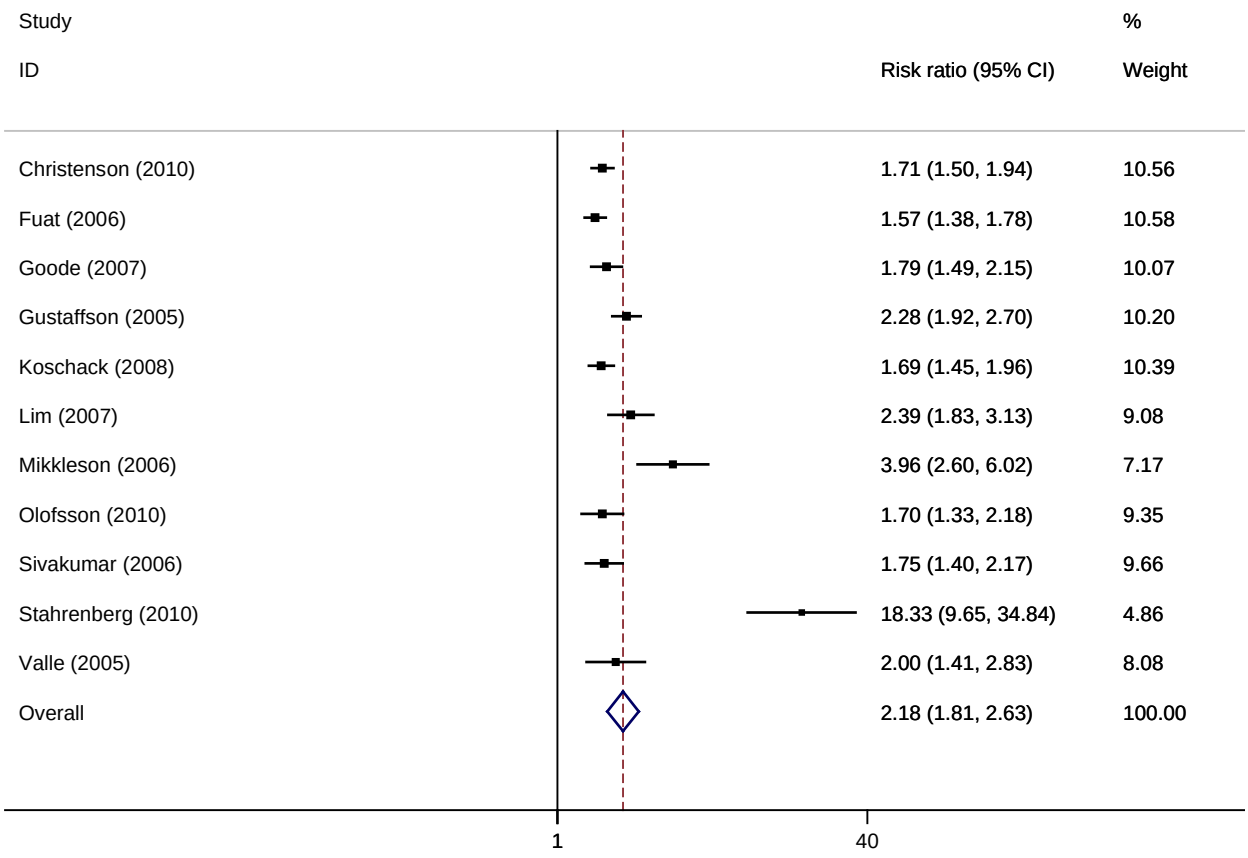

Figure I-28. Summary LR- (PC NT-proBNP, manufacturer cutpoints [pg/ml]), random effect

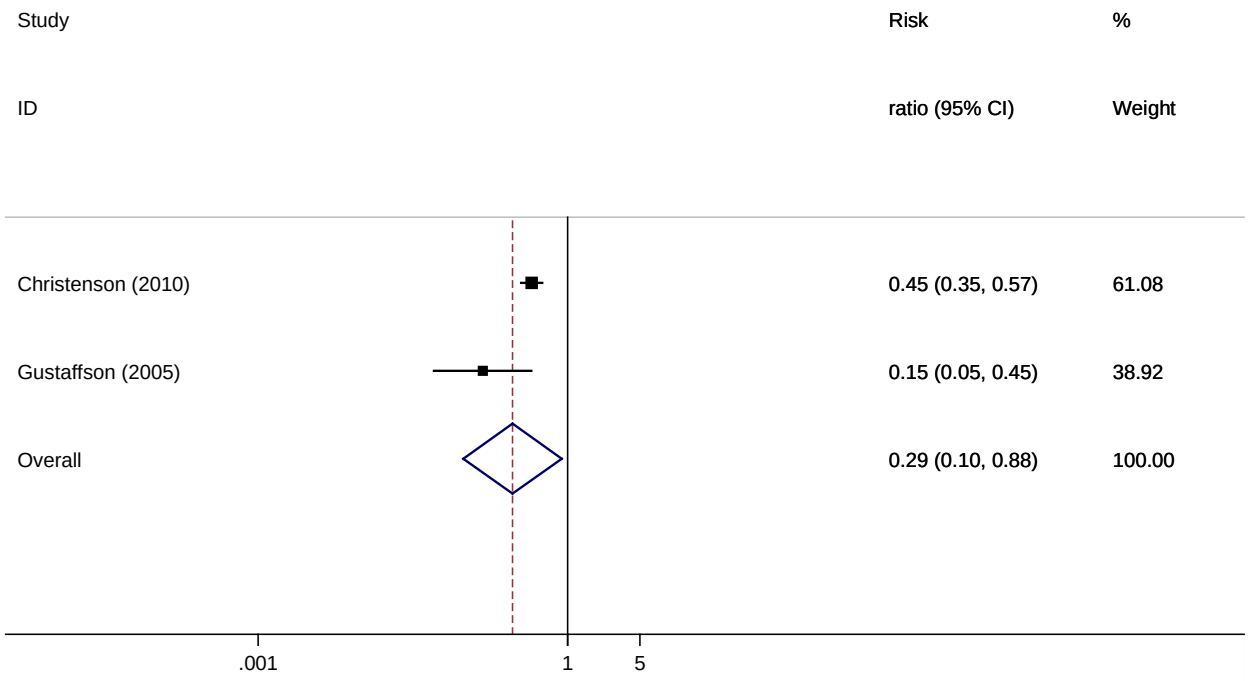

Figure I-29. Summary LR- (PC NT-proBNP, lowest cutpoints [pg/ml]), random effect

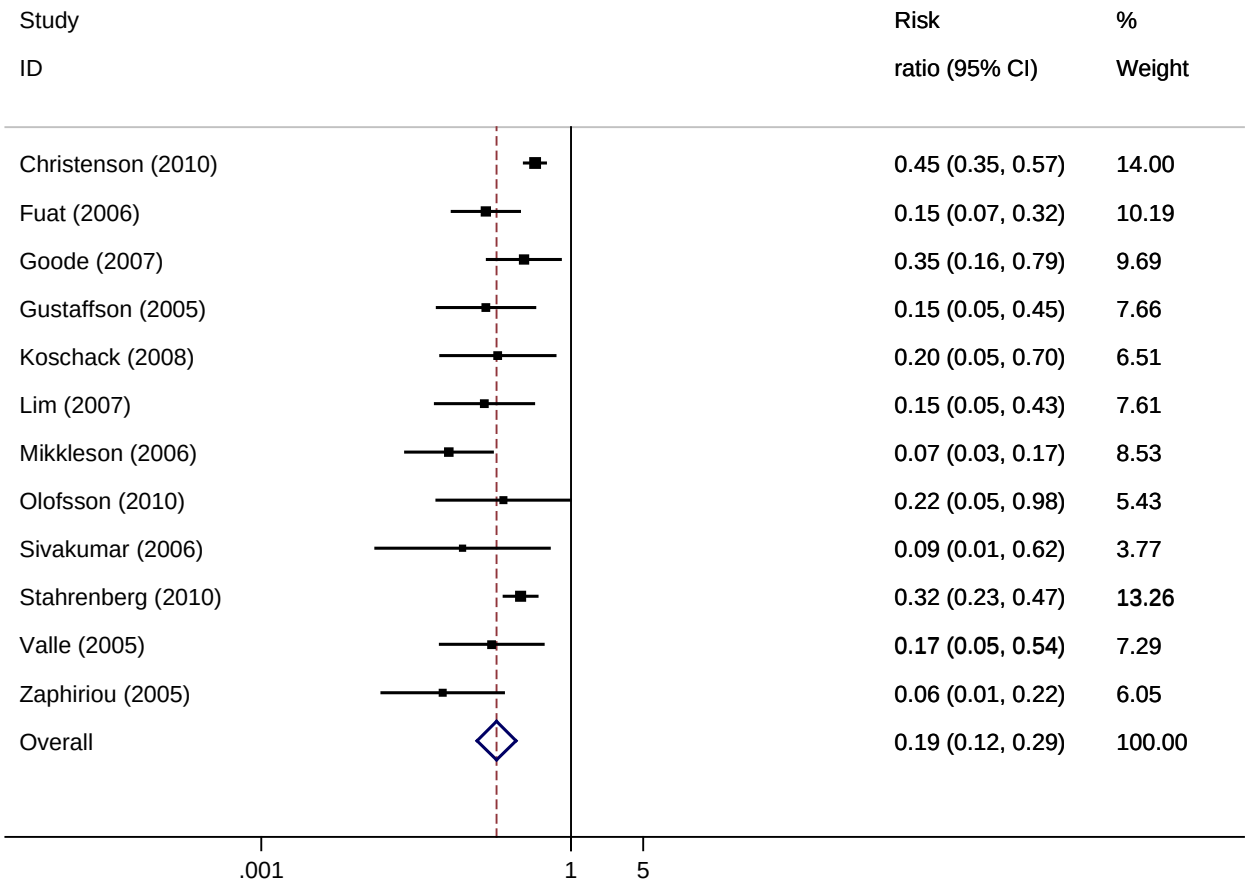

Figure I-30. Summary LR- (PC NT-proBNP, optimal cutpoints [pg/ml]), random effect

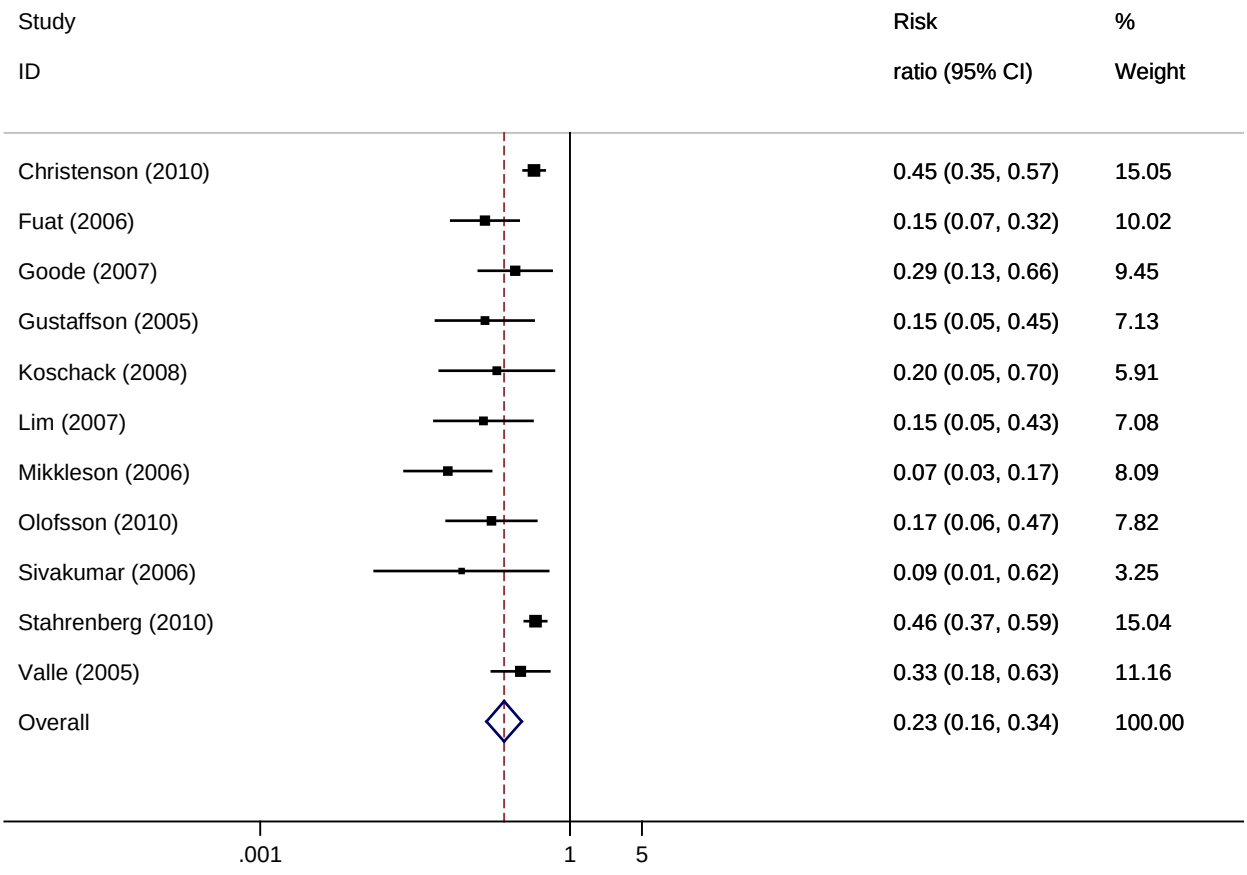

Figure I-31. Summary log DOR (PC NT-proBNP, manufacturer cutpoints [pg/ml]), random effect

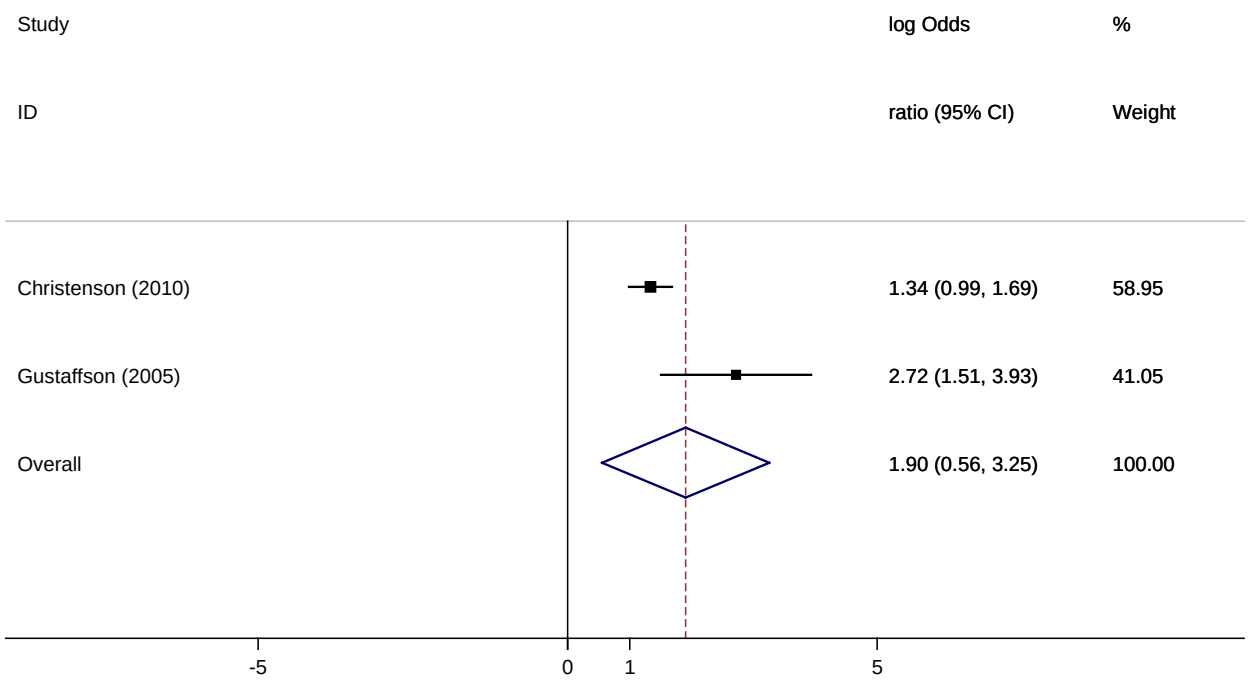

Figure I-32. Summary log DOR (PC NT-proBNP, lowest cutpoints [pg/ml]), random effect

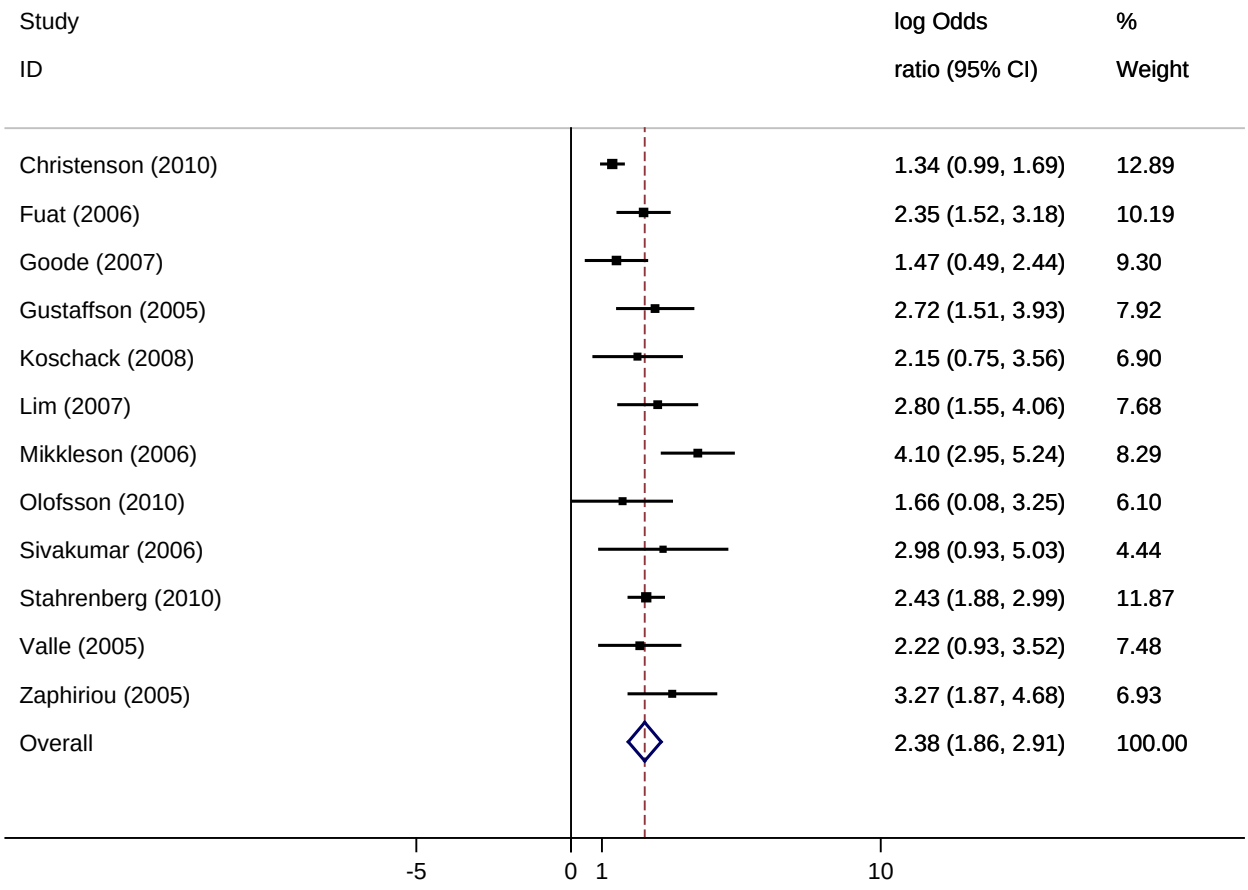

Figure I-33. Summary log DOR (PC NT-proBNP, optimal cutpoints [pg/ml]), random effect

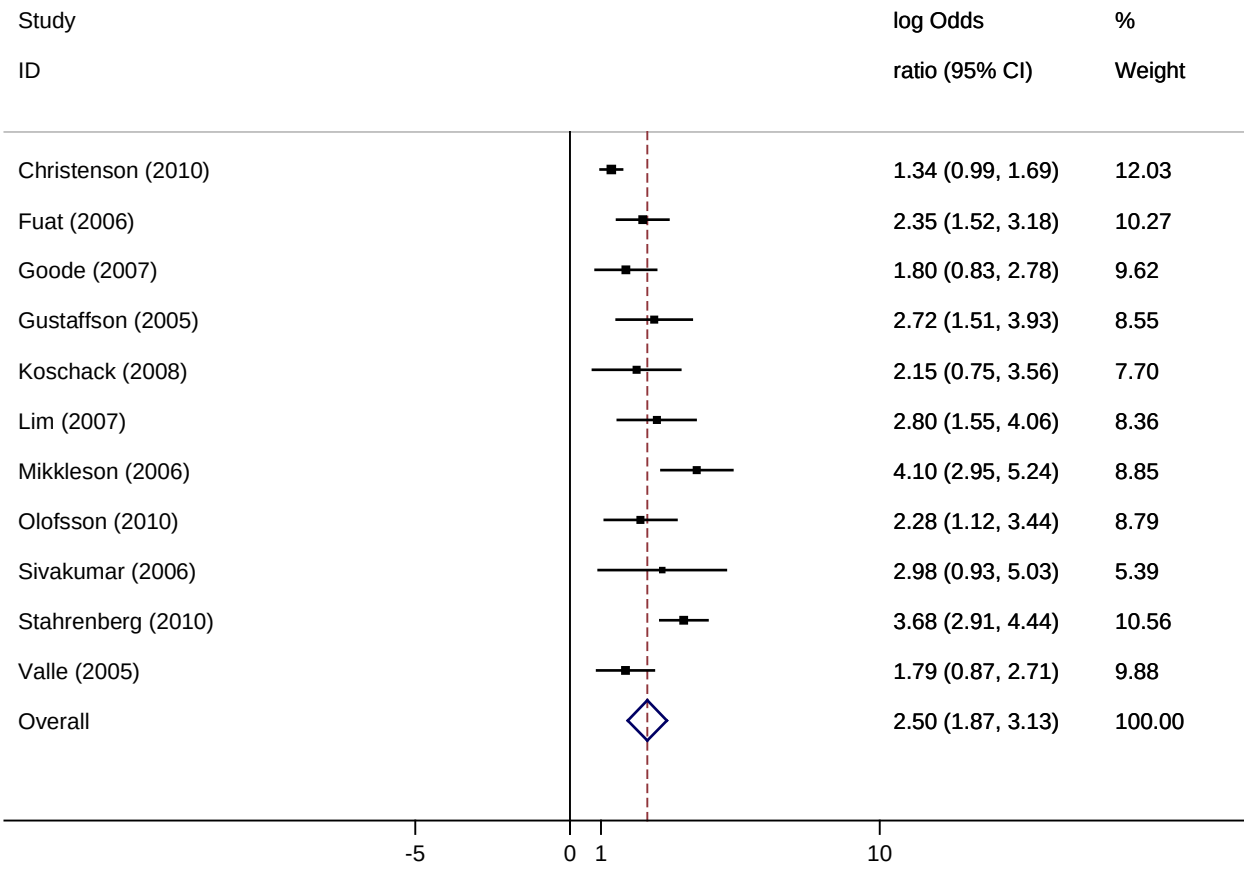

Figure I-34. Summary ROC-curve (PC NT-proBNP, lowest cutpoints [pg/ml]), random effect

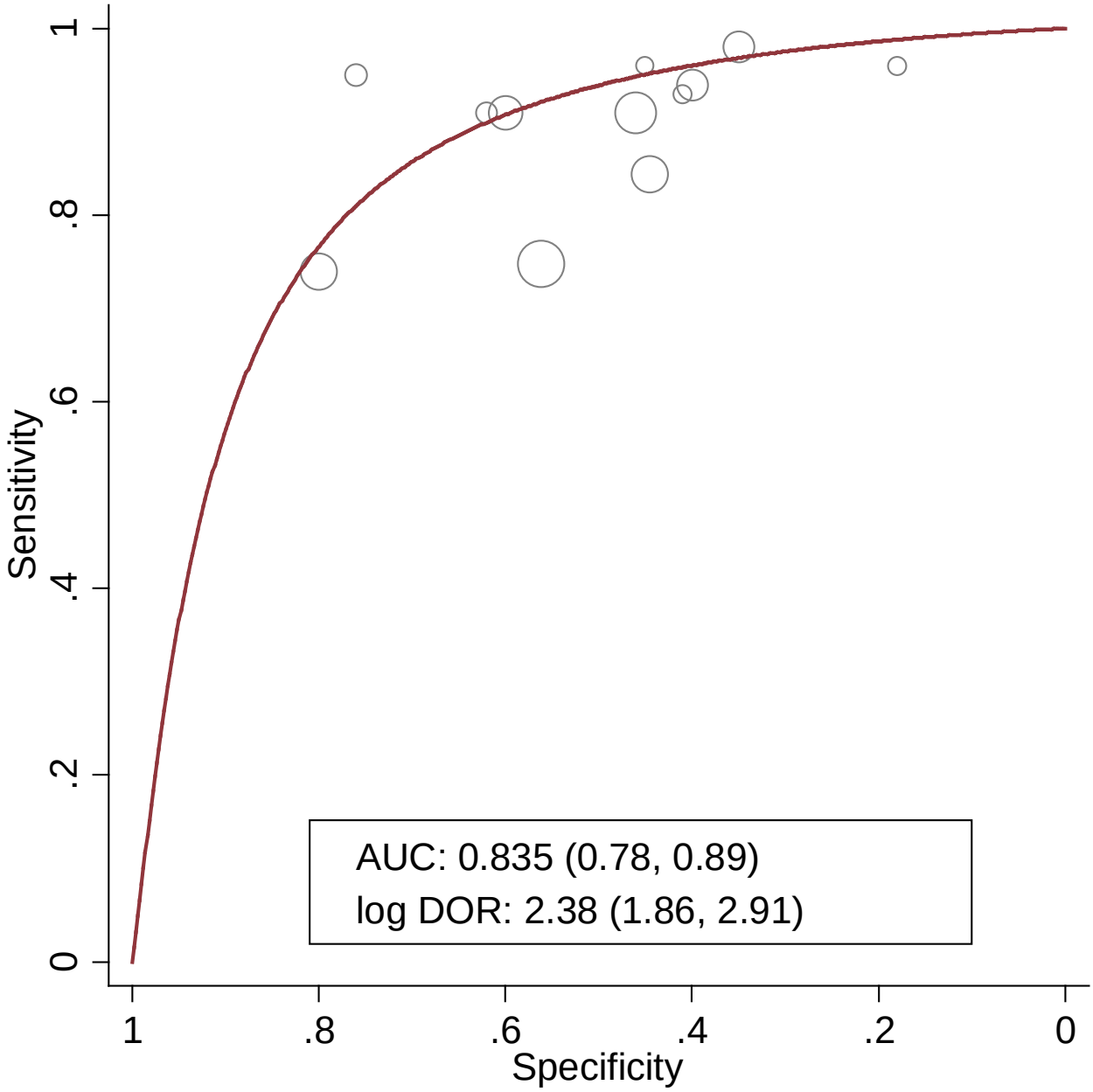

Figure I-35. Summary ROC-curve (PC NT-proBNP, optimal cutpoints [pg/ml]), random effect

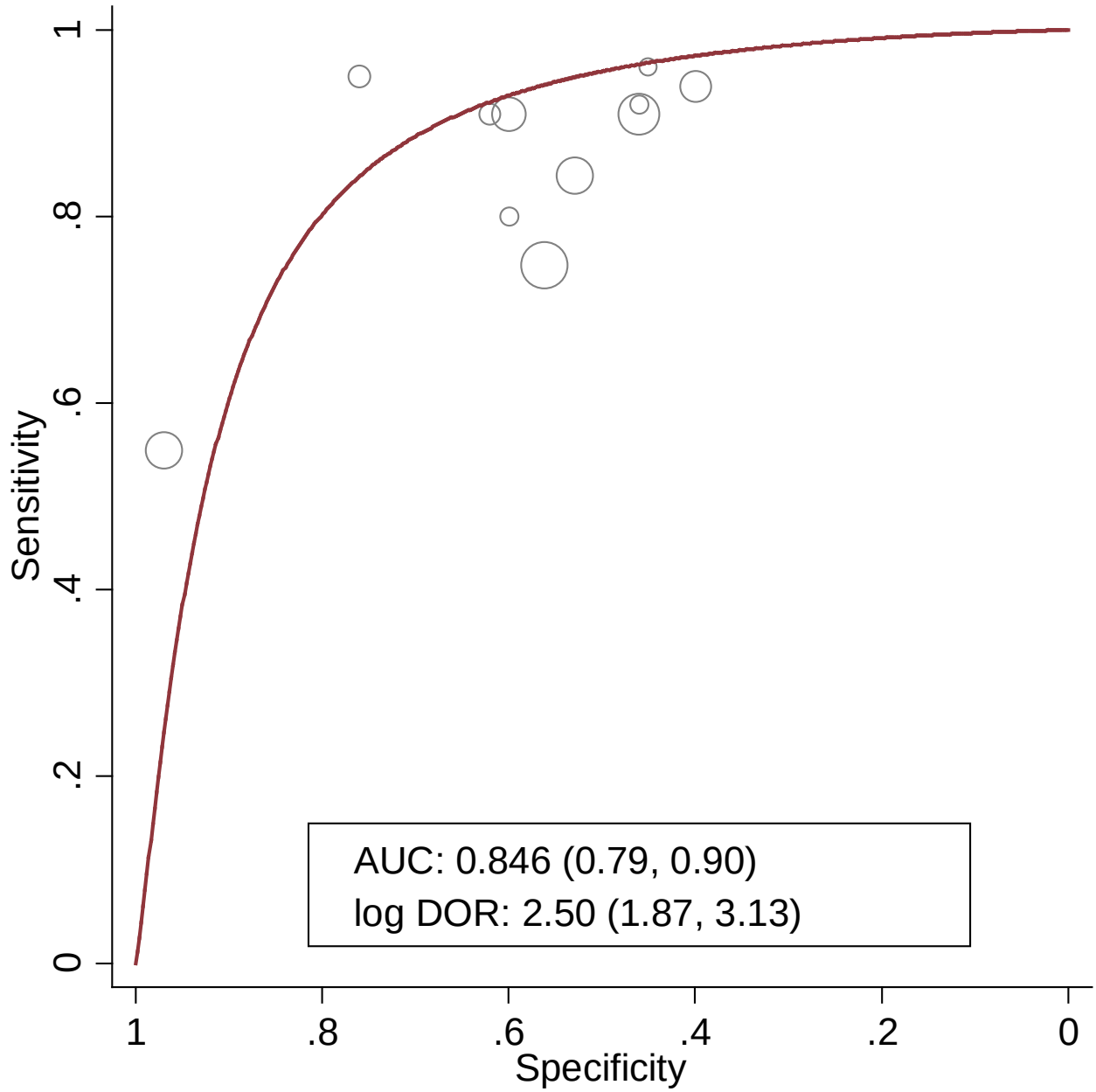
Sensitivity
0
.2
.4
.6
.8
1
Specificity
1
.8
.6
.4
.2
0
AUC: 0.846 (0.79, 0.90)
log DOR: 2.50 (1.87, 3.13)

Table I-3. Risk of Bias and Applicability in all Diagnosis Studies using BNP in primary care

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	F ✓ & Timing	Patient selection	Index Test	Reference Standard
Aspromonte,[2] 2006	?	?	?	✓	✕	✕	✕
Fuat,[5] 2006	?	✓	✓	✓	✕	✓	✓
Arques,[1] 2005	✓	✓	✓	✓	✕	✓	✓
Zaphiriou,[12] 2005	✓	✓	✓	✓	✕	✕	✕
Jeyaseelan,[6] 2007	?	✓	✓	✓	✕	✓	✓
Park,[11] 2010	?	✓	?	✓	✕	✓	✓
Christenson,[4] 2010	✓	✓	✓	✓	✕	✓	✓
Murtagh, [10] 2012	?	?	?	?	?	?	?
Macabasco-O'Connell,[8] 2010	?	✓	✓	✓	✕	✓	✓
Mak,[9] 2008	?	✓	✓	✓	✕	✓	✓
Barrios,[3] 2011	✓	?	✓	✓	✕	✕	✕
Kelder,[7] 2011	✓	✓	✕	✓	✓	✓	✓

Results of QUADAS 2 Quality Assessment
✓ = Low Risk ✕= High Risk ? = Unclear

Figure I-36. Proportion (%) of all diagnostic studies using BNP with low, high, or unclear concerns regarding risk of bias in primary care

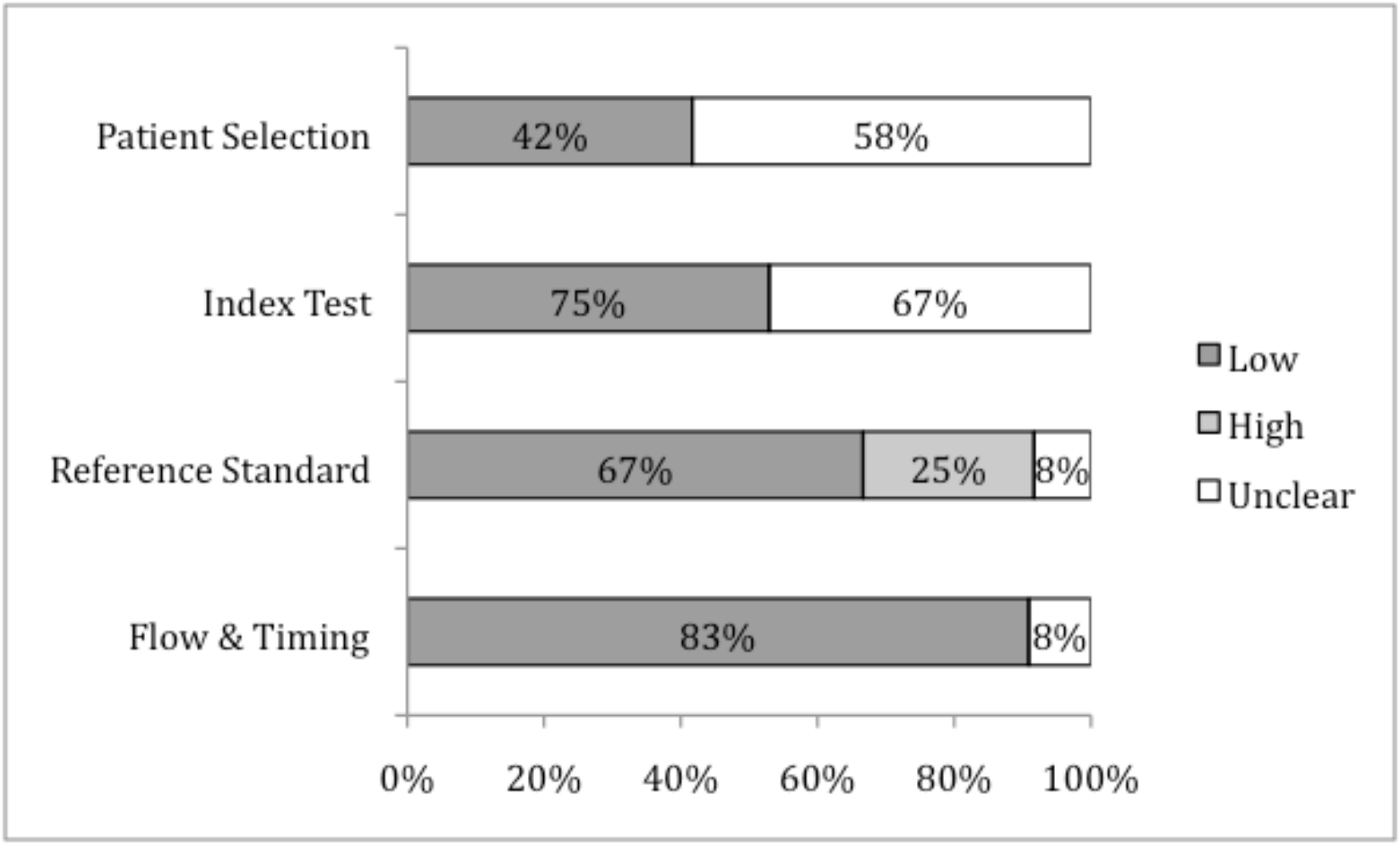

Figure **I-37. Proportion (%) of diagnostic studies using BNP with low, high, or unclear concerns regarding applicability in primary care**

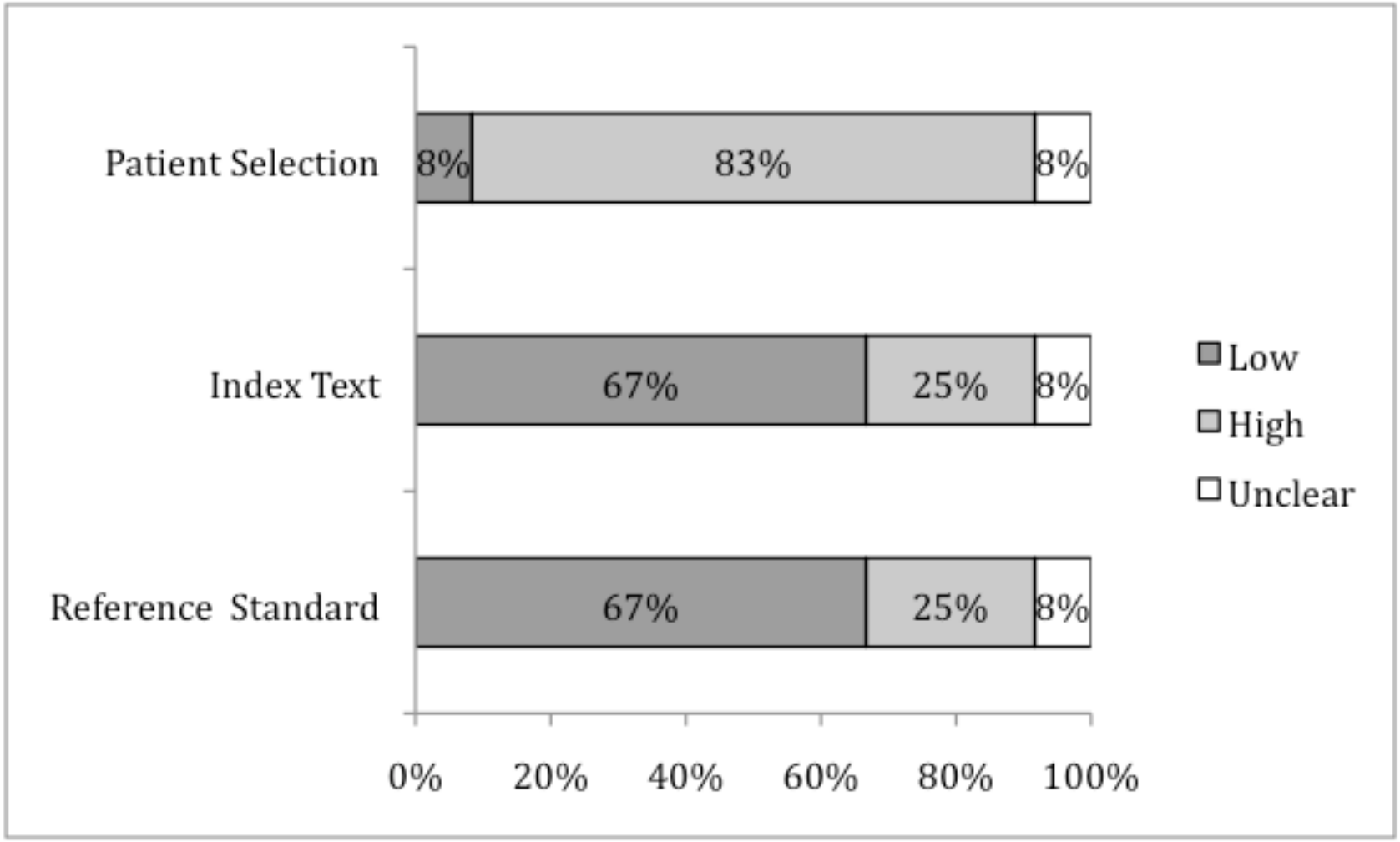

Table I-4. Risk of Bias and Applicability in all Diagnostic Studies using NT-ProBNP in primary care

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	F & Timing	Patient selection	Index Test	Reference Standard
Hobbs,[17] 2004	✔	✔	✔	✔	✔	✔	✔
Nielsen,[21] 2004	✔	✔	✕	✔	✔	✔	✔
Gustafsson,[15] 2003	?	✔	✔	✔	?	✔	✔
Lim,[19] 2007	?	✔	✔	✔	?	✔	✕
Shelton,[23] 2006	✔	✔	✔	✔	✕	✕	✕
Mikkelsen,[20] 2006	✔	?	✔	✔	✕	✕	✕
Fuat,[5] 2006	?	✔	✔	✔	✕	✔	✔
Sivakumar,[24] 2006	✔	✔	✔	✔	✕	✔	✔
Gustafsson,[16] 2005	?	✔	✔	✔	✕	✕	✕
Valle,[26] 2005	?	?	?	?	✕	✕	✕
Kelder, [27] 2011	?	✔	✔	?	✔	✔	✔
Zaphiriou,[12] 2005	✔	✔	✔	✔	✕	✕	✕
Park,[11] 2010	?	✔	?	✔	✕	✔	✔
Christenson,[4] 2010	✔	✔	✔	✔	✕	✔	✔
Olofsson,[22] 2010	✕	✔	✔	✔	✕	✔	✔
Goode,[14] 2008	?	✔	✔	✔	?	✔	✔
Koschack,[18] 2008	?	✔	?	✔	✕	✔	✔
Goode,[13] 2007	?	✔	✔	✔	✕	✕	✕
Stahrenberg,[25] 2010	?	✔	?	✔	✕	✔	✔
Kelder,[7] 2011	✔	✔	✕	✔	✔	✔	✔

Results of QUADAS 2 Quality Assessment

✔ = ✔ Risk ✕= ✕ Risk ? = ? risk

Figure **I-38. Proportion (%) of diagnostic studies using NT-ProBNP with low, high, or unclear concerns regarding risk of Bias in primary care**

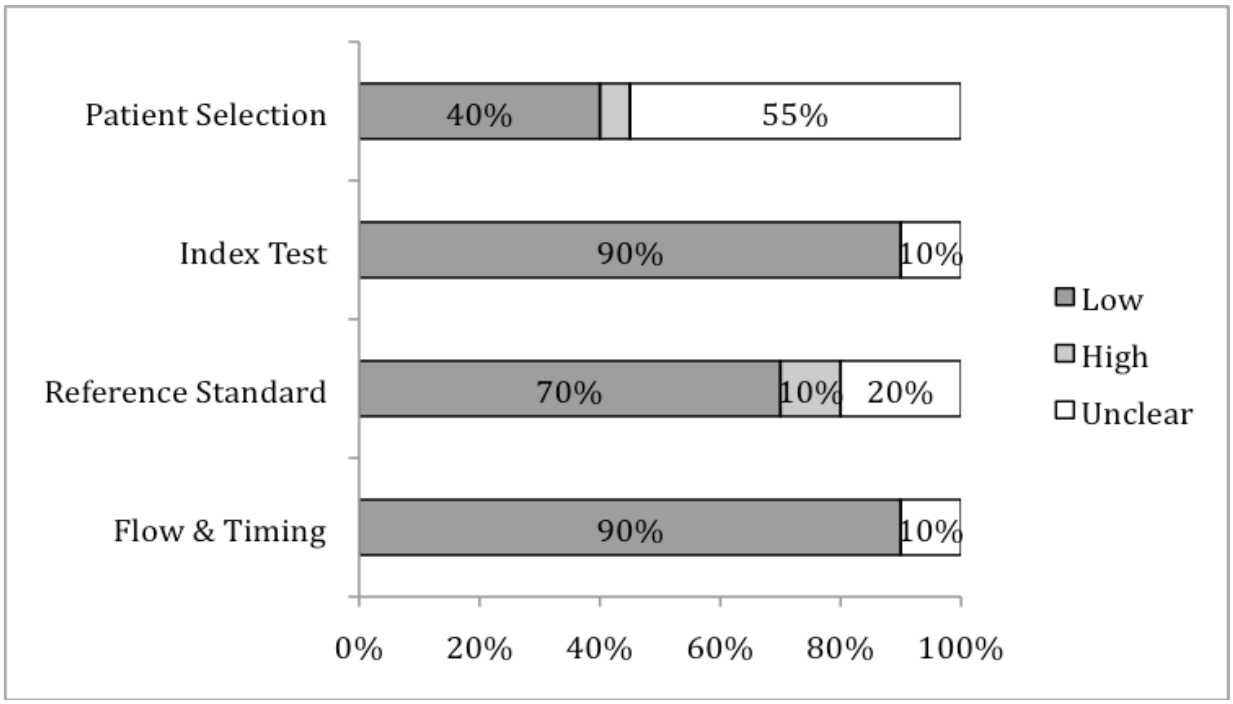

Figure I-39. Proportion (%) of diagnostic studies using NT-ProBNP with low, high, or unclear concerns regarding applicability in primary care

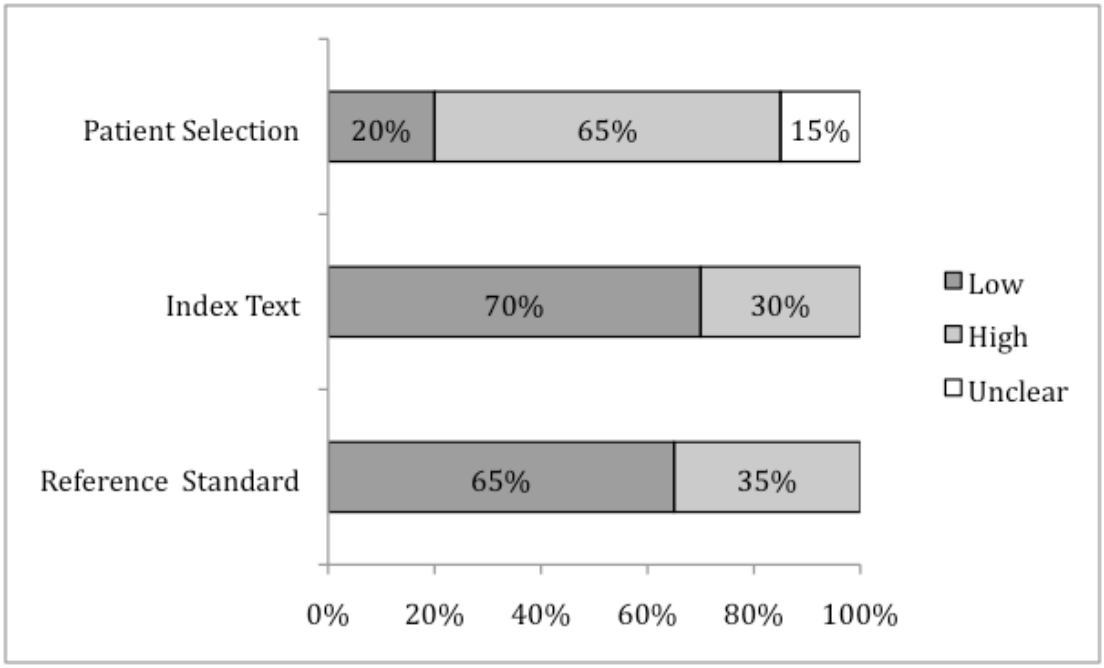

Table I-5a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoint for diagnostic studies utilizing BNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Macabasco-O'Connell,[8] 2010 Mak,[9] 2008	Sensitivity	Case-series (n=7), cohort (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=2319	0.8 (0.71-0.89)	High	High
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Mak,[9] 2008 Zaphiriou,[12] 2005	Specificity	Case-series (n=7), cohort (n=1)	Low	Direct – Specificity is a tool used and understood by clinicians	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=2319	0.61 (0.43-0.80)	Moderate	Moderate

Table I-5b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoint for diagnostic studies utilizing BNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Macabasco-O'Connell,[8] 2010 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Sensitivity	Case-series (n=9), cohort (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=3439	0.84 (0.77-0.92)	High	High
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Macabasco-O'Connell,[8] 2010 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Specificity	Case-series (n=9), cohort (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=3439	0.54 (0.42-0.66)	Moderate	Moderate

Table I-5c. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on manufacturer cutpoint for diagnostic studies utilizing BNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Jeyaseelan,[6] 2007 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Sensitivity	Case-series (n=7), cohort (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=3,089	0.73 (0.63-0.84)	High	High
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Jeyaseelan,[6] 2007 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Specificity	Case-series (n=7), cohort (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=3,089	0.67 (0.50-0.85)	Moderate	Moderate

Table I-6a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoint for diagnostic studies utilizing NT-proBNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustaffson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikkleson,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005	Sensitivity	Case-series (n=9), cohort (n=1), unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=3321	0.86 (0.79-0.93)	High	High
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustaffson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikkleson,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005	Specificity	Case-series (n=9), cohort (n=1), unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=3321	0.58 (0.42-0.75)	Moderate	Moderate

Table I-6b. Strength of evidence estimates of two primary outcomes, Sensitivity and Specificity, based on lowest cutpoint for diagnostic studies utilizing NT-proBNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustaffson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikkleson,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005 Zaphiriou,[12] 2005	Sensitivity	Case-series (n=10), cohort (n=1), unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=3627	0.90 (0.85-0.95)	High	High
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustaffson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikkleson,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005 Zaphiriou,[12] 2005	Specificity	Case-series (n=10), cohort (n=1), unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=3321	0.5 (0.41-0.60)	High	High

*QUADAS2

Table I-7. Summary test statistics of publication bias using diagnostic odds ratios, for primary care settings, stratified by assay and presented separately for different cutpoints

Department	Assay	Groups	n study	Begg z	Begg p	Egger t	Egger p
Primary care	BNP	Manufacturer cutpoint	8	0.49	0.621	0.73	0.490
		Optimum cutpoint	8	0.49	0.621	0.85	0.429
		Lowest cutpoint	10	1.34	0.180	1.79	0.111
	NT-proBNP	Manufacturer cutpoint	2	-	-	-	-
		Optimum cutpoint	11	0.70	0.484	**2.56**	**0.030**
		Optimum cutpoint = lowest cutpoint	7	0.15	0.881	**3.10**	**0.020**
		Optimum cutpoint > lowest cutpoint	4	0.00	1.00	-8.79	0.290
		Lowest cutpoint	12	0	1.00	**2.70**	**0.022**
		Lowest cutpoint = optimum cutpoint	7	0.15	0.881	**3.10**	**0.020**
		Lowest cutpoint < optimum cutpoint	5	0.00	1.00	-0.42	0.796

Background. Sensitivity and specificity are inversely related with each other in different cutpoints, (Hasselblad, 1995); therefore Song and coworker suggested to utilize DOR for estimating publication bias because it contains both sensitivity and specificity. (Song, 2002) Due to higher degree of random variation, studies with small sample size will have wider distribution of results than studies of larger sample. (Light, 1984) The possibility of publication is high for larger studies with positive results, and small/negative studies may not be published and often lead to asymmetry in the funnel. (Song, 2002) In the meta-analysis of screening and diagnostic data, commonly acceptable measures of test accuracy are not yet established. (Walter, 1999) Precision of the asymmetry of funnel plots can be measured using Begg's adjusted rank correlation method and Egger statistical approach. (Begg, 1994, Egger, 1997) Begg's test assess the correlation between test accuracy estimates and their variance,(Begg, 1994) but Egger's test determine whether there is an association between test accuracy estimates and their precision using regression analysis.(Egger, 1997) In our current analysis, we consider publication bias if Begg's and Egger's test reveals publication bias. The tests for publication bias exposed significant bias in the following conditions in our meta-analysis: 1) optimum cutpoint; 2) lowest cutpoint; and 3) publication year for BNP at emergency department, but not for the Primary Care Settings.

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

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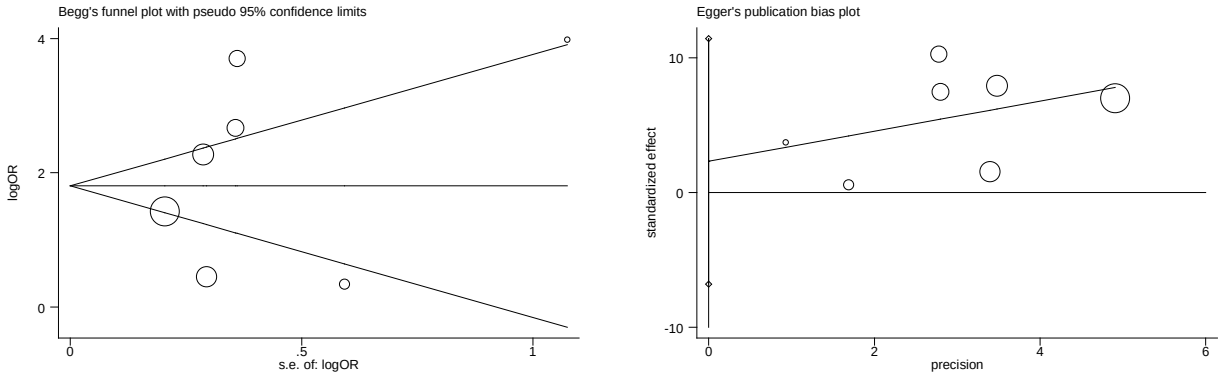
Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. Int J Epidemiol. 2002 Feb;31(1):88-95.

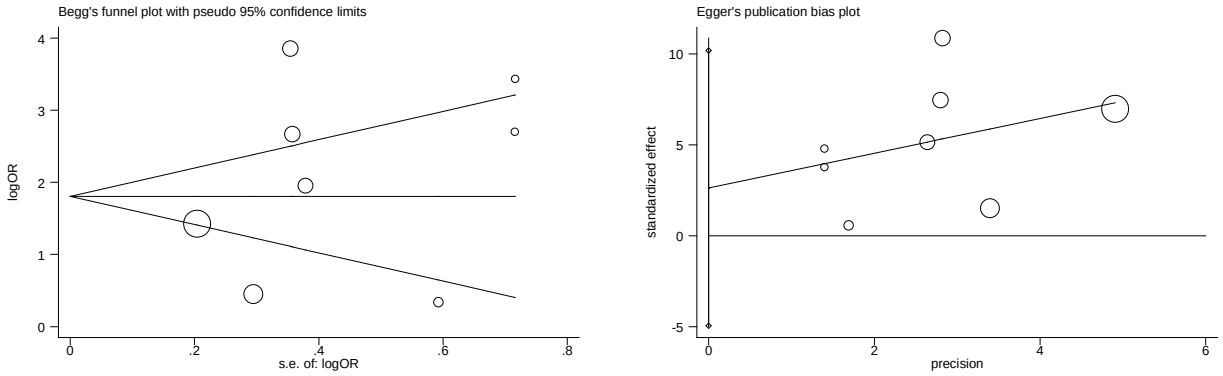
Walter SD, Jadad AR. Meta-analysis of screening data: a survey of the literature. Stat Med 1999;18:3409–24.

Figure I-40. Publication bias primary care: BNP

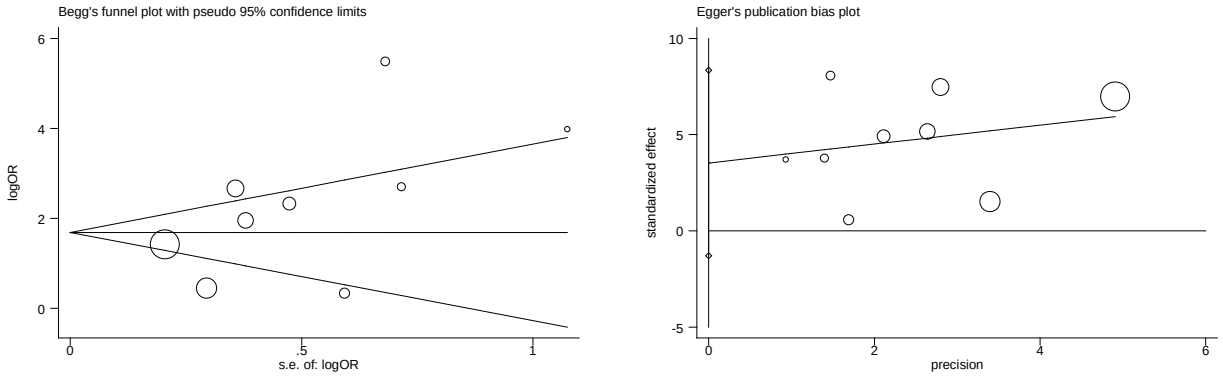
Begg's | Egger's



Manufacturer cutpoint



Optimum cutpoint

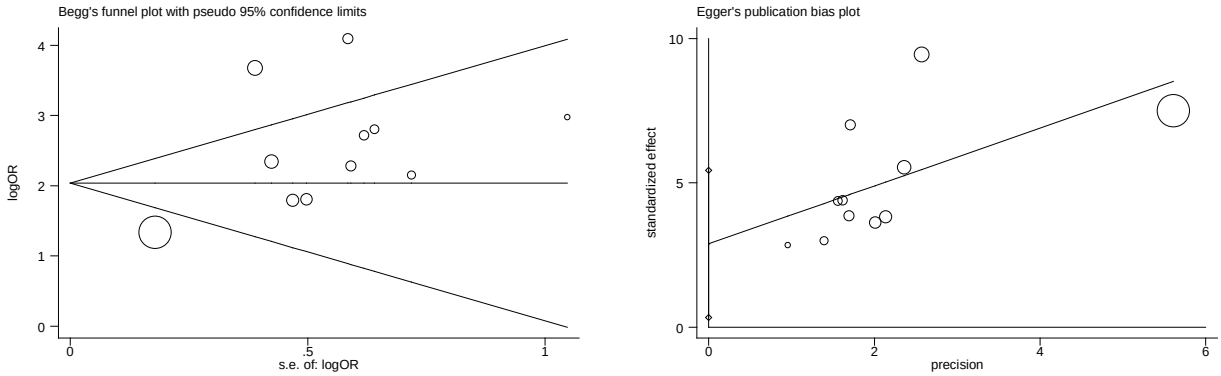


Lowest cutpoint

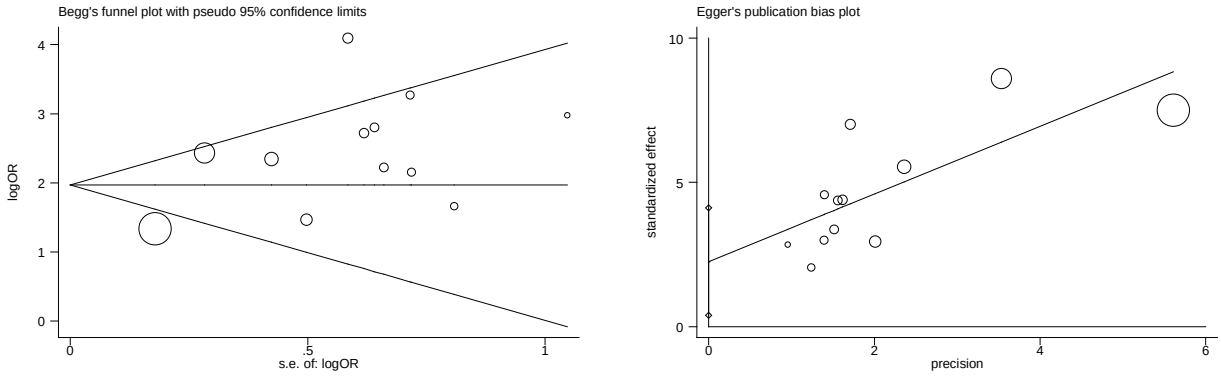
Figure I-41. Publication bias primary care: NT-proBNP

Begg's

Egger's



Optimum cutpoint



Lowest cutpoint

Appendix I. Reference List

1. Arques S, Roux E, Sbragia P, et al. Accuracy of tissue Doppler echocardiography in the emergency diagnosis of decompensated heart failure with preserved left ventricular systolic function: Comparison with B-type natriuretic peptide measurement. Echocardiograph. 2005;22(8):657-64.

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APPENDIX J.

KQ3 Evidence Set

Appendix J. KQ3 Evidence Set – Table of Contents

Table J-1. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing BNP J-1
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Appendix J. Reference List J-12

Table J-1. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing BNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Vrtovec,[1] 2003	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Horwich,[2] 2006	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Ralli,[3] 2005	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Boffa,[4] 2009	√	√	X	X	X	X	√	√	√	√	√	X	?	√	√	√	√
Adlbrecht,[5] 2009	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Scardovi,[6] 2008	√	√	√	?	?	√	√	√	?	?	√	X	√	X	X	√	√
Vrtovec,[7] 2008	√	√	√	?	?	√	√	√	?	?	√	X	√	X	X	√	?
Bermingam,[8] 2011	√	√	√	?	√	√	X	√	?	√	√	?	√	?	?	√	X
Neuhold,[9] 2008	X	X	√	√	√	√	√	√	√	√	X	X	√	?	?	√	√
Kruger,[10] 2006	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Kozdag,[11] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Dries,[12] 2010	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√	√	√	√
Popescu,[13] 2007	√	√	√	?	?	√	√	√	?	?	√	?	X	√	√	√	√
Scardovi[14] 2007	√	√	√	?	?	√	√	√	?	?	√	X	X	?	?	√	√
Moerti,[15] 2009	√	√	√	?	?	√	√	?	√	√	√	√	√	√	√	√	√
Meyer,[16] 2005	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table J-2. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Rothenburger,[17] 2004	√	√	√	X	?	√	√	NA	√	NA	√	?	√	√	√	√	√
Gardner,[18] 2003	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Gardner,[19] 2005	√	√	√	√	√	√	√	√	?	?	√	?	√	√	√	√	√
Hartmann,[20] 2004	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Corell,[21] 2007	√	√	√	√	√	√	√	√	X	X	√	√	√	X	X	√	√
Schou,[22] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Guder,[23] 2007	√	√	√	√	√	X	√	√	√	√	√	X	√	√	√	√	√
Mikkelsen,[24] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Jankowska,[25] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Bruch,[26] 2006	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Masson,[27] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bruch,[28] 2006	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Kistorp,[29] 2005	√	√	√	X	√	√	√	√	√	√	√	√	√	√	√	√	√
George,[30] 2005	√	√	√	?	√	?	√	√	?	?	√	?	√	?	?	√	√
George,[31] 2005	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Gardner,[32] 2005	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Gardner,[33] 2005	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Sherwood,[34] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Jankowska,[35] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√	√	√
Codognotto,[36] 2010	√	√	?	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Dini,[37] 2010	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√
Berger,[38] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Tsutamoto,[39] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Nishiyama,[40] 2009	√	√	√	?	?	√	√	√	?	?	?	?	√	X	X	√	?
Al Najjar,[41] 2009	√	√	√	√	√	√	√	√	X	X	√	?	√	√	√	√	√
Frankenstein,[42] 2009	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Cleland,[43] 2009	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√

Table J-2. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP (cont'd)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Charach,[44] 2009	√	√	√	√	√	√	√	√	?	?	√	?	√	X	X	√	√
Zielinski,[45] 2009	√	√	√	√	?	√	√	√	√	√	√	√	X	X	X	√	√
Poletti,[46] 2008	√	√	X	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Epelman,[47] 2009	√	√	√	√	X	√	√	√	√	√	√	X	X	√	√	√	√
Dini,[48] 2009	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Bayes-Genis,[49] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Frankenstein,[50] 2009	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Kubanek,[51] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Wedel,[52] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Pfisterer,[53] 2009	√	√	√	√	√	√	√		√	NA	√	√	√	√	√	√	√
Koc,[54] 2009	X	√	√	√	√	√	√	NA	√	NA	√	?	X	√	X	√	√
Michowitz,[55] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Honold,[56] 2008	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	√
Tsutamoto,[57] 2008	√	√	√	√	√	√	√	NA	√	NA	√	?	√	X	X	√	√
Hinderliter,[58] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Frankenstein,[59] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Kallistratos,[60] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Masson,[61] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X
Grewal,[62] 2008	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Bruch,[63] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	?	?	√	√
Dini,[64] 2008	√	√	√	?	?	√	√	√	?	?	√	√	√	X	X	√	√
Amir,[65] 2008	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pascual-Figal,[66] 2008	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Moertl,[67] 2008	√	√	√	√	X	√	√	√	√	√	√	√	X	√	√	√	√
Koc,[68] 2008	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Pfister,[69] 2008	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Gardner,[70] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Tsutamoto,[71] 2007	√	√	√	?	?	√	√	?	?	?	?	?	√	X	X	√	√

Table J-2. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP (cont'd)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
vonHaehling,[72] 2007	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Schou,[73] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Frankenstein,[74] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Kempf,[75] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Michowitz,[76] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	?
Bayes-Genis,[77] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Yin,[78] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Petretta,[79] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	X	√	√
Tsutamoto,[80] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
MacGowan,[81] 2010	√	√	?	√	√	√	√	√	√	√	√	?	X	?	?	√	√
Song,[82] 2010	√	√	√	√	√	√	√	X	√	√	√	√	X	√	√	√	√
Jankowska,[83] 2010	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	X
Jankowska,[84] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Tang,[85] 2011	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	X
Schierbeck,[86] 2011	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Raposeiras-Roubin,[87] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
von Haehling,[88] 2010	√	√	√	X	√	√	√	√	√	√	√	X	√	√	√	√	√
van den Broek,[89] 2011	√	√	√	?	?	√	√	X	√	√	√	X	√	√	√	√	√
Kawahara,[90] 2011	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Pfister,[91] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Frankenstein,[92] 2011	√	√	√	X	?	√	√	√	?	?	√	X	√	√	√	√	√
Bajraktari,[93] 2011	√	√	√	?	√	√	√	√	√	√	√	?	X	X	X	√	√
Carlsen,[94] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	√	X	X	√	√
Broch,[95] 2012	√	√	√	?	?	√	√	√	√	√	√	√	√	?	√	u	√
Tziakas,[96] 2012	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bayes-Genis,[97] 2012	?	?	?	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Franke,[98] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√	√	√	√
Jungbauer,[99] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Table J-2. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP (cont'd)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Anand,[100] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	√	X	X	√	√
de Antonio,[101] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Balling,[102] 2012	√	√	√	√	√	√	√		?	?	√	√	√	√	√	√	√
Al-Najjar,[103] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√
Christensen,[104] 2012	√	√	√	?	?	√	√	√	?	?	√	√	√	√	√	√	√
Moertl,[15] 2009	√	√	√	?	?	√	√	?	√	√	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table J-3. Risk of bias for prognostic surgical studies using the Hayden Criteria assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Assmus,[105] 2007	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Berger,[106] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	X	X	X	√	√
Cleland,[107] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table J-4. Risk of bias for prognostic surgical studies using the Hayden Criteria assessing BNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Lellouche,[108] 2007	√	√	√	√	√	√	√	√	√	√	X	?	X	X	X	√	√
Glick,[109] 2006	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
El Saed,[110] 2009	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	X
Leibowitz,[111] 2008	X	√	√	√	X	√	√	NA	√	NA	√	?	X	X	X	√	√
Pitzalis,[112] 2006	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Koch,[113] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table J-5. Risk of bias for prognostic studies using the Hayden Criteria for both stable and decompensated population assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Dini,[114] 2008	√	√	√	√	√	√	√	NA	√	NA	√	√	X	X	X	√	√
Dini,[115] 2012	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table J-6. Risk of bias for prognostic studies using the Hayden Criteria for both stable and decompensated population assessing BNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Maisel,[116] 2004	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Logeart,[117] 2004	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Aspromonte,[118] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Stoiser,[119] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Cournot,[120] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√	√	√
Sun,[121] 2007	√	√	√	√	√	√	√	√	√	√	?	X	√	X	X	√	√
Gegenhuber,[122] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Kellett,[123] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	?	?	√	√
Valle,[124] 2005	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Dokainish,[125] 2005	√	√	√	X	?	√	√	√	√	√	√	X	X	X	X	√	√
DiSomma,[126] 2010	√	√	X	?	?	√	√	NA	√	NA	√	X	√	√	?	√	√
Zairis,[127] 2010	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Reichlin,[128] 2010	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Faggiano,[129] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	X	?	√	√
Farmakis,[130] 2010	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Dunlay,[131] 2009	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Singer,[132] 2009	√	√	√	√	X	√	√	√	√	√	√	X	√	X	X	√	√
Parissis,[133] 2009	√	X	?	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Cohen-Solal,[134] 2009	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X
Dhaliwal,[135] 2009	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	√
Nunez,[136] 2008	√	√	√	?	?	√	√	NA	?	NA	?	?	√	X	X	√	√
Feola,[137] 2008	√	√	√	√	√	√	√	NA	√	NA	√	?	X	X	X	√	√
Cournot,[138] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Valle,[139] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X

Table J-6. Risk of bias for prognostic studies using the Hayden Criteria for both stable and decompensated population assessing BNP (cont'd)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Parissis,[140] 2008	√	√	√	√	√	√	√	√	√	√	√	X	X	?	?	√	√
Valle,[141] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	X	X	X	√	√
Dieplinger,[142] 2009	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√
Nunez,[143] 2010	√	√	√	?	?	√	√	√	?	?	√	X	√	?	?	√	√
Pimenta,[144] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√	√	√
Noue,[145] 2011	√	√	√	?	?	√	√	√	?	?	√	X	X	X	X	√	√
Nahum,[146] 2010	√	√	√	√	√	?	√	√	√	√	√	X	X	X	√	√	√
Rychli,[147] 2011	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√	√	√
Arques,[148] 2011	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Allen,[149] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Coyne,[150] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Maisel,[151] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√	√	√	√
Arenja,[152] 2012	√	√	√	?	?	√	√	√	?	?	√		√	√	√	√	√
Neuhold,[9]2010	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Sakhuja,[153] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Maisel,[154] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Boisot,[155] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Noveanu,[156] 2011	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Rehman,[157] 2008	√	√	√	√	√	√	√	√	√	√	X	X	√	X	X	√	√
Peacock,[158] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest;
2. a) completeness of follow-up described, b) completeness of follow-up adequate;
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported;
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided;
5. a) confounders measured, b) confounders accounted for;
6. a) analysis described;
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table J-7. Risk of bias for prognostic studies using the Hayden Criteria for both stable and decompensated population assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Bettencourt,[159] 2004	√	√	√	√	√	√	√	√	?	?	√	√	√	X	X	√	√
Baggish,[160] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bettencourt,[161] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Perna,[162] 2006	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Sakhuja,[153] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
van Kimmenade,[163] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
van Kimmenade,[164] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Marcucci,[165] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Januzzi,[166] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√
Bayes-Genis,[167] 2005	√	√	√	X	√	√	√	NA	√	NA	√	?	√	X	?	√	√
Bayes-Genis,[168] 2007	√	√	√	√	√	√	√	NA	X	NA	√	?	X	?	?	√	√
Ferreira,[169] 2007	√	√	√	√	√	√	√	NA	?	NA	√	X	X	X	X	√	√
Martins,[170] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Siswanto,[171] 2006	√	√	√	?	?	√	√	√	√	√	X	X	X	√	√	√	√
Park,[172] 2010	√	√	√	√	√	√	√	√	√	√	√	?	X	√	X	√	√
Davutoglu,[173] 2010	√	√	√	√	√	X	√	√	√	√	√	X	√	X	X	√	X
Dini,[174] 2010	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	√
Mohammed,[175] 2010	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Baggish,[176] 2010	√	?	?	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Maisel,[154] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Lourenco,[177] 2009	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Manzano-Fernández,[178] 2009	√	√	√	?	?	√	√	√	?	?	√	X	X	√	√	√	√

Table J-7. Risk of bias for prognostic studies using the Hayden Criteria for both stable and decompensated population assessing NT-proBNP (cont'd)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Kubler,[179] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	√	X	X	√	√
Paul,[180] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Boisot,[155] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Verdiani,[181] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	√	X	X	√	√
Andersson,[182] 2008	√	√	√	√	√	√	√	NA	√	NA	√	√	√	X	X	√	√
Petretta,[183] 2007	√	√	√	√	√	√	√	√	√	√	?	X	√	√	√	√	√
Metra,[184] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Lassus,[185] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	?	?	√	√
Luers,[186] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Carrasco-Sanchez,[187] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Noveanu,[156] 2011	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Rehman,[157] 2008	√	√	√	√	√	√	√	√	√	√	X	X	√	X	X	√	√
Pascual-Figal,[188] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Ho,[189] 2011	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Michtalik,[190] 2011	√	√	√	√	√	√	√	√	?	?	√	?	X	X	X	√	√
Korewicki,[191] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√		√	√
Krackhardt,[192] 2011	√	√	√	?	?	√	√	NA	?	NA	√	√	√	X	X	√	√
Peacock,[158] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√
Harutyunyan,[193] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NTBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for;
6. a) analysis described;
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP
8.

Appendix J. Reference List

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APPENDIX K.

KQ4 Evidence Set

Appendix K. KQ 4 Evidence Set – Table of Contents

Table K-1. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for decompensated heart failure population.....K-1
Table K-2. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for stable heart failure population.....K-2

Appendix K. Reference List.....K-3

Table K-1. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for decompensated heart failure population.

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Zairus,[1] 2010	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Maisel,[2] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Dunlay,[3] 2009	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Nunez,[4] 2008	√	√	√	?	?	√	√	NA	?	NA	?	?	√	X	X	√	√
Nunez,[5] 2010	√	√	√	?	?	√	√	√	?	?	√	X	√	?	?	√	√
Pascal-Figuel,[6] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
8. a) completeness of follow-up described, b) completeness of follow-up adequate
9. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
10. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
11. a) confounders measured, b) confounders accounted for
12. a) analysis described
13. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table K-2. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for stable heart failure population

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Mikkelsen,[7] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Schou,[8] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Masson,[9] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Dini,[10] 2010	√	√	√	?	X	√	√	√	√	√	√	X	√	X	X	√	√
Dini,[11] 2009	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Dini,[12] 2008	√	√	√	√	√	√	√	NA	√	NA	√	√	X	X	X	√	√
Dini,[13] 2008	√	√	√	?	?	√	√	√	?	?	√	√	√	X	X	√	√
Bajraktari,[14] 2011	√	√	√	?	√	√	√	√	√	√	√	?	X	X	X	√	√
Cleland,[15] 2009 Corona	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Wedel,[16] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Jankowska,[17] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
von Haehling,[18] 2010	√	√	√	X	√	√	√	√	√	√	√	X	√	√	√	√	√
Bayes Genis,[19] 2012	?	?	?	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Antonio,[20] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Christensen,[21] 2012	√	√	√	?	?	√	√	√	?	?	√	√	√	√	√	√	√
Harutyunyan,[22] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described; 7 a) The study was designed to test the prognostic value of BNP/NT-proBNP

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