SUPPLEMENTAL MATERIAL:

Appendix 1 – Study Protocol .......................... Pages 1 - 6
Appendix 2 - Data sources and search strategy .... Page 7
Appendix 3 – QUADAS-2 questionnaire .......... Pages 8 - 10
Appendix 4 – Excluded full-text studies .......... Pages 11 - 12
Appendix 5 – Secondary analysis of E/e’ correlation with LVFP Pages 13 - 26
Appendix 6 – Secondary analysis of sensitivity/specificity of E/e’ cutoffs to predict elevated LVFP Pages 27 - 41
Appendix 7 – Optimal cutoffs and AUC for elevated LVFP Pages 42 - 44
Appendix 8 – Secondary analysis of sensitivity/specificity of E/e’ cutoffs to predict normal LVFP Pages 45 - 58
APPENDIX 1

Evidence-based assessment of diagnostic accuracy of tissue Doppler echocardiographic index, E/e’ for estimation of LV filling pressure and diastolic dysfunction/ heart failure with preserved ejection fraction.

Protocol for Systematic review and Meta-analysis study.

We will follow PRISMA guidelines \(^1\) and Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy \(^2\) in conducting this study.

Summary

Left ventricular Diastolic dysfunction (LVDD) causing heart failure with preserved ejection fraction (HFpEF) is a major clinical problem. Although echocardiography is recommended for noninvasive evaluation of LVDD/HFpEF and is currently routinely used in clinical practice and research, the diagnostic accuracy of echocardiographic variables is not well defined. We hypothesize that commonly utilized echocardiographic tissue Doppler index E/e’ for estimating left ventricular filling pressure and diagnosis of LVDD/HFpEF is not very well validated.

Background

Target conditions being diagnosed

Diastolic dysfunction is an important cause of Heart failure (HF) with preserved ejection fraction (pEF) and a major medical and public health issue. \(^3\)–\(^6\) The diagnosis of HFpEF is more challenging than the diagnosis of HF with reduced EF because it is largely one of excluding other potential non-cardiac causes of symptoms suggestive of HF. Epidemiological studies indicate that varying severity of diastolic dysfunction is frequently present in asymptomatic population. \(^3\) Diastolic dysfunction is predicative of developing overt heart failure and all-cause mortality. \(^3,4\) Furthermore, there is increasing prevalence of HFpEF but no significant improvement in survival with time when compared to HF with reduced EF. \(^5,6\)

Index tests

Echocardiography is the cornerstone for the noninvasive evaluation and quantitation of diastolic dysfunction. \(^7,8\) Myocardial stiffness and relaxation abnormalities in diastolic dysfunction result in elevated LVFP that is indirectly evaluated by echocardiography. \(^7,8\)

Pulsed-wave Doppler technique is performed in the apical 4-chamber view to obtain peak early (E) and late (A) mitral inflow velocities, which primarily reflect pressure gradient between the left atrium and left ventricle during early and late diastolic filling, respectively. \(^7\) Tissue Doppler imaging (TDI) is implemented to acquire mitral annular velocities. \(^7,8\) In conjunction with mitral peak early filling velocity E, the ratio of E/e’ can be applied for the estimation of LVFP. \(^7\) The American Society of Echocardiography (ASE) guidelines suggest that LVFP is elevated when E/e’ > 12-15 (based on location) or normal when E/e’ < 8. \(^7,8\)

Reference tests

“Gold” or superior (standard) reference tests to evaluate LV diastolic function are based on invasive LV catheterization. These include LVFP measurements, LV relaxation time constant (tau) and parameters of LV myocardial and/or chamber stiffness. There are accepted cutoffs for each of invasive measurements, so that values above cutoff typically indicate elevated LVFP and/ LV diastolic dysfunction. For the LVFP, such cutoffs are LVEDP >16 mmHg or PCWP >12 mmHg; for LV myocardial wall diastolic relaxation time, it is Tau > 48 ms; for myocardial/chamber stiffness, corresponding cutoffs are based on specific parameter calculated. \(^7,8\)
Rationale

Despite the clinical importance of mitral flow and tissue Doppler parameters in evaluating diastolic dysfunction, there is lack of rigorous evaluation of their diagnostic accuracy when compared to invasive standards. Apart from routine clinical use, these echocardiographic indices are extensively used in clinical trials and applied research to assess the changes in LV diastolic function or LVFP. We therefore decided to evaluate diagnostic accuracy and clinical utility of E/e' in prediction LVFP and/or HFpEF.

Objectives

1. To perform a search of publications in medical scientific journals evaluating clinical evidence of the relationship between echocardiographic E/e’ and LV filling pressure, LV relaxation time constant or LV myocardium/chamber stiffness in preserved ejection fraction. We consider the invasive measurements of LV diastolic function as a reference test.
2. To summarize the clinical evidences/diagnostic accuracy of echocardiographic E/e’ for estimating LV filling pressure and the diagnosis of LVDD/HFpEF.

Methods

Study search methodology:

Original clinical studies that evaluate invasive parameters of diastolic function including LVFP and echocardiographic tissue Doppler E/e’ index at rest in patient cohorts with preserved ejection fraction will be screened and analyzed from PubMed, Scopus, Embase, and Cochrane databases (Figure 1). We will also review bibliography of important papers based on our clinical experience and book monographs. Only human medical studies published in English will be analyzed.

Search strategy:

We will develop the optimal search strategy for each library with assistance of UAB Reference Service of the UAB Lister Hill medical library.

Inclusion criteria for the studies:

The studies will be included if the study methodology stated that participants have preserved/normal LVEF (LVEF ≥40 %). For studies with mixed groups or studies with no a priori criteria for normal LVEF, the studies will be included if the dataset for LVEF corresponding to Mean-2SD ≥40 % is available or can be extracted. For a normal distribution, the latter condition assumes that about 98 % of participants have LVEF ≥ 40%. This approach allows for inclusion of all clinically relevant studies since LVEF threshold between 40-50% is typically used to distinguish normal/preserved LVEF from reduced LVEF group. However the inclusion of studies for primary and secondary analysis will be based on the outline described in the statistical section.

Exclusion criteria for studies:

Studies will be excluded if the study group has >10% of patients with moderate to severe valvular heart disease, cardiomyopathy (hypertrophic, restrictive), age < 18 years, congenital heart disease, acute coronary syndrome, septic shock, cardiac transplant, significant arrhythmias that precluded from interpretation of index and / or reference test and less than 10 participants with preserved EF. Studies will be excluded if study reference tests are only based on non-invasive criteria of LVDD/HFpEF.

Index tests:

Ratio of echocardiographic mitral flow and tissue Doppler derived parameter- E/e’ lateral, E/e’ septal or E/e’ mean.
Reference tests:

Invasive LVFP measurements of LV end diastolic pressure (LVEDP), LV mean diastolic pressure (LVMDP), LV Pre-A diastolic pressure (LV pre-A DP) or pulmonary capillary wedge pressure (PCWP); LV relaxation time constant (Tau); LV stiffness parameters.

Clinical diagnosis of LVDD/HFpEF confirmed based on clinical sign and symptoms with evidence of elevated LVFP or impaired LV relaxation/ chamber stiffness with or without additional biochemical markers and/or other ancillary tests.

Data collection and analysis:

Selection of studies:

Studies will be screened from the list of citation pooled from PubMed, Scopus, Embase, and Cochrane databases based on search criteria. Other sources would also be evaluated for additional studies. Initial screening includes the analysis of the title and abstract of the cited study to identify studies that could contain data of our interest. A full text of these studies will be evaluated. If the study does not fit our conditions after in-depth text evaluation, the reason for study exclusion will be documented. Disagreements between reviewers will be solved by discussion.

![Flowchart for Systematic review](image-url)
Inclusion and classification of studies:

Studies for primary analysis: The study contains either data of Pearson’s correlation(s) between E/e’ and reference standard(s) or the study contains data sufficient to create 2x2 diagnostic tables (true positive, false positive, false negative, true negative) for E/e’ cutoff(s) recommended by ASE to identify elevated/normal LVFP and LVDD/HFpEF. Such data is available for the participants with LVEF ≥ 50%.

Studies for supplemental analysis: 1) the study contains data required for the primary analysis but such data is available for the participants with LVEF ≥ 40%; 2) the study does not contain data sufficient to create 2x2 table for recommended by ASE E/e’ cutoffs but contains other valuable diagnostic data (ROC AUC value and/or optimal E/e’ cutoff value).

Data extraction:

Data will be extracted from selected studies according to a data collection form. Disagreements will be solved by consensus. Extracted information about evaluated studies and digital data will be input in the MS Word and Excel tables.

The following study information/digital data (what is available) will be collected:

1. PMID number (if available).
2. Year of publication.
3. Number of patients with preserved LVEF.
4. Mean age, mean LVEF or LVEF cutoff.
5. Number of males/females.
6. Number of patients with HFpEF, coronary artery disease, systemic hypertension, diabetes mellitus in study cohort.
7. Clinical indications for catheterization.
8. Index test(s).
9. Reference test(s).
10. Correlation size between echocardiographic index test values and invasive reference test values.
11. True positive, false positive, true negative, and false negative data for specific index and reference test cutoff.
12. ROC AUC values for specific reference test cutoff.

If data of interest not fully provided, additional calculations will be made to extract data of interest from graphical presentations and/or tables where available.

Assessment of methodological quality of evaluated studies:

Assessment of methodological quality of evaluated studies will be performed by a modified QUADAS-2 (see Appendix S3). Risk of bias will be tested for four domains which are patient selection, index test, reference test, and flow and timing; Applicability was tested for patient selection, index and reference test domains. This questionnaire is expanded to incorporate the findings from the study of Naaktgeboren et al, 2013 to include the risks of differential verification on index test accuracy in clinical study.

Statistical analysis and data synthesis:

Statistical methodology would be based on approaches described in Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Forest plots of sensitivity, specificity with 95% confidence intervals will be computed in OneMetaAnalyst. Heterogeneity amongst the studies will be estimated by I² statistic. The correlation will be classified as negligible when r is between 0 – 0.3, low when r is 0.3 – 0.5, moderate when r is 0.5 – 0.7 and high when r is 0.7 – 0.9. To obtain summary points taking into account within-study variability and between-study variability (heterogeneity), we will perform hierarchical summary receiver operating characteristic (HSROC) analysis. The Rutter and Gatsonis HSROC model will be constructed in OneMetaAnalyst for each category of diagnostic analysis. The summary sensitivity and specificity values will be also utilized to calculate the relationship of positive predictive value (diagnostic precision) with prevalence for elevated or normal LVFP ranging from 5% to 95%. The latter relationships will be compiled and graphed using Matlab R2013b. Additional statistical methodologies may be required based on discussion with experts in this field. We will also explore heterogeneity by using the different sources of heterogeneity as covariate(s) in HSROC analysis. Emphasis will be placed on evaluating the robustness of evidence and its clinical applicability taking into account expected heterogeneity in the studies.
Sensitivity analysis:

We will perform secondary analyses including forest plots, HSROC analysis and summary estimates of sensitivity and specificity for the subgroups of studies if a sufficient number of studies are present for identified subgroups.

References:

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| Search 1 | diastol* AND (echo* OR Doppl* OR ultrasound* OR acous*). Limits: English, Journal Article, Humans. Time range: 1/1/1980 - 11/14/2013 (identified 12733 document citations). |
|---------|--------------------------------------------------------------------------------------------------|
| Search 2 | diastol* AND catheter* AND Doppler* AND pressure. Limits: English, Journal Article, Humans. Time range: 1/1/1970 - 04/28/2014 (identified 738 document citations [551 new and 187 duplicates]) |
| Search 3 | echocardiography AND tissue doppler AND catheterization. Limits: English. Time range: not specified - 02/06/2015 (identified 503 document citations [291 new and 212 duplicates]) |
| Search 4 | (ventric* pressure*) OR "ventricular pressure"[MeSH Terms] OR "ventricular dysfunction"[MeSH Terms] AND (Doppler* OR E/e* OR "echocardiography, doppler"[MeSH Terms]). Limits: English. Time range: not specified - 02/16/2015 (identified 9776 document citations [5216 new and 4560 duplicates]). All studies of our interest, which were selected from the results of Searches 1, 2, and 3 in PubMed, were also identified in the document citations of the Search 4. |

| Search 1 | (TITLE-ABS-KEY (echocardiography) OR TITLE-ABS-KEY (tissue Doppler) AND TITLE-ABS-KEY (catheterization) AND DOCTYPE ("ar") AND SUBJAREA (mult OR agri OR bioc OR immu OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND (LIMIT-TO (LANGUAGE, "English"))). Time range: not specified - 02/06/2015 (identified 512 document citations [167 new and 345 PubMed duplicates]) |
|---------|--------------------------------------------------------------------------------------------------|
| Search 2 | (TITLE-ABS-KEY (ventric* pressure*) OR TITLE-ABS-KEY (ventricular dysfunction) AND TITLE-ABS-KEY (doppler*) OR TITLE-ABS-KEY (e/e*) OR TITLE-ABS-KEY (echocardiography,doppler)) AND SUBJAREA (mult OR medi OR nurs OR vete OR dent OR heal) AND NOT INDEX (medline), AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SUBJAREA, "MEDI")) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "cp")). Time range: not specified - 02/16/2015 (identified 1413 document citations, as not indexed in Medline) |

| Search 1 | (ventric* near/2 pressure or ventric* near/3 'diastolic pressure' or ventric* near/3 'filling pressure' or 'ventricular pressure'/exp or 'ventricular pressure' or 'ventricular dysfunction'/exp or 'diastolic heart failure'/exp or 'diastolic heart failure' or 'heart failure with normal' or 'heart failure with preserved' and ('doppler' or 'e/e' or 'echocardiography doppler'/exp or 'echocardiography doppler') and ([article]/lim or [article in press]/lim or [conference paper]/lim or [letter]/lim) and [english]/lim and [embase]/lim) and [embase]/lim and not [medline]/lim. Time range: not specified - 03/05/2015 (identified 594 document citations, as not indexed in Medline) |

Cochrane Library (March 2015) (total of 48 original citations (conference abstracts))

| Search 1 | "filling pressure" AND "Doppler" (gives 78 citations [5 new and 73 duplicates]) |
|---------|----------------------------------------------------------------------------------|
| Search 2 | "filling pressure" AND "E/e" (gives 42 citations [6 new and 36 duplicates]) |
| Search 3 | "diastolic dysfunction" AND "e/e" (gives 46 citations [10 new and 36 duplicates]) |
| Search 4 | "diastolic dysfunction" AND "tissue Doppler" (gives 70 citations [26 new and 44 duplicates]) |
| Search 5 | "diagnostic accuracy" AND "diastolic dysfunction" (gives 3 citations [0 new and 3 duplicates]) |
| Search 6 | "diagnostic accuracy" AND "diastolic heart failure" (gives 0 citations [0 new and 0 duplicates]) |
| Search 7 | "diagnostic accuracy" AND "tissue doppler" (gives 6 citations [1 new and 5 duplicates]) |
| Search 8 | "diagnostic accuracy" AND "E/e" (gives 2 citations [0 new and 2 duplicates]) |
APPENDIX 3

TOOL FOR ASSESSMENT OF RISK OF BIAS AND APPLICABILITY

(Modified from QUADAS-2 publications listed in the end)

PMID:  
Title:  
Reviewer:  
Date:  
Group  
Primary/Supplemental  

Note: Intent is to evaluate the paper to assess application for our study question (and not to critique the paper)

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Description:

| Study Design          | Case-Control | Cross-Sectional | Cohort | Randomized Control Trial |
|-----------------------|--------------|-----------------|--------|--------------------------|
| Data Collection       | Prospective  | Retrospective   | Unknown|
| Setting of patient selection | Clinic/ Cath lab/Echo/ ER/ ICU/ In-hospital/ Out-patient/ Community/ Others |
| Clinical characterization | complete data sheet (appendix A) |

Signaling Questions:

Was a consecutive sample of patients enrolled?  Yes/No/Unclear
Was a case-control design avoided?  Yes/No/Unclear
Did the study avoid inappropriate exclusions? (confirmed cases of diastolic dysfunction)  Yes/No/Unclear
Did the study avoid inappropriate inclusions (valvular heart disease, HCM, RCM, Afib)?  Yes/No/Unclear
Could the selection of patients have introduced bias?  RISK: LOW /HIGH/UNCLEAR

Comments: specify why bias

B. Concerns regarding applicability

Consider prior testing, presentation, intended use of index test and setting, severity of the target condition, demographic features, co-morbidities, preserved LVEF patients mixed with depressed LVEF patients

Is there concern that the included patients do not match our study question?  CONCERN: LOW /HIGH/UNCLEAR

Comments: specify why bias

DOMAIN 2: INDEX TEST: E/e’ lateral/septal/mean

A. Risk of Bias

Were the index test results interpreted without knowledge of the results of the reference standard?  Yes/No/Unclear
(Yes only if specific mention of blinding/averaging of several measurements)
If a threshold was used, was it pre-specified?  Yes/No/Unclear/ Not applicable
Could the conduct or interpretation of the index test have introduced bias?  RISK: LOW/ HIGH/UNCLEAR

Comments: specify why bias
**A. Risk of Bias**

Is the reference standard likely to correctly classify the target condition?  
Yes/No/Unclear

Were the reference standard results interpreted without knowledge of the results of the index test?  
Yes/No/Unclear

If 2, was there a partial verification bias?  
Yes/No/Unclear/ Not applicable

Was the use of reference standard only dependent on the results of the index test?  
Yes/No/Unclear

Was reference standard not applied to a large percentage of the participants?  
Yes/No/Unclear

If 3, was composite reference standard/panel diagnosis used?  
Yes/No/ Not applicable

If 4, was there Differential Verification bias?  
Yes/No/ Unclear/ Not applicable

Was the choice of reference standard completely dependent on the results of the index test?  
Yes/No/Unclear

If the answer to the first question is no, how accurate is the inferior reference standard?  
Yes/No/Unclear

Was large percentage of the participants diagnosed by use of the inferior reference standard?  
Yes/No/Unclear

If follow-up is used as the inferior reference standard, does it identify almost all hidden cases present at the time of the index test but very few new cases that develop afterward? Does follow-up detect the same type of cases as the preferred reference standard?  
Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias regarding our study question? RISK: LOW /HIGH/UNCLEAR

Comments: specify why bias

**B. Concerns regarding applicability:**

Was consistent Definition of Target Condition used?  
Yes/No/Unclear

Were there concerns regarding Test technology?  
Yes/No/Unclear

Were there concerns regarding Test execution?  
Yes/No/Unclear

Is there concern that the test condition as defined by the reference standard does not match the study question? CONCERN: LOW /HIGH/UNCLEAR

Comments: specify why bias
DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
Did all patients receive a reference standard? Yes/No/Unclear
Did patients receive the same reference standard? Yes/No/Unclear
Were all patients included in the analysis? Yes/No/Unclear
Could the patient flow have introduced bias related to our study question? RISK: LOW /HIGH/UNCLEAR

Comments: specify why bias

Appendix A: Data sheet

Sample Size: Overall
Sample Size for Preserved EF
What was LVEF criterion for preserved EF:
Clinical characteristics of Preserved LVEF:

| Variable                        | Yes | No | Not Quantified | Comments |
|---------------------------------|-----|----|----------------|----------|
| Number                          | (%) |    |                |          |
| Dyspnea                         |     |    |                |          |
| NYHA class                      |     |    |                |          |
| 6 MWD                           |     |    |                |          |
| Chest Pain                      |     |    |                |          |
| Exercise stress test            |     |    |                |          |
| Left Ventricular Hypertrophy    |     |    |                |          |
| Heart Failure                   |     |    |                |          |
| BNP                             |     |    |                |          |
| Ethnicity/ Race                 |     |    |                |          |
| Gender                          |     |    |                |          |
| Age                             |     |    |                |          |
| Body Habitus (weight, BSA, BMI) |     |    |                |          |
| Habits (smoking, Etoh, Drugs)   |     |    |                |          |
| Co morbidities                  |     |    |                |          |
| Hypertension                    |     |    |                |          |
| Diabetes                        |     |    |                |          |
| CAD                             |     |    |                |          |
| CKD                             |     |    |                |          |
| Sleep Apnea                     |     |    |                |          |
| COPD                            |     |    |                |          |
| Obesity                         |     |    |                |          |
| Medications                     |     |    |                |          |
| Socio Economic Status           |     |    |                |          |
| (education, salary etc)         |     |    |                |          |

References
1. Whiting PF et at Quadas 2 Annals of Internal Medicine 2011, 155: 529
2. Whiting PF et al J of clinical Epidemiology 2013, 66: 1093
3. Naaktgeboren et al Annals of Internal Medicine 2013: 159: 195
4. Groot et al. BMJ 2011;343:d4770
### APPENDIX 4

**Full-text studies excluded with the reasons**

Studies are identified with PMID (if available)

**TEE approach:**

|   |   |   |
|---|---|---|
| 1 | 8078825 |   |
| 2 | 9052288 |   |
| 3 | 12356384 |   |
| 4 | 23190400 |   |

**LVEF not specified**

|   |   |   |
|---|---|---|
| 5 | 1905874 |   |
| 6 | 1985353 |   |
| 7 | 1987211 |   |
| 8 | 2214134 |   |
| 9 | 2278168 |   |
| 10 | 2360494 |   |
| 11 | 2498005 |   |
| 12 | 2683699 |   |
| 13 | 2782257 |   |
| 14 | 2871286 |   |
| 15 | 2958532 |   |
| 16 | 3177175 |   |
| 17 | 3209254 |   |
| 18 | 7730680 |   |
| 19 | 7771173 |   |
| 20 | 7817903 |   |
| 21 | 8319326 |   |
| 22 | 8496538 |   |
| 23 | 8606285 |   |
| 24 | 8933237 |   |
| 25 | 9046493 |   |
| 26 | 9237029 |   |
| 27 | 9247521 |   |
| 28 | 10149211 |   |
| 29 | 10969625 |   |
| 30 | 11368862 |   |

**Data available only for mixed LVEF group (extraction of data for LPvEF patients not possible)**

|   |   |   |
|---|---|---|
| 31 | 11593199 |   |
| 32 | 11884251 |   |
| 33 | 12487633 |   |
| 34 | 16195393 |   |
| 35 | 18325734 |   |
| 36 | 24319341 |   |
| 37 | 1827808 |   |
| 38 | 7780619 |   |
| 39 | 8736006 |   |
| 40 | 1607511 |   |
| 41 | 3392336 |   |
| 42 | 8245357 |   |
| 43 | 8557907 |   |
| 44 | 9015003 |   |
| 45 | 10913476 |   |
| 46 | 10913478 |   |
| 47 | 11279327 |   |
| 48 | 11391284 |   |
| 49 | 11560356 |   |
| 50 | 11770447 |   |
| 51 | 11968390 |   |
| 52 | 12487633 |   |
| 53 | 14563593 |   |
| 54 | 14652601 |   |
| 55 | 15653227 |   |
| 56 | 15891754 |   |
| 57 | 16500488 |   |
| 58 | 16516591 |   |
| 59 | 16682317 |   |
| 60 | 20197576 |   |

**Data available only for low LVEF group**

|   |   |   |
|---|---|---|
| 61 | 23103948 |   |
| 62 | 18986412 |   |
| 63 | 19168324 |   |
| 64 | 19560662 |   |
| 65 | 18612440 |   |
| 66 | 18635276 |   |
| 67 | 18771556 |   |
| 68 | 17069599 |   |
| 69 | 17196474 |   |
| 70 | 17451867 |   |
| 71 | 17484986 |   |
| 72 | 17541761 |   |
| 73 | 17652894 |   |
| 74 | 17658724 |   |
| 75 | 17884382 |   |
| 76 | 18514937 |   |
| 77 | 18538465 |   |
| 78 | 16682317 |   |
| 79 | 16682317 |   |
| 80 | 17560894 |   |
| 81 | 21245360 |   |
| 82 | 22567531 |   |

**No results of our interest:**

|   |   |   |
|---|---|---|
| 83 | Moladoust H. et al, Echocardiography: A Jnl. of CV Ultrasound & Allied Tech. (2009) 26 (4), 403-411 |   |
| 84 | Said K. et al, The Egyptian Heart Journal (2012) 64, 69-74 |   |
| 85 | 11944011 |   |
| 86 | 19602775 |   |

**Moladoust H. et al, Echocardiography: A Jnl. of CV Ultrasound & Allied Tech. (2009) 26 (4), 403-411**

**Said K. et al, The Egyptian Heart Journal (2012) 64, 69-74**
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 120. | 9043850 | 162. | 15781734 | 204. | 16803936 | 244. | 23316319 | 255. | 3280641 |
| 121. | 9104907 | 163. | 15948097 | 205. | 16970713 | 245. | 11796546 |
| 122. | 9137220 | 164. | 16016464 | 206. | 24839086 | 246. | 11263606 |
| 123. | 9203493 | 165. | 16229380 | 207. | 10440167 | 247. | 11263607 |
| 124. | 9424066 | 166. | 16284230 | 208. | 11175032 | 248. | 11270316 |
| 125. | 9950969 | 167. | 16344121 | 209. | 11595603 | 249. | 11585994 |
| 126. | 10230946 | 168. | 16434758 | 210. | 12714167 | 250. | 23582091 |
| 127. | 10441218 | 169. | 16575023 | 211. | 15307890 | 251. | 10636281 |
| 128. | 10980082 | 170. | 16949491 | 212. | 16171419 | 252. | 10849514 |
| 129. | 11158951 | 171. | 17207727 | 213. | 24621836 | 253. | 10910486 |
| 130. | 11407738 | 172. | 17313636 | 214. | 24839086 | 254. | 11079674 |
| 131. | 11408426 | 173. | 17390199 | 215. | 24943993 | 216. | 24954460 |
| 132. | 11433812 | 174. | 17394966 | 217. | 24958524 | 218. | 25249511 |
| 133. | 11433813 | 175. | 17488411 | 219. | 25441329 | 220. | 25510308 |
| 134. | 11433824 | 176. | 18198205 | 221. | 21602549 | 222. | 23883877 |
| 135. | 11482709 | 177. | 18471459 | 223. | 24869961 | 224. | 24902871 |
| 136. | 11490324 | 178. | 18597919 | 225. | Cong T. et al, Experimental & Clinical Cardiology (2014) 20 (1), 2479-2490 |
| 137. | 11550110 | 179. | 19203992 | 226. | 2296893 |
| 138. | 11585994 | 180. | 20058507 | 227. | 2672760 |
| 139. | 11593203 | 181. | 20553318 | 228. | 15325936 |
| 140. | 11696830 | 182. | 20625213 | 229. | 9247519 |
| 141. | 11796872 | 183. | 20682947 | 230. | 3177234 |
| 142. | 11809440 | 184. | 20970305 | 231. | 2360518 |
| 143. | 11917193 | 185. | 21262980 | 232. | 2913110 |
| 144. | 12094170 | 186. | 21316304 | 233. | 7710749 |
| 145. | 12707119 | 187. | 21426391 | 234. | 9385913 |
| 146. | 12714167 | 188. | 21683506 | 235. | 2360518 |
| 147. | 12766750 | 189. | 22577437 | 236. | 2913110 |
| 148. | 12804750 | 190. | 22705767 | 237. | 7710749 |
| 149. | 12848693 | 191. | 22739787 | 238. | 9385913 |
| 150. | 12940700 | 192. | 23146480 | 239. | 11153819 |
| 151. | 14640103 | 193. | 23194487 | 240. | 15389248 |
| 152. | 14641374 | 194. | 23689521 | 241. | 18091642 |
| 153. | 14652600 | 195. | 23879336 | 242. | 20609653 |
| 154. | 14670073 | 196. | 24319341 | 243. | 21723693 |
| 155. | 14672750 | 197. | 22066607 | 244. | 11179524 |
| 156. | 14717717 | 198. | 2705380 | 245. | 15084546 |
| 157. | 14752488 | 199. | 9183590 | 246. | 17291934 |
| 158. | 15172419 | 200. | 11502702 | 247. | 22645191 |
| 159. | 15309696 | 201. | 12167386 | 248. |   |
| 160. | 15476639 | 202. | 15979445 | 249. |   |
| 161. | 15480886 | 203. | 16174119 | 250. |   |

Patients with comorbidities
(excluded from our analysis)

255. 3280641
256. 1869739
257. 11121596
258. 21718357
259. 18636341
260. 22473456
261. 23555178
262. 24334557
263. 11093099
264. 22632828
265. 23628301
266. 25611697
267. 23074579
268. 23940422
269. 24626519
270. 24995376
271. 25414078
272. Wang W. et al, Acta Cardiol Sin (2012), 28, 206-215
273. Ahn J. et al, e-Herz (2013), DOI 10.1007/s00059-013-4010-0
274. 21718351

Repetitive data

275. 20813283
5.1. Subgroup analysis for E/e’ lateral and LVFP

E/e’ lateral: Dataset for subgroup analysis (see also Tables 1 and 2)

| LVFP | r     | se    | Data          | Timing         | % HFpEF | % CAD | % HTN | % DM | Indication for cath |
|------|-------|-------|---------------|----------------|---------|-------|-------|------|---------------------|
| LVEDP Kidawa et al, 2005 (24) | 0.58  | 0.118 | Primary       | Simultaneously | unclear | unclear | unclear | unclear | angiography          |
| LVEDP Manouras et al, 2013 (48) EF>55% | 0.33  | 0.157 | Primary       | Simultaneously | unclear | no CAD | unclear | unclear | angiography          |
| LVEDP Kasner et al, 2010 (37) | 0.57  | 0.148 | Primary       | Simultaneously | ~60% HF | no CAD | ~60% HTN | ~10% DM | dyspnea/angio        |
| LVEDP Previtali et al, 2012 (46) | 0.1   | 0.134 | NOT Simultan. | no HF         | unclear | unclear | unclear | unclear | angiography          |
| LVEDP Hadano et al, 2005 (23) | 0.41  | 0.115 | Primary       | NOT Simultan. | unclear | some CAD | unclear | unclear | angiography          |
| LVEDP Kasner et al, 2007 (26) | 0.71  | 0.097 | Primary       | NOT Simultan. | ~80% HF | no CAD | ~60% HTN | ~10% DM | dyspnea/angio        |
| LVEDP Özer et al, 2011 (43) | 0.3   | 0.145 | Primary       | NOT Simultan. | unclear | all CAD | ~60% HTN | ~40% DM | angiography          |
| LVEDP Hajahmadi Poorrafsanjani et al, 2014 (50) | 0.4   | 0.107 | Primary       | NOT Simultan. | unclear | unclear | unclear | unclear | angiography          |
| LVMDP Ommen et al, 2000 (15) | 0.4   | 0.127 | Primary       | Simultaneously | unclear | unclear | unclear | unclear | angiography          |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
Heterogeneity amongst the studies was estimated by I² statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
D. PCWP (simultaneous and NOT simultaneous)

| Studies                          | Estimate (95% C.I.) |
|----------------------------------|---------------------|
| Rivas–Gott et al, 2003 (18)      | 0.700 (0.508, 0.922) |
| Nagaseh et al, 1998 (14)         | 0.720 (0.522, 0.918) |
| Subgroup Simultaneously (I²=0 %, P=0.887) | 0.710 (0.572, 0.848) |
| Maeder et al, 2011 (42)          | -0.040 (-0.376, 0.296) |
| Gonzalez–Vitchez et al, 2002 (16)| 0.540 (0.239, 0.841)  |
| Hadano et al, 2005 (23)          | 0.540 (0.332, 0.748)  |
| Subgroup NOT Simultaneously (I²=78.01 %, P=0.011) | 0.363 (0.020, 0.706) |
| Overall (I²=76.06 %, P=0.002)    | 0.520 (0.304, 0.737)  |

E. Pre-A (primary and supplemental data)

| Studies                          | Estimate (95% C.I.) |
|----------------------------------|---------------------|
| Previtali et al, 2012 (46)       | 0.110 (-0.153, 0.373) |
| Manouras et al, 2013 (48) EF>55% | 0.400 (0.100, 0.700)  |
| Mansencal et al, 2004 (20)       | 0.180 (-0.274, 0.634) |
| Hsiao et al, 2011 (40)           | 0.230 (0.037, 0.423)  |
| Subgroup Primary (I²=0 %, P=0.566) | 0.228 (0.096, 0.360) |
| Poerner et al, 2003 (17) E/A>0.9 | 0.490 (0.302, 0.678)  |
| Subgroup Supplemental (I²=NA, P=NA) | 0.490 (0.302, 0.678) |
| Overall (I²=43.5 %, P=0.132)     | 0.302 (0.150, 0.454)  |

F. Pre-A (simultaneous and NOT simultaneous)

| Studies                          | Estimate (95% C.I.) |
|----------------------------------|---------------------|
| Manouras et al, 2013 (48) EF>55% | 0.400 (0.100, 0.700) |
| Subgroup Simultaneously (I²=NA, P=NA) | 0.400 (0.100, 0.700) |
| Previtali et al, 2012 (46)       | 0.110 (-0.153, 0.373) |
| Mansencal et al, 2004 (20)       | 0.180 (-0.274, 0.634) |
| Hsiao et al, 2011 (40)           | 0.230 (0.037, 0.423)  |
| Poerner et al, 2003 (17) E/A>0.9 | 0.490 (0.302, 0.678)  |
| Subgroup NOT Simultaneously (I²=55.4 %, P=0.081) | 0.278 (0.092, 0.464) |
| Overall (I²=43.5 %, P=0.132)     | 0.302 (0.150, 0.454)  |
For combined LVFP analysis, if the study measured two LVFP parameters we chose one that had the highest correlation coefficient.

G. $E/e'_\text{\textit{lateral}}$: combined LVFP – (primary and supplemental data)

| Studies                                                                 | Estimate (95% C.I.) |
|------------------------------------------------------------------------|---------------------|
| LVMDP Ommen et al, 2000 (15)                                           | 0.400 (0.180, 0.620) |
| LVEDP Kidawa et al, 2005 (24)                                          | 0.580 (0.349, 0.811) |
| LVEDP Krasner et al, 2010 (37)                                         | 0.570 (0.280, 0.860) |
| PCWP Rivas-Goetz et al, 2003 (18)                                      | 0.700 (0.508, 0.892) |
| Pre-A Manouras et al, 2013 (48) EF>55%                                 | 0.400 (0.192, 0.608) |
| LVEDP Ozer et al, 2011 (43)                                            | 0.300 (0.016, 0.584) |
| Pre-A Mansencal et al, 2004 (20)                                       | 0.190 (-0.275, 0.635) |
| LVEDP Hajjmosadi Poumatsanani et al, 2014 (50)                         | 0.400 (0.220, 0.582) |
| PCWP Maeder et al, 2011 (42)                                           | -0.040 (-0.375, 0.295) |
| PCWP Gonzalez–Vidoch et al, 2002 (16)                                  | 0.540 (0.238, 0.842) |
| Pre-A Previtali et al, 2012 (46)                                       | 0.110 (-0.153, 0.373) |
| LVEDP Krasner et al, 2007 (26)                                         | 0.710 (0.520, 0.900) |
| PCWP Hadano et al, 2005 (23)                                           | 0.540 (0.332, 0.748) |
| Subgroup Primary ($I^2=64.6\%, P=0.001$)                              | 0.440 (0.325, 0.555) |
| PCWP Naghavi et al, 1998 (14) EF>45% Sinus Tachycardia >100bpm         | 0.720 (0.522, 0.918) |
| Pre-A Poerner et al, 2003 (17) E/A=0.9                                 | 0.490 (0.302, 0.678) |
| LVEDP Yesildag et al, 2011 (44) EF>40%                                 | 0.740 (0.487, 0.993) |
| Subgroup Supplemental ($I^2=65.17\%, P=0.161$)                       | 0.639 (0.475, 0.803) |
| Overall ($I^2=64.84\%, P=0.000$)                                      | 0.483 (0.382, 0.583) |

H. $E/e'_\text{\textit{lateral}}$: combined LVFP – (simultaneous and NOT simultaneous)

| Studies                                                                 | Estimate (95% C.I.) |
|------------------------------------------------------------------------|---------------------|
| LVMDP Ommen et al, 2000 (15)                                           | 0.400 (0.180, 0.620) |
| LVEDP Kidawa et al, 2005 (24)                                          | 0.580 (0.349, 0.811) |
| LVEDP Krasner et al, 2010 (37)                                         | 0.570 (0.280, 0.860) |
| PCWP Rivas-Goetz et al, 2003 (18)                                      | 0.700 (0.508, 0.892) |
| Pre-A Manouras et al, 2013 (48) EF>55%                                 | 0.400 (0.192, 0.608) |
| Subgroup Simultaneously ($I^2=43.49\%, P=0.115$)                     | 0.556 (0.447, 0.685) |
| LVEDP Ozer et al, 2011 (43)                                            | 0.300 (0.016, 0.584) |
| Pre-A Mansencal et al, 2004 (20)                                       | 0.180 (-0.275, 0.635) |
| LVEDP Hajjmosadi Poumatsanani et al, 2014 (50)                         | 0.400 (0.190, 0.610) |
| PCWP Maeder et al, 2011 (42)                                           | -0.040 (-0.375, 0.295) |
| Pre-A Poerner et al, 2003 (17) E/A=0.9                                 | 0.400 (0.202, 0.598) |
| PCWP Gonzalez–Vidoch et al, 2002 (16)                                  | 0.540 (0.238, 0.842) |
| Pre-A Previtali et al, 2012 (46)                                       | 0.110 (-0.153, 0.373) |
| LVEDP Yesildag et al, 2011 (44) EF>40%                                 | 0.740 (0.497, 0.993) |
| LVEDP Krasner et al, 2007 (26)                                         | 0.710 (0.520, 0.900) |
| PCWP Hadano et al, 2005 (23)                                           | 0.540 (0.322, 0.748) |
| Subgroup NOT Simultaneously ($I^2=70.63\%, P=0.000$)                 | 0.422 (0.274, 0.569) |
| Overall ($I^2=64.84\%, P=0.000$)                                      | 0.493 (0.382, 0.583) |
I. \(E/e'_{\text{lateral}}\): combined LVFP – (HFpEF prevalence)

| Studies | Estimate (95% C.I.) |
|---------|---------------------|
| Pre-A Previtali et al. 2012 (46) | 0.110 (-0.153, 0.373) |
| Pre-A Mansencal et al. 2004 (20) | 0.180 (-0.275, 0.635) |
| PCWP Maeder et al. 2011 (42) | -0.040 (-0.375, 0.295) |
| LVEDP Kasner et al. 2010 (37) | 0.570 (0.280, 0.860) |

J. \(E/e'_{\text{lateral}}\): combined LVFP – (CAD prevalence)

| Studies | Estimate (95% C.I.) |
|---------|---------------------|
| Pre-A Mansencal et al. 2004 (20) | 0.180 (-0.275, 0.635) |
| LVEDP Ozer et al. 2011 (43) | 0.300 (0.016, 0.584) |
| Subgroup All CAD (I^2=0 %, P=0.661) | 0.266 (0.025, 0.507) |
| PCWP Hadano et al. 2005 (23) | 0.540 (0.332, 0.748) |
| LVEDP Kasner et al. 2010 (37) | 0.570 (0.280, 0.860) |
| Subgroup Some CAD (I^2=20 %, P=0.098) | 0.400 (0.192, 0.608) |
| Overall (I^2=48.41 %, P=0.084) | 0.489 (0.346, 0.633) |

K. \(E/e'_{\text{lateral}}\): Primary data variables measured simultaneously (shown as table 4B in the main text)

| Studies | Estimate (95% C.I.) |
|---------|---------------------|
| LVMDP Ommen et al. 2000 (15) | 0.460 (0.189, 0.620) |
| LVMDP Kidawa et al. 2005 (24) | 0.560 (0.349, 0.811) |
| LVEDP Kasner et al. 2010 (37) | 0.570 (0.280, 0.860) |
| LVEDP Manouras et al. 2013 (48) EF55 % | 0.330 (0.022, 0.638) |
| Subgroup LVEDP (I^2=40 %, P=0.401) | 0.513 (0.357, 0.669) |
| PCWP Rivas-Gotz et al. 2003 (18) | 0.760 (0.508, 0.922) |
| Subgroup PCWP (I^2=20 %, P=0.178) | 0.508 (0.390, 0.626) |
### 5.2. Subgroup analysis for E/e’_{septal} and LVFP

**E/e’_{septal}: Dataset for subgroup analysis (see also Tables 1 and 2)**

| LVFP | r   | se  | Data   | Timing      | % HfEF | % CAD | % HTN | % DM | Indication for cath               |
|------|-----|-----|--------|-------------|--------|-------|-------|------|-----------------------------------|
| LVEDP |     |     |        |             |        |       |       |      |                                   |
| LVEDP Manouras et al, 2013 (48) EF>55% | 0.03 | 0.167 | Primary | Simultaneously       | unclear | no CAD | unclear | unclear | angiography                      |
| LVEDP Kidawa et al, 2005 (24)        | 0.29 | 0.138 | Primary | Simultaneously       | unclear | unclear | unclear | unclear | angiography                      |
| LVEDP Previtali et al, 2012 (46)     | 0.22 | 0.132 | Primary | NOT Simultan.       | no HF   | unclear | unclear | unclear |                                  |
| LVEDP Özer et al, 2011 (43)          | 0.54 | 0.128 | Primary | NOT Simultan.       | unclear | all CAD  | ~60% HTN | ~40% DM | angiography                      |

| PCWP |     |     |        |             |        |       |       |      |                                   |
|------|-----|-----|--------|-------------|--------|-------|-------|------|-----------------------------------|
| PCWP Rivas-Gotz et al, 2003 (18) | 0.55 | 0.115 | Primary | Simultaneously       | unclear | unclear | unclear | unclear | ICU/Cath lab                      |
| PCWP Maeder et al, 2011 (42)        | 0.23 | 0.167 | Primary | NOT Simultan.       | ~40% HF | unclear | unclear | unclear | HF/PAH/volunteers                 |
| PCWP Tatsumi et al, 2014 (51)       | 0.64 | 0.172 | Primary | NOT Simultan.       | unclear | unclear | unclear | unclear |                              |

| Pre-A |     |     |        |             |        |       |       |      |                                   |
|-------|-----|-----|--------|-------------|--------|-------|-------|------|-----------------------------------|
| Pre-A Manouras et al, 2013 (48) EF>55% | 0.02 | 0.161 | Primary | Simultaneously       | unclear | no CAD | unclear | unclear | angiography                      |
| Pre-A Previtali et al, 2012 (46)     | 0.28 | 0.129 | Primary | NOT Simultan.       | no HF   | unclear | unclear | unclear |                                  |
| Pre-A Hsiao et al, 2011 (40)         | 0.31 | 0.096 | Primary | NOT Simultan.       | unclear | all CAD  | ~70% HTN | ~50% DM | angiography                      |

| LVMDP |     |     |        |             |        |       |       |      |                                   |
|-------|-----|-----|--------|-------------|--------|-------|-------|------|-----------------------------------|
| LVMDP Ommen et al, 2000 (15)         | 0.47 | 0.112 | Primary | Simultaneously       | unclear | unclear | unclear | unclear |                                  |
| LVMDP Rudko et al, 2008 (32)         | 0.47 | 0.145 | Primary | Simultaneously       | ~20% HF | ~80% CAD | ~50% HTN | unclear |                                  |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre-A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HfEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
Heterogeneity amongst the studies was estimated by I² statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
E. Pre-A (primary and supplemental data)

| Studies                        | Estimate (95% C.I.) |
|-------------------------------|---------------------|
| Hsiao et al, 2011 (40)        | 0.310 (0.122, 0.498) |
| Previtali et al, 2012 (46)    | 0.280 (0.026, 0.534) |
| Manours et al, 2013 (48) EF>55%| 0.020 (-0.296, 0.336) |
| Subgroup Primary (I²=19.47 % , P=0.289) | 0.239 (0.084, 0.395) |
| Poerner et al, 2003 (17)      | 0.400 (0.203, 0.597) |
| Subgroup Supplemental (I²=NA , P=NA) | 0.400 (0.203, 0.597) |
| Overall (I²=25.82 % , P=0.257) | 0.288 (0.155, 0.421) |

F. Pre-A (simultaneous and NOT simultaneous)

| Studies                        | Estimate (95% C.I.) |
|-------------------------------|---------------------|
| Manours et al, 2013 (48) EF>55%| 0.020 (-0.296, 0.336) |
| Subgroup Simultaneously (I²=NA , P=NA) | 0.020 (-0.296, 0.336) |
| Hsiao et al, 2011 (40)        | 0.310 (0.122, 0.498) |
| Previtali et al, 2012 (46)    | 0.280 (0.026, 0.534) |
| Poerner et al, 2003 (17)      | 0.400 (0.203, 0.597) |
| Subgroup NOT Simultaneously (I²=0 % , P=0.717) | 0.337 (0.217, 0.457) |
| Overall (I²=25.82 % , P=0.257) | 0.288 (0.155, 0.421) |

SUBGROUP ANALYSIS for COMBINED LVFP and E/e’ septal

For combined LVFP analysis, if the study measured two LVFP parameters we chose that had the highest correlation coefficient.

G. E/e’ septal: combined LVFP (primary and supplemental data)

| Studies                        | Estimate (95% C.I.) |
|-------------------------------|---------------------|
| LVEDP Özer et al, 2011 (43)   | 0.540 (0.289, 0.791) |
| LVEDP Manours et al, 2013 (48) EF>55% | 0.030 (-0.297, 0.357) |
| Pre–A Previtali et al, 2012 (46) | 0.280 (0.027, 0.533) |
| LVEDP Kitawa et al, 2005 (24) | 0.290 (0.020, 0.560) |
| LVMDP Ommen et al, 2000 (15)  | 0.470 (0.250, 0.690) |
| PCWP Maeder et al, 2011 (42)  | 0.230 (-0.097, 0.557) |
| PCWP Tatsumi et al, 2014 (51) | 0.640 (0.303, 0.977) |
| PCWP Rivas–Gotz et al, 2003 (18) | 0.550 (0.325, 0.775) |
| Pre–A Hsiao et al, 2011 (40)  | 0.310 (0.122, 0.498) |
| LVMDP Rudko et al, 2008 (32)  | 0.470 (0.186, 0.754) |
| Subgroup Primary (I²=34.63 % , P=0.132) | 0.389 (0.287, 0.490) |
| LVEDP Yesildag et al, 2011 (44) EF>40% | 0.730 (0.471, 0.989) |
| Pre–A Poerner et al, 2003 (17) E/A>0.9 | 0.400 (0.202, 0.598) |
| LVEDP Min et al, 2007 (27) B<E/e’<15 | 0.030 (-0.239, 0.299) |
| Subgroup Supplemental (I²=86.23 % , P=0.001) | 0.388 (0.027, 0.750) |
| Overall (I²=56.03 % , P=0.007) | 0.388 (0.281, 0.495) |
H. E/e' septal: combined LVFP (simultaneous and NOT simultaneous)

Studies                         Estimate (95% C.I.)
LVEDP Manouras et al, 2013 (48) EF>55% 0.030 (-0.297, 0.357)
LVEDP Kidawa et al, 2005 (24) 0.290 (0.020, 0.560)
LV/MDP Ommen et al, 2000 (15) 0.470 (0.050, 0.890)
LV/MDP Rivas–Goltz et al, 2003 (18) 0.550 (0.325, 0.775)
LV/MDP Rudko et al, 2008 (32) 0.470 (0.186, 0.754)
LV/EDP Min et al, 2007 (27) 0.020 (-0.229, 0.269)
Subgroup Simultaneously (I^2=64.71 %, P=0.015) 0.321 (0.146, 0.501)
LV/EDP Ozer et al, 2011 (43) 0.540 (0.289, 0.791)
Pre–A Previati et al, 2012 (46) 0.280 (0.027, 0.533)
PCWP Maeder et al, 2011 (42) 0.230 (-0.097, 0.557)
PCWP Tatsumi et al, 2014 (51) 0.640 (0.303, 0.977)
Pre–A Hsiao et al, 2011 (40) 0.310 (-0.122, 0.498)
LV/EDP Yoshihagi et al, 2011 (44) EF≥40% 0.720 (0.471, 0.969)
Pre–A Poerner et al, 2003 (17) E/A=0.9 0.400 (0.202, 0.598)
Subgroup NOT Simultaneously (I^2=49.28 %, P=0.066) 0.439 (0.306, 0.571)
Overall (I^2=56.03 %, P=0.007) 0.388 (0.281, 0.495)

I. E/e' septal: combined LVFP (CAD prevalence)

Studies                         Estimate (95% C.I.)
LV/EDP Manouras et al, 2013 (48) EF>55% 0.030 (-0.297, 0.357)
Subgroup no CAD (I^2=2% NA, P=NA) 0.030 (-0.297, 0.357)
LV/MDP Rudko et al, 2008 (32) 0.470 (0.186, 0.754)
LV/EDP Min et al, 2007 (27) 0.020 (-0.229, 0.269)
Subgroup some CAD (I^2=79.45 %, P=0.027) 0.247 (-0.184, 0.679)
Pre–A Hsiao et al, 2011 (40) 0.310 (0.122, 0.498)
LV/EDP Ozer et al, 2011 (43) 0.540 (0.289, 0.791)
Subgroup all CAD (I^2=51.81 %, P=0.151) 0.409 (0.186, 0.633)
Overall (I^2=64.91 %, P=0.022) 0.286 (0.091, 0.481)

J. E/e' septal: Primary data variable measured simultaneously (shown as table 4B in the main text)

Studies                         Estimate (95% C.I.)
LV/EDP Manouras et al, 2013 (48) EF>55% 0.030 (-0.297, 0.357)
LV/EDP Kidawa et al, 2005 (24) 0.290 (0.020, 0.560)
Subgroup LV/EDP (I^2=30.57 %, P=0.230) 0.177 (-0.076, 0.430)
LV/MDP Ommen et al, 2000 (15) 0.470 (0.250, 0.690)
LV/MDP Rudko et al, 2008 (32) 0.470 (0.186, 0.754)
Subgroup LV/MDP (I^2=49 %, P=1.000) 0.470 (0.296, 0.644)
PCWP Rivas–Goltz et al, 2003 (18) 0.550 (0.325, 0.775)
Subgroup PCWP (I^2=2% NA, P=NA) 0.550 (0.325, 0.775)
Pre–A Manouras et al, 2013 (48) EF≥55% 0.020 (-0.296, 0.336)
Subgroup Pre–A (I^2=2% NA, P=NA) 0.020 (-0.296, 0.336)
Overall (I^2=61.21 %, P=0.024) 0.327 (0.151, 0.503)
5.3. Subgroup analysis for $E/e'_\text{mean}$ and LVFP

### E/$e'_\text{mean}$: Dataset for subgroup analysis (see also Tables 1 and 2)

| LVFP   | r    | se   | Data         | Timing         | % HFpEF | % CAD | % HTN | % DM | Indication for cath             |
|--------|------|------|--------------|----------------|---------|-------|-------|------|---------------------------------|
| LVEDP  |      |      |              |                |         |       |       |      |                                 |
| LVEDP  | 0.18 | 0.164| Primary      | Simultaneously | unclear  | no CAD | unclear| unclear| angiography                     |
| LVEDP  | 0.68 | 0.07 | Primary      | NOT Simult.    | unclear  | some CAD| ~90% HTN| ~40% DM| angiography                     |
| LVEDP  | 0.35 | 0.143| Primary      | NOT Simult.    | unclear  | all CAD | ~60% HTN| ~40% DM| angiography                     |
| LVEDP  | 0.23 | 0.131| Primary      | NOT Simult.    | 0% HF   | unclear| unclear| unclear|                                 |

| Pre-A  |      |      |              |                |         |       |       |      |                                 |
|--------|------|------|--------------|----------------|---------|-------|-------|------|                                 |
| Pre-A  | 0.21 | 0.163| Primary      | Simultaneously | unclear  | no CAD | unclear| unclear| angiography                     |
| Pre-A  | 0.25 | 0.098| Primary      | NOT Simult.    | unclear  | all CAD| ~70% HTN| ~50% DM| angiography                     |
| Pre-A  | 0.02 | 0.135| Primary      | NOT Simult.    | 0% HF   | unclear| unclear| unclear|                                 |
| Pre-A  | 0.39 | 0.168| Primary      | NOT Simult.    | unclear  | unclear| unclear| unclear| dyspnea                         |
| Pre-A  | 0.63 | 0.071| Primary      | NOT Simult.    | unclear  | some CAD| ~90% HTN| ~60% DM| angiography                     |
| Pre-A  | 0.57 | 0.09 | Supplement   | NOT Simult.    | unclear  | unclear| unclear| unclear|                                 |

| LVMDP  |      |      |              |                |         |       |       |      |                                 |
|--------|------|------|--------------|----------------|---------|-------|-------|------|                                 |
| LVMDP  | 0.45 | 0.121| Primary      | Simultaneously | unclear  | unclear| unclear| unclear|                                 |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre-A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
A. LVEDP (primary and supplemental data)

| Studies                          | Estimate (95% C.I.)       |
|---------------------------------|---------------------------|
| Manouras et al., 2013 (48) EF>55% | 0.180 (-0.141, 0.501)     |
| Dokanish et al., 2010 (35)      | 0.680 (0.543, 0.817)      |
| Özer et al., 2011 (43)          | 0.350 (0.070, 0.630)      |
| Provitali et al., 2012 (46)     | 0.330 (0.037, 0.647)      |
| Subgroup Primary (I^2=80.95 %, P=0.001) | 0.380 (0.107, 0.653)     |
| Bruch et al., 2005 (22) EF>45%  | 0.680 (0.398, 0.962)      |
| Poerner et al., 2003 (17) E/A=0.6 | 0.450 (0.258, 0.642)      |
| Subgroup Supplemental (I^2=42.76 %, P=0.186) | 0.541 (0.321, 0.765)     |
| Overall (I^2=71.47 %, P=0.004) | 0.447 (0.270, 0.623)      |

B. LVEDP (simultaneous and NOT simultaneous)

| Studies                          | Estimate (95% C.I.)       |
|---------------------------------|---------------------------|
| Manouras et al., 2013 (48) EF>55% | 0.180 (-0.141, 0.501)     |
| Subgroup Simultaneously (I^2=NA, P=NA) | 0.180 (-0.141, 0.591)    |
| Previtali et al., 2012 (46)     | 0.230 (-0.027, 0.487)     |
| Poerner et al., 2003 (17) E/A=0.6 | 0.450 (0.258, 0.642)      |
| Özer et al., 2011 (43)          | 0.350 (0.070, 0.630)      |
| Bruch et al., 2005 (22) EF>45%  | 0.680 (0.398, 0.962)      |
| Dokanish et al., 2010 (35)     | 0.680 (0.543, 0.817)      |
| Subgroup NOT Simultaneously (I^2=96.6 %, P=0.011) | 0.450 (0.312, 0.567)     |
| Overall (I^2=71.5 %, P=0.004) | 0.447 (0.270, 0.623)      |

C. PCWP (primary and supplemental data)

| Studies                          | Estimate (95% C.I.)       |
|---------------------------------|---------------------------|
| Rivas–Gotz et al., 2003 (18)    | 0.570 (0.349, 0.791)      |
| Wang et al., 2007 (29)          | 0.650 (0.299, 1.001)      |
| Maeder et al., 2011 (42)        | 0.130 (-0.203, 0.463)     |
| Bhella et al., 2011 (39)        | 0.650 (0.154, 1.146)      |
| Subgroup Primary (I^2=61.4 %, P=0.103) | 0.491 (0.252, 0.730)     |
| Bruch et al., 2005 (22) EF>45%  | 0.560 (0.242, 0.878)      |
| Subgroup Supplemental (I^2=NA, P=NA) | 0.560 (0.242, 0.878)     |
| Overall (I^2=36.41 %, P=0.178) | 0.505 (0.323, 0.688)      |

Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
D. PCWP (simultaneous and NOT simultaneous)

| Studies                        | Estimate (95% C.I.)       |
|-------------------------------|---------------------------|
| Rivas-Gotz et al, 2003 (18)   | 0.570 (0.349, 0.791)      |
| vWeng et al, 2007 (29)        | 0.650 (0.290, 1.001)      |
| Biella et al, 2011 (39)       | 0.650 (0.124, 1.144)      |
| Subgroup Simultaneously (I^2=90%, P=0.010) | 0.600 (0.425, 0.775) |
| Maeder et al, 2011 (42)       | 0.130 (-0.203, 0.463)     |
| Bruch et al, 2005 (22) EF>55% | 0.560 (0.242, 0.878)      |
| Subgroup NOT Simultaneously (I^2=70.09%, P=0.067) | 0.340 (-0.073, 0.759) |
| Overall (I^2=36.41%, P=0.178) | 0.505 (0.323, 0.688)      |

E. Pre-A (primary and supplemental data)

| Studies                        | Estimate (95% C.I.)       |
|-------------------------------|---------------------------|
| Dokanash et al, 2008 (30)     | 0.390 (0.060, 0.720)      |
| Manouras et al, 2013 (48) EF>55% | 0.210 (-0.109, 0.529) |
| Dokanash et al, 2010 (34)     | 0.630 (0.491, 0.769)      |
| Hosso et al, 2011 (40)        | 0.250 (0.059, 0.442)      |
| Previtali et al, 2012 (49)    | 0.020 (-0.244, 0.284)     |
| Subgroup Primary (I^2=61.97%, P=0.000) | 0.311 (0.069, 0.554) |
| Poerner et al, 2003 (17) E/A>0.9 | 0.570 (0.394, 0.746) |
| Subgroup Supplemental (I^2=NA, P=NA) | 0.570 (0.394, 0.746) |
| Overall (I^2=79.86%, P=0.000) | 0.362 (0.164, 0.560)      |

F. Pre-A (simultaneous and NOT simultaneous)

| Studies                        | Estimate (95% C.I.)       |
|-------------------------------|---------------------------|
| Manouras et al, 2013 (48) EF>55% | 0.210 (-0.109, 0.529) |
| Subgroup Simultaneously (I^2=NA, P=NA) | 0.210 (-0.109, 0.529) |
| Hsiao et al, 2011 (40)        | 0.250 (0.058, 0.442)      |
| Dokanash et al, 2010 (34)     | 0.630 (0.491, 0.769)      |
| Dokanash et al, 2008 (30)     | 0.390 (0.060, 0.720)      |
| Previtali et al, 2012 (49)    | 0.020 (-0.244, 0.284)     |
| Poerner et al, 2003 (17) E/A>0.9 | 0.570 (0.394, 0.746) |
| Subgroup NOT Simultaneously (I^2=92.36%, P=0.000) | 0.386 (0.169, 0.604) |
| Overall (I^2=79.86%, P=0.000) | 0.362 (0.164, 0.560)      |
For combined LVFP analysis, if the study measured two LVFP parameters we chose that had the highest correlation coefficient.

**G. E/e’ mean: combined LVFP (primary and supplemental data)**

| Studies                                      | Estimate (95% C.I.) |
|----------------------------------------------|---------------------|
| Pre-A Manouras et al., 2013 (48) EF>55%     | 0.210 (-0.109, 0.529) |
| LVMSP Ommen et al., 2000 (15)               | 0.450 (0.213, 0.687)  |
| PCWP Wang et al., 2007 (29)                 | 0.650 (0.299, 1.001)  |
| PCWP Rivas-Gotz et al., 2003 (18)           | 0.370 (0.340, 0.791)  |
| PCWP Bhella et al., 2011 (39)               | 0.650 (0.154, 1.146)  |
| LV/EDP Dokiian et al., 2010 (35)            | 0.680 (0.543, 0.817)  |
| PCWP Maeder et al., 2011 (42)               | 0.430 (-0.203, 0.463) |
| Pre-A Dokiian et al., 2005 (30)             | 0.570 (0.058, 0.442)  |
| Pre-A Hsiao et al., 2011 (40)               | 0.250 (-0.027, 0.487) |
| LV/EDP Previtali et al., 2012 (46)          | 0.200 (-0.070, 0.630) |
| LV/EDP Ozar et al., 2011 (43)               | 0.350 (0.070, 0.630)  |
| Subgroup Primary (H2p=63.07 %, P=0.003)      | 0.416 (0.266, 0.545)  |
| LV/EDP Bruch et al., 2005 (22) EF>45%       | 0.680 (0.398, 0.962)  |
| Pre-A Porner et al., 2003 (17) EF>0.9       | 0.570 (0.394, 0.746)  |
| Subgroup Supplemental (H2p=0.0 %, P=0.517)  | 0.601 (0.451, 0.750)  |
| Overall (H2p=60.49 %, P=0.002)              | 0.452 (0.340, 0.563)  |

**H. E/e’ mean: combined LVFP (simultaneous and NOT simultaneous)**

| Studies                                      | Estimate (95% C.I.) |
|----------------------------------------------|---------------------|
| Pre-A Manouras et al., 2013 (48) EF>55%     | 0.210 (-0.109, 0.529) |
| LVMSP Ommen et al., 2000 (15)               | 0.450 (0.213, 0.687)  |
| PCWP Wang et al., 2007 (29)                 | 0.650 (0.299, 1.001)  |
| PCWP Rivas-Gotz et al., 2003 (18)           | 0.370 (0.340, 0.791)  |
| PCWP Bhella et al., 2011 (39)               | 0.650 (0.154, 1.146)  |
| Subgroup Simultaneously (H2p=15.66 %, P=0.313) | 0.491 (0.347, 0.635)  |
| LV/EDP Dokiian et al., 2010 (35)            | 0.680 (0.543, 0.817)  |
| PCWP Maeder et al., 2011 (42)               | 0.130 (-0.203, 0.463) |
| Pre-A Dokiian et al., 2008 (30)             | 0.390 (0.061, 0.719)  |
| Pre-A Hsiao et al., 2011 (40)               | 0.250 (-0.056, 0.442) |
| LV/EDP Previtali et al., 2012 (46)          | 0.230 (-0.027, 0.487) |
| LV/EDP Bruch et al., 2005 (22) EF>45%       | 0.680 (0.398, 0.962)  |
| Pre-A Porner et al., 2003 (17) EF>0.9       | 0.570 (0.394, 0.746)  |
| LV/EDP Ozar et al., 2011 (43)               | 0.350 (0.070, 0.630)  |
| Subgroup NOT Simultaneously (H2p=72.66 %, P=0.001) | 0.426 (0.273, 0.582)  |
| Overall (H2p=60.49 %, P=0.002)              | 0.452 (0.340, 0.563)  |

**I. E/e’ mean: combined LVFP (HFpEF prevalence)**

| Studies                                      | Estimate (95% C.I.) |
|----------------------------------------------|---------------------|
| PCWP Bhella et al., 2011 (39)                | 0.650 (0.154, 1.146) |
| LV/EDP Bruch et al., 2005 (22) EF>45%       | 0.680 (0.398, 0.962)  |
| Subgroup all HF (H2p=0.0 %, P=0.918)        | 0.673 (0.428, 0.918)  |
| LV/EDP Previtali et al., 2012 (46)          | 0.230 (-0.027, 0.487) |
| Subgroup no HF (H2p=2NA, P=2NA)             | 0.230 (-0.027, 0.487) |
| PCWP Maeder et al., 2011 (42)               | 0.130 (-0.203, 0.463) |
| Subgroup <40% HF (H2p=2NA, P=2NA)           | 0.130 (-0.203, 0.463) |
| Overall (H2p=66.5 %, P=0.030)               | 0.405 (0.122, 0.687)  |
J. **E/e′**_mean_: combined LVFP (CAD prevalence)

| Studies                        | Estimate (95% C.I.) |
|-------------------------------|---------------------|
| Pre–A Hsiao et al, 2011 (40)  | 0.250 (0.058, 0.442) |
| LVEDP Özzer et al, 2011 (43)  | 0.350 (0.070, 0.630) |
| Subgroup All CAD (*I^2*=0 %, *P*=0.564) | 0.282 (0.124, 0.440) |
| Pre–A Manouras et al, 2013 (48) EF>55% | 0.210 (-0.109, 0.529) |
| PCWP Bhella et al, 2011 (39)  | 0.650 (0.154, 1.146) |
| Subgroup no CAD (*I^2*=53.21 %, *P*=0.144) | 0.387 (-0.036, 0.811) |
| LVEDP Dokanish et al, 2010 (35) | 0.680 (0.543, 0.817) |
| LVEDP Bruch et al, 2005 (22) EF>45% | 0.680 (0.398, 0.962) |
| Subgroup some CAD (*I^2*=0 %, *P*=1.000) | 0.680 (0.557, 0.803) |
| Overall (*I^2*=74.07 %, *P*=0.002) | 0.465 (0.264, 0.667) |

K. **E/e′**_mean_: combined LVFP (HTN prevalence)

| Studies                        | Estimate (95% C.I.) |
|-------------------------------|---------------------|
| PCWP Bhella et al, 2011 (39)  | 0.650 (0.154, 1.146) |
| Subgroup ~100% HTN (*I^2*=NA, *P*=NA) | 0.650 (0.154, 1.146) |
| LVEDP Dokanish et al, 2010 (35) | 0.680 (0.543, 0.817) |
| Subgroup ~90% HTN (*I^2*=NA, *P*=NA) | 0.680 (0.543, 0.817) |
| LVEDP Bruch et al, 2005 (22) EF>45% | 0.680 (0.398, 0.962) |
| Subgroup ~80% HTN (*I^2*=NA, *P*=NA) | 0.680 (0.398, 0.962) |
| Pre–A Hsiao et al, 2011 (40)  | 0.250 (0.058, 0.442) |
| Subgroup ~70% HTN (*I^2*=NA, *P*=NA) | 0.250 (0.058, 0.442) |
| LVEDP Özzer et al, 2011 (43)  | 0.350 (0.070, 0.630) |
| Subgroup ~60% HTN (*I^2*=NA, *P*=NA) | 0.350 (0.070, 0.630) |
| Pre–A Manouras et al, 2013 (48) EF>40% | 0.480 (0.262, 0.698) |
| Subgroup ~40% HTN (*I^2*=NA, *P*=NA) | 0.480 (0.262, 0.698) |
| Overall (*I^2*=68.45 %, *P*=0.007) | 0.504 (0.333, 0.676) |

L. **E/e′**_mean_: Primary data variables measured simultaneously (shown as table 4B in the main text)

| Studies                        | Estimate (95% C.I.) |
|-------------------------------|---------------------|
| LVEDP Manouras et al, 2013 (48) EF>55% | 0.180 (-0.141, 0.501) |
| Subgroup LVEDP (*I^2*=NA, *P*=NA) | 0.180 (-0.141, 0.501) |
| PCWP Rivas–Gotz et al, 2003 (18) | 0.570 (0.349, 0.791) |
| PCWP Wang et al, 2007 (29)    | 0.650 (0.299, 1.001) |
| PCWP Bhella et al, 2011 (30)  | 0.650 (0.154, 1.146) |
| Subgroup PCWP (*I^2*=0 %, *P*=0.910) | 0.660 (0.425, 0.775) |
| Pre–A Manouras et al, 2013 (48) EF>55% | 0.210 (-0.109, 0.529) |
| Subgroup Pre–A (*I^2*=NA, *P*=NA) | 0.210 (-0.109, 0.529) |
| LVMDP Ommen et al, 2000 (15)  | 0.450 (0.213, 0.687) |
| Subgroup LVMDP (*I^2*=NA, *P*=NA) | 0.450 (0.213, 0.687) |
| Overall (*I^2*=36.54 %, *P*=0.163) | 0.443 (0.287, 0.599) |
### APPENDIX 6

Secondary analysis of sensitivity/specifcity of E/e’ cutoffs to predict elevated LVFP

#### 6.1. Subgroup analysis for $E/e'_{lateral} > 12$ to identify elevated LVFP

$E/e'_{lateral}$: Dataset for subgroup analysis (see also Tables 1 and 2)

| Study | TP | FN | FP | TN | SENS. lower | upper | SPEC. lower | upper | Data | Timing | % HFpEF | % CAD | % HTN | % DM | Indication for cath | LR+ |
|-------|----|----|----|----|------------|-------|------------|-------|------|--------|--------|------|------|-----|-------------------|-----|
| LV EP Kidawa et al, 2005 (24) | 6 | 13 | 1 | 25 | 0.316 | 0.149 | 0.548 | 0.962 | 0.772 | 0.959 Primary | Simultaneously | unclear | unclear | unclear | angiography | 8.3 |
| PCWP Rivas-Gotz et al, 2003 (18) | 15 | 20 | 1 | 15 | 0.429 | 0.277 | 0.594 | 0.937 | 0.665 | 0.991 Primary | Simultaneously | Un unclear | Un unclear | unclear | ICU/Cath lab | 6.8 |
| LV EP Previtali et al, 2012 (46) | 10 | 28 | 8 | 16 | 0.263 | 0.148 | 0.424 | 0.667 | 0.461 | 0.824 Primary | NOT simultaneous | 0% HF | unclear | unclear | unclear | 0.8 |
| LV EP Hadano et al, 2005 (23) | 5 | 7 | 4 | 47 | 0.417 | 0.185 | 0.692 | 0.922 | 0.809 | 0.970 Primary | NOT simultaneous | unclear | some CAD | unclear | unclear | 5.3 |
| LV EP Özer et al, 2011 (43) | 6 | 17 | 1 | 21 | 0.261 | 0.122 | 0.472 | 0.955 | 0.739 | 0.994 Primary | NOT simultaneous | unclear | all CAD | ~60% HTN | ~40% DM | angiography | 5.8 |
| Pre-A Mansencal et al, 2004 (20) | 0 | 5 | 0 | 15 | 0.083 | 0.005 | 0.622 | 0.969 | 0.650 | 0.998 Primary | NOT simultaneous | ~5% HF | all CAD | ~10% HTN | unclear | angiography | 2.7 |
| LVEDP Poerner et al, 2007 (28) EF>~40% | 31 | 17 | 29 | 64 | 0.646 | 0.502 | 0.767 | 0.688 | 0.587 | 0.774 Supplement | NOT simultaneous | Un unclear | some CAD | ~60% HTN | ~30% DM | angiography | 2.1 |
| PCWP Nagueh et al, 1998 (14) EF>45% Sinus Tachycardia >100bpm | 11 | 15 | 0 | 17 | 0.426 | 0.257 | 0.614 | 0.972 | 0.678 | 0.998 Supplement | Simultaneously | Un unclear | Un unclear | Un unclear | ICU/Cath lab | 15.2 |
| LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients | 8 | 12 | 2 | 8 | 0.400 | 0.214 | 0.620 | 0.800 | 0.359 | 0.950 Supplement | Simultaneously | ~70% HF | no CAD | ~70% HTN | ~30% DM | dyspnea | 2.0 |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre-A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
A. Combined LVFP (primary and supplemental data)

Primary studies combined (n=6, as in Figure 3)
- Sensitivity (summary) 0.30 (0.09 - 0.48)
- Specificity (summary) 0.92 (0.83 - 1.0)

Supplemental studies combined (n=3)
- Sensitivity (summary) 0.50 (0.10 - 0.84)
- Specificity (summary) 0.85 (0.50 - 1.0)

All studies combined (n=9)
- Sensitivity (summary) 0.36 (0.18 - 0.51)
- Specificity (summary) 0.91 (0.81 - 0.99)

TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens = sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
B. Combined LVFP (Simultaneous and not simultaneous measurements)

Simultaneous studies combined (n=4)
Sensitivity (summary) 0.39 (0.18 - 0.58)
Specificity (summary) 0.94 (0.40 - 1.0)

Not Simultaneous studies combined (n=5)
Sensitivity (summary) 0.30 (0.06 - 0.59)
Specificity (summary) 0.90 (0.76 – 1.0)

All studies combined (n=9)
Sensitivity (summary) 0.36 (0.18 - 0.51)
Specificity (summary) 0.91 (0.81 - 0.99)
C. Separate analysis for LVFP measurements

| Studies                      | Sensitivity Estimate (95% C.I.) | TP / (TP + FN) |
|------------------------------|---------------------------------|----------------|
| LVEDP Hamroc et al, 2005 (23)| 0.417 (0.115, 0.622)            | 0/12           |
| LVEDP Kostka et al, 2005 (24)| 0.316 (0.149, 0.488)            | 6/19           |
| LVEDP Berners et al, 2010 (38)| 0.400 (0.214, 0.620)            | 8/26           |
| LVEDP Periss et al, 2014 (43)| 0.263 (0.122, 0.412)            | 6/32           |
| LVEDP Preiss et al, 2012 (44)| 0.243 (0.145, 0.424)            | 10/14          |
| LVEDP Periss et al, 2017 (28) | 0.446 (0.210, 0.707)            | 31/48          |

| Subgroup LVEDP (P=0.001, 95% CI) | Estimate (95% C.I.) | TN / (TP + FN) |
|----------------------------------|---------------------|----------------|
|                                  | 0.362 (0.209, 0.570) | 67/11          |
|                                  | 0.962 (0.773, 0.994) | 24/34          |
|                                  | 0.810 (0.659, 0.950) | 8/13           |
|                                  | 0.999 (0.733, 0.994) | 21/22          |
|                                  | 0.667 (0.462, 0.864) | 14/24          |
|                                  | 0.680 (0.587, 0.774) | 64/95          |
|                                  | 0.841 (0.649, 0.938) | 181/206        |

There are insufficient number of studies that measured PCWP (n=2) to perform a meaningful analysis.

LR+ = 2.7
LR+ = 4.0
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

Primary Not Simultaneous studies (n=4)
- Sensitivity (summary) 0.22 (0.01 - 0.53)
- Specificity (summary) 0.92 (0.70 - 1.0)

All primary studies combined (n=6)
- Sensitivity (summary) 0.36 (0.18 - 0.51)
- Specificity (summary) 0.92 (0.83 - 1.0)

HSROC analysis

LR+ = 2.8

LR+ = 3.8

There are insufficient number of studies that performed simultaneous measurements (n=2) to perform a meaningful analysis.
### 6.2. Subgroup analysis for $E/e'_\text{mean}$ >13 to identify elevated LVFP

$E/e'_\text{mean}$: Dataset for subgroup analysis (see also Tables 1 and 2)

| Study | TP | FN | FP | TN | SENS. | SPEC. | Data | Timing | % HFpEF | % CAD | % HTN | % DM | Indication for cath | LR+ |
|-------|----|----|----|----|-------|-------|------|--------|---------|-------|------|-----|-------------------|-----|
| LVEDP Manouras et al, 2013 (48) EF>55% | 2  | 22 | 1  | 10 | 0.083 | 0.909 | Primary | Simultaneously | unclear | no CAD | unclear | unclear | angiography | 0.9 |
| PCWP Bhella et al, 2011 (39) | 3  | 2  | 0  | 5  | 0.583 | 0.917 | Primary | Simultaneously | 100% HF | no CAD | 100% HTN | ~60% DM | research | 7.0 |
| PCWP Dokainish et al, 2004 (19) | 6  | 5  | 2  | 6  | 0.545 | 0.750 | Primary | Simultaneously | unclear | uncertain | ~60% HTN | ~20% DM | ICU/CCU | 2.2 |
| LVEDP Dokainish et al, 2010 (35) | 57 | 42 | 3  | 20 | 0.576 | 0.870 | Primary | NOT simultaneously | unclear | some CAD | ~90% HTN | ~40% DM | angiography | 4.4 |
| LVEDP Özer et al, 2011 (43) | 6  | 17 | 1  | 21 | 0.261 | 0.955 | Primary | NOT simultaneously | unclear | all CAD | ~60% HTN | ~40% DM | angiography | 5.8 |
| Pre-A Dini et al, 2010 (33) | 9  | 17 | 2  | 27 | 0.346 | 0.931 | Primary | NOT simultaneously | 100% HF | unclear | unclear | unclear | dyspnea | 5.0 |
| LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients | 6  | 14 | 1  | 9  | 0.300 | 0.900 | Supplemente | Simultaneously | ~70% HF | no CAD | ~70% HTN | ~30% DM | dyspnea | 3.0 |
| LVEDP Bruch et al, 2005 (22) EF>45% | 9  | 2  | 5  | 10 | 0.818 | 0.667 | Supplemente | NOT simultaneously | 100% HF | some CAD | ~80% HTN | unclear | dyspnea | 2.5 |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
A. Combined LVFP (primary and supplemental data)

Primary studies combined (n=6, as in Figure 3)
Sensitivity (summary) 0.37 (0.13 - 0.61)
Specificity (summary) 0.91 (0.81 - 0.99)

All studies combined (n=8)
Sensitivity (summary) 0.42 (0.19 - 0.65)
Specificity (summary) 0.89 (0.77 - 0.98)

There are insufficient number of studies that provided supplemental data (n=2) to perform a meaningful analysis.

TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens. = sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
B. Combined LVFP (Simultaneous and not simultaneous measurements)

**HSROC analysis**

- **Simultaneous studies combined (n=4)**
  - Sensitivity (summary) 0.31 (0.04 - 0.67)
  - Specificity (summary) 0.89 (0.67 – 1.0)

- **NOT Simultaneous studies combined (n=4)**
  - Sensitivity (summary) 0.50 (0.11 – 0.84)
  - Specificity (summary) 0.88 (0.65 – 1.0)

- **All studies combined (n=8)**
  - Sensitivity (summary) 0.42 (0.19 - 0.65)
  - Specificity (summary) 0.89 (0.77 - 0.98)

LR+ = 2.8

LR+ = 4.2

LR+ = 3.8
C. Separate analysis for LVFP measurements

| Studies | Estimate [95% C.I.] | TP / (TP + FN) | TN / (FP + TN) |
|---------|---------------------|----------------|----------------|
| LVFP Mounier et al. 2013 (48) EF<55% | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| LVFP Franssen et al. 2010 EF≤60% | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| LVFP Danesh et al. 2010 (29) | 0.176 (0.013, 0.418) | 5/6 | 0.962 (0.843, 0.996) | 10/11 |
| LVFP Donker et al. 2011 (36) | 0.184 (0.025, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| LVFP Brun et al. 2005 (22) EF<40% | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| Subgroup LVFP EF<40% | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| PCWP Muraru et al. 2011 (30) | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| PCWP Dorsman et al. 2000 (28) | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| Subgroup PCWP EF<40% | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| Pre-A Div et al. 2010 (29) | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| Subgroup Pre-A EF<40% | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |
| Overall (EF<40%) | 0.182 (0.021, 0.342) | 6/11 | 0.949 (0.820, 0.982) | 12/11 |

**Sensitivity (summary)** 0.39 (0.07 - 0.73)

**Specificity (summary)** 0.88 (0.69 – 0.99)

HSROC analysis

LVEDP studies (n=4)

| Sensitivity | Specificity |
|-------------|-------------|
| 0.182 (0.021, 0.342) | 0.949 (0.820, 0.982) |
| 0.176 (0.013, 0.418) | 0.962 (0.843, 0.996) |
| 0.184 (0.025, 0.342) | 0.949 (0.820, 0.982) |
| 0.182 (0.021, 0.342) | 0.949 (0.820, 0.982) |

LR+ = 3.2

All studies combined (n=8)

| Sensitivity | Specificity |
|-------------|-------------|
| 0.182 (0.021, 0.342) | 0.949 (0.820, 0.982) |
| 0.176 (0.013, 0.418) | 0.962 (0.843, 0.996) |
| 0.184 (0.025, 0.342) | 0.949 (0.820, 0.982) |
| 0.182 (0.021, 0.342) | 0.949 (0.820, 0.982) |

LR+ = 3.8

There are insufficient number of studies that measured PCWP (n=2) to perform a meaningful analysis.
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

| Studies | Sensitivity Estimate [95% C.I.] | TP / (TP + FN) |
|---------|---------------------------------|----------------|
| PCWP Bhuja et al, 2011 (52) | 0.589 [0.314, 0.774] | 3/5 |
| LVEEP Maneerat et al, 2013 (48) | 0.983 [0.821, 0.978] | 2/24 |
| LVEEP Dakshin et al, 2004 (16) | 0.545 [0.360, 0.707] | 6/31 |
| Subgroup Simultaneously (P²=77.65 %, P=0.012) | 0.369 [0.088, 0.763] | 11/49 |
| LVEEP Dakshin et al, 2010 (35) | 0.374 [0.477, 0.669] | 5/73 |
| LVEEP Ober et al, 2011 (15) | 0.262 [0.120, 0.472] | 6/23 |
| Pw-X Dr et al, 2010 (33) | 0.356 [0.145, 0.563] | 9/24 |
| Subgroup NOT Simultaneously (P²=78.76 %, P=0.069) | 0.456 [0.332, 0.611] | 72/148 |
| Overall (P²=76.11 %, P=0.861) | 0.382 [0.225, 0.568] | 83/188 |

Primary Simultaneous studies (n=3)
- Sensitivity (summary) 0.33 (0.03 – 0.77)
- Specificity (summary) 0.88 (0.53 – 1.0)

Primary NOT Simultaneous studies (n=3)
- Sensitivity (summary) 0.39 (0.07 – 0.73)
- Specificity (summary) 0.92 (0.71 – 1.0)

All Primary studies (n=6)
- Sensitivity (summary) 0.37 (0.13 - 0.61)
- Specificity (summary) 0.91 (0.81 – 0.99)

HSROC analysis

LR+ = 2.8

LR+ = 4.9

LR+ = 4.1
6.3. Subgroup analysis for $E'/septal > 15$ to identify elevated LVFP

$E'/septal$: Dataset for subgroup analysis (see also Tables 1 and 2)

| Study                          | TP | FN | FP | TN | SENS. lower | upper | SPEC. lower | upper | Data | Timing | % HFpEF | % CAD | % HTN | % DM | Indication for cath | LR+ |
|-------------------------------|----|----|----|----|-------------|-------|-------------|-------|------|--------|---------|-------|-------|------|----------------------|-----|
| PCWP Rivas-Gott et al, 2003 (18) | 12 | 24 | 1 | 15 | 0.333 | 0.200 | 0.500 | 0.937 | 0.665 | 0.99 Primary | Simultaneously | Unclear | Unclear | Unclear | ICU/Cath lab | 5.3 |
| LVMDP Ommen et al, 2000 (15)   | 4  | 14 | 0 | 43 | 0.237 | 0.097 | 0.472 | 0.989 | 0.843 | 1.00 Primary | Simultaneously | Unclear | Unclear | Unclear | Unclear | 21.5 |
| LVMDP Rudko et al, 2008 (32)   | 2  | 16 | 0 | 25 | 0.132 | 0.039 | 0.364 | 0.981 | 0.756 | 1.00 Primary | Simultaneously | ~20% HF | ~80% CAD | ~50% HTN | Unclear | 6.9 |
| LVEDP Özer et al, 2011 (43)    | 7  | 16 | 1 | 21 | 0.304 | 0.153 | 0.515 | 0.955 | 0.739 | 0.99 Primary | NOT simultaneously | Unclear | all CAD | ~60% HTN | ~40% DM angiography | 6.8 |
| LVEDP Penicka et al, 2010 (38) | 4  | 16 | 0 | 10 | 0.214 | 0.088 | 0.436 | 0.955 | 0.552 | 1.00 Supplemental | Simultaneously | ~70% HF | no CAD | ~70% HTN | ~30% DM dyspnea | 4.8 |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre-A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
A. Combined LVFP (primary and supplemental data)

Primary studies (n=4)
- Sensitivity (summary) 0.24 (0.06 – 0.46)
- Specificity (summary) 0.98 (0.92 – 1.0)

All studies (n=5)
- Sensitivity (summary) 0.23 (0.10 - 0.39)
- Specificity (summary) 0.98 (0.94 – 1.0)

Heterogeneity amongst the studies was estimated by I² statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
B. Combined LVFP (Simultaneous and not simultaneous measurements)

Simultaneous studies (n=4)
- Sensitivity (summary) 0.22 (0.08 – 0.44)
- Specificity (summary) 0.98 (0.93 – 1.0)

All studies (n=5)
- Sensitivity (summary) 0.23 (0.10 - 0.39)
- Specificity (summary) 0.98 (0.94 – 1.0)

HSROC analysis
C. Separate analysis for LVFP measurements

There are insufficient number of studies that measured LVEDP (n=2) or LVDP (n=2) to perform a meaningful analysis.
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

Simultaneous studies

All studies

Primary Simultaneous studies (n=3)
Sensitivity (summary) 0.22 (0.04 – 0.54)
Specificity (summary) 0.98 (0.87 – 1.0)

HSROC analysis
All Primary studies (n=4)
Sensitivity (summary) 0.24 (0.06 – 0.46)
Specificity (summary) 0.98 (0.92 – 1.0)
## APPENDIX 7

### Optimal cutoffs and AUC for elevated LVFP

#### 7.1. Identification of elevated LVFP based on ‘optimal’ E/e’mean cutoffs from ROC analysis

| Study                  | N    | LVFP cutoff | E/e’ cutoff | Prev. (%) | TP   | FP   | FN   | TN   | Sens. (95% CI) | Spec. (95% CI) | Sens. (95% CI) | Spec. (95% CI) | AUC (95% CI) |
|------------------------|------|-------------|-------------|-----------|------|------|------|------|----------------|----------------|----------------|----------------|--------------|
| Kidawa, 2005 (24)      | 50   | LVEDP≥15    | >8          | 54        | -    | -    | -    | 0.76 | 0.76           |                |                |                |              |
| Hadano, 2005* (23)     | 63/65| LVEDP>16    | >9          | 19        | 10   | 5    | 37   | 0.67 [0.41, 0.86] | 0.77 [0.63, 0.87] |                |                | 0.81           |              |
| Previtali, 2012* (46)  | 62/57| LVEDP>16    | >9          | 61        | 24   | 13   | 11   | 0.63 [0.46, 0.78] | 0.46 [0.26, 0.67] |                |                | 0.47           |              |
| Arques, 2013 (47)      | 63   | LVEDP>16    | >6.6        | 58        | 15   | 3    | 6    | 0.71 [0.49, 0.87] | 0.80 [0.53, 0.93] |                |                | 0.79           |              |
| Rivas-Gotz, 2003 (18)  | 55   | PCWP >15    | >10         | -         | -    | -    | -    | 0.79 | 0.80           |                |                |                |              |
| Hadano, 2005* (23)     | 63/65| PCWP >12    | >9          | 19        | 9    | 12   | 3    | 0.75 [0.43, 0.96] | 0.76 [0.63, 0.87] |                |                | 0.84           |              |
| Nagueh, 1997* (E/A<1)  | 23/26| PCWP >12    | >8          | 22        | 4    | 10   | 1    | 0.80 [0.29, 0.99] | 0.44 [0.22, 0.69] |                |                | 0.64           |              |
| Maeder, 2011 (42)      | 36   | PCWP >12    | -           | 25        | -    | -    | -    | -    | -              |                |                |                |              |
| Mansencal, 2004* (20)  | 20/20| Pre-A >15   | >6          | 25        | 5    | 6    | 9    | 1.00 [0.48, 1.00] | 0.60 [0.32, 0.84] |                |                | 0.79           |              |
| Hsiao, 2011 (40)       | 100  | Pre-A >15   | >9.7        | -         | -    | -    | -    | 64   | 63             |                |                |                |              |

| Study                  | N    | LVFP cutoff | E/e’ cutoff | Prev. (%) | TP   | FP   | FN   | TN   | Sens. (95% CI) | Spec. (95% CI) | Sens. (95% CI) | Spec. (95% CI) | AUC (95% CI) |
|------------------------|------|-------------|-------------|-----------|------|------|------|------|----------------|----------------|----------------|----------------|--------------|
| Poerner, 2007 (28)     | 176  | LVEDP>16    | >10         | 41        | 48   | 37   | 24   | 0.67 [0.55, 0.77] | 0.64 [0.54, 0.74] |                |                | 0.69           |              |
| Jaubert, 2010 (36)     | 59   | LVEDP>16    | >6.7        | 66        | 22   | 4    | 17   | 0.56 [0.40, 0.72] | 0.80 [0.56, 0.94] |                |                | 0.89 [0.56, 0.80] |              |
| Manouras, 2015 (48)    | 65   | LVEDP>16    | >8          | 72        | -    | -    | -    | 0.73 | 0.65           |                |                |                | 0.70 [0.63, 0.77] |              |
| Nagueh, 1998* (14)     | 43/49| PCWP >12    | >9          | 60        | 20   | 3    | 6    | 0.77 [0.56, 0.91] | 0.82 [0.57, 0.96] |                |                | 0.84           |              |
| Manours, 2013 (48)     | 65   | Pre-A >12   | >8          | 68        | 33   | 7    | 11   | 0.74 [0.60, 0.86] | 0.67 [0.45, 0.83] |                |                | 0.71 [0.62, 0.79] |              |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; Prev.=Prevalence of patients with elevated LVFP; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=Sensitivity; Spec.=Specificity; AUC=area under receiver operating characteristic (ROC) curve; CI=confidence interval. Empty cells are due to no data available.

*TP, FP, FN, TN values were extracted from the graphical data representation of LVFP vs. E/e’ in study results; for such study, column presenting patient number (N) include 2 numbers: first number is actual counted patients in the plot, and second number is total patients in the study group.

In studies that did not provide the optimal cutoff, we created ROC curve and identified the optimal cutoff as the point on the ROC curve closest to (0, 1 on x-y coordinate).

Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
### 7.2. Identification of elevated LVFP based on ‘optimal’ E/e’ mean cutoffs from ROC analysis

**LVEF≥50%**

| Study          | N  | LVFP cutoff | E/e’ cutoff | Prev. (%) | TP | FP | FN | TN | Sens. (95% CI) | Spec. (95% CI) | Sens. (95% CI) | Spec. (95% CI) | AUC (95% CI) |
|----------------|----|--------------|-------------|-----------|----|----|----|----|----------------|----------------|----------------|----------------|--------------|
| Dokainish, 2010 (35) | 122 | LVEDP≥20     | >12         | 56        | -  | -  | -  | -  | 0.75            | 0.78            | -              | -              | 0.79         |
| Prevital, 2012 (46)   | 57  | LVEDP≥15     | >12:08      | 72        | -  | -  | -  | -  | 0.44            | 0.71            | -              | -              | 0.52         |
| Rivas-Gotz, 2003 (49) | 55  | PCWP >15     | >10         | -         | -  | -  | -  | -  | 0.82            | 0.72            | -              | -              | -            |
| Dokainish, 2004 (59)  | 19  | PCWP >15     | >11         | 47        | 7  | 2  | 3  | 8  | 0.78[0.40, 0.97]| 0.80[0.44, 0.97]| -              | -              | -            |
| Maeder, 2011 (42)     | 36  | PCWP >12     | -           | 25        | -  | -  | -  | -  | -              | 0.80[0.40, 0.97]| -              | -              | -            |
| Bhella et al, 2011 (39)| 1010| PCWP >12     | >10         | 50        | 4  | 1  | 1  | 4  | 0.80[0.28, 0.99]| 0.80[0.28, 0.99]| -              | 0.62[0.39, 0.85]| -              | -            |
| Dokainish, 2008 (30)  | 32  | Pre-A >15    | >15         | -         | -  | -  | -  | -  | 0.77            | 0.77            | -              | -              | -            |
| Dokainish, 2010 (54)  | 122 | Pre-A ≥15    | >13         | 56        | -  | -  | -  | -  | 0.70            | 0.93            | -              | -              | -            |
| Hsiao, 2011 (40)      | 100 | Pre-A >15    | >11         | -         | -  | -  | -  | -  | 0.60            | 0.60            | -              | 0.82          |
| Hsiao, 2012 (12)      | 376 | Pre-A >15    | >11         | -         | -  | -  | -  | -  | 0.66            | 0.64            | -              | 0.62          |
| Manouras, 2013* (49)  | 3538| Pre-A >12    | >8          | 69        | 12 | 4  | 12| 7  | 0.50[0.31, 0.69]| 0.64[0.34, 0.86]| -              | -              | 0.78         |

**LVEF≥40%**

| Study          | N  | LVFP cutoff | E/e’ cutoff | Prev. (%) | TP | FP | FN | TN | Sens. (95% CI) | Spec. (95% CI) | Sens. (95% CI) | Spec. (95% CI) | AUC (95% CI) |
|----------------|----|--------------|-------------|-----------|----|----|----|----|----------------|----------------|----------------|----------------|--------------|
| Bruch, 2005 (22) | 28  | LVEDP≥15     | >11         | n/a       | -  | -  | -  | -  | 0.94            | 0.90            | -              | -              | 0.98[0.96, 1.00]|
| Ng, 2008 (31)   | 20  | LVEDP≥12     | -           | 60        | -  | -  | -  | -  | -              | 0.69            | -              | -              | 0.70         |
| Manouras, 2013 (48)| 65  | LVEDP >16    | >9          | 72        | -  | -  | -  | -  | -              | 0.66[0.58, 0.74]| -              | -              | 0.69         |
| Manouras, 2013* (48)| 626 | Pre-A >12    | >8          | 71        | 28 | 8  | 1  | 6  | 0.64[0.48, 0.78]| 0.56[0.31, 0.78]| -              | -              | 0.70[0.61, 0.79]| 0.55

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre-A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; Prev.=Prevalence of patients with elevated LVFP; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=Sensitivity; Spec.=Specificity; AUC=area under receiver operating characteristic (ROC) curve; CI=confidence interval. Empty cells are due to no data available.

*=TP, FP, FN, TN values were extracted from the graphical data representation of LVFP vs. E/e’ in study results; for such study, column presenting patient number (N) include 2 numbers: first number is actual counted patients in the plot, and second number is total patients in the study group.

In studies that did not provide the optimal cutoff, we created ROC curve and identified the optimal cutoff as the point on the ROC curve closest to (0, 1 on x-y coordinate).

Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
### 7.3. Identification of elevated LVFP based on ‘optimal’ E/e’ _septal_ cutoffs from ROC analysis

#### LVEF≥50%

| Study                        | N  | LVFP cutoff | E/e’ cutoff | Prev. (%) | TP | FP | FN | TN | Sens. (95% CI) | Spec. (95% CI) | Sens. (95% CI) | Spec. (95% CI) | AUC (95% CI) |
|------------------------------|----|-------------|-------------|-----------|----|----|----|----|----------------|----------------|----------------|----------------|-----------|
| Min, 2007* (8<E/e'<15) (27) | 55 | LVEDP >16   | >10         | 73        | 27 | 10 | 13 | 5  | 0.68 [0.51, 0.81] | 0.33 [0.12, 0.62] | -              | -              | 0.47        |
| Ommen, 2000* (15)           | 45 | LVEDP >16   | >9.62       | 51        | 12 | 11 | 2  | 5  | 0.52 [0.31, 0.73] | 0.91 [0.71, 0.99] | -              | -              | 0.69 [0.62, 0.76] |
| Rivas-Gotz, 2003 (18)       | 55 | PCWP >15    | >12         | -         | -  | -  | -  | -  | 0.70           | 0.60           | -              | -              | -          |
| Maeder, 2011 (42)           | 36 | PCWP >12    | -           | 25        | -  | -  | -  | -  | -              | -              | -              | -              | 0.66 [0.44, 0.88] |
| Hsiao, 2011 (40)            | 100| Pre-A >15   | >13.1       | -         | -  | -  | -  | -  | 64             | 61             | -              | -              | -          |
| Ommen, 2000* (15)           | 61 | LVMDP >12   | >11         | 30        | 15 | 15 | 3  | 28 | 0.83 [0.59, 0.96] | 0.65 [0.49, 0.79] | -              | -              | 0.79        |
| Rudko, 2008* (32)           | 43 | LVMDP >12   | >9          | 42        | 14 | 6  | 4  | 19 | 0.78 [0.52, 0.94] | 0.76 [0.55, 0.91] | -              | -              | 0.75        |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre-A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; Prev.=Prevalence of patients with elevated LVFP; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=Sensitivity; Spec.=Specificity; AUC=area under receiver operating characteristic (ROC) curve; CI=confidence interval. Empty cells are due to no data available.

*TP, FP, FN, TN values were extracted from the graphical data representation of LVFP vs. E/e’ in study results; for such study, column presenting patient number (N) include 2 numbers: first number is actual counted patients in the plot, and second number is total patients in the study group.

In studies that did not provide the optimal cutoff, we created ROC curve and identified the optimal cutoff as the point on the ROC curve closest to (0, 1 on x-y coordinate).

Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
APPENDIX 8

Secondary analysis of sensitivity/specificity of E/e’ cutoffs to predict normal LVFP

8.1. Subgroup analysis for E/e’<8 lateral to identify normal LVFP

E/e’ lateral: Dataset for subgroup analysis (see also Tables 1 and 2)

| study                              | TP  | FN  | FP  | TN  | SENS. lower | SENS. upper | SPEC. lower | SPEC. upper | Data          | Timing          | % HFpEF | % CAD | % HTN | % DM | Indication for cath | LR+ |
|------------------------------------|-----|-----|-----|-----|-------------|-------------|-------------|-------------|---------------|----------------|----------|-------|-------|-----|---------------------|-----|
| LVEDP Kidawa et al, 2005 (24)     | 19  | 7   | 4   | 15  | 0.731       | 0.866       | 0.789       | 0.554       | 0.919         | Simultaneously | unclear | unclear | unclear | unclear | angiography         | 3.5 |
| PCWP Rivas-Gotz et al, 2003 (18)  | 12  | 4   | 6   | 29  | 0.750       | 0.903       | 0.829       | 0.667       | 0.921         | Simultaneously | unclear | unclear | unclear | unclear | ICU/Cath            | 4.4 |
| LVEDP Hadano et al, 2005 (23)     | 35  | 16  | 3   | 9   | 0.686       | 0.798       | 0.750       | 0.448       | 0.917         | NOT simultaneous | unclear | some CAD | unclear | unclear | 2.7               |
| LVEDP Previtali et al, 2012 (46)  | 6   | 18  | 13  | 25  | 0.250       | 0.456       | 0.658       | 0.496       | 0.790         | Primary        | NOT simultaneous | 0% HF   | unclear | unclear | unclear | angio/ICU            | 0.7 |
| Pre-A Mansencal et al, 2004 (20)  | 12  | 3   | 3   | 2   | 0.800       | 0.934       | 0.400       | 0.100       | 0.800         | Primary        | NOT simultaneous | ~5% HF  | all CAD | ~10% HTN | unclear | angiography         | 0.7 |
| LVEDP Penicka et al, 2010 (38)    | 6   | 4   | 8   | 12  | 0.600       | 0.842       | 0.600       | 0.380       | 0.786         | Supplementary  | Simultaneously | ~70% HF  | no CAD | ~70% HTN | ~30% DM | dyspnea             | 1.5 |
| PCWP Nagueh et al, 1998 (14) EF>45% Sinus Tachycardia >100bpm | 12  | 5   | 6   | 20  | 0.706       | 0.872       | 0.769       | 0.572       | 0.892         | Supplementary  | Simultaneously | unclear | unclear | unclear | unclear | ICU/Cath            | 3.1 |
| LVEDP Poerner et al, 2007 (28) EF>40% | 21  | 72  | 6   | 42  | 0.226       | 0.322       | 0.875       | 0.748       | 0.943         | Supplementary  | NOT simultaneous | some CAD | ~60% HTN | ~30% DM | angiography         | 1.8 |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
A. Combined LVFP (primary and supplemental data)

Primary studies combined (n=5, as in Figure 4)
Sensitivity (summary) 0.64 (0.37 - 0.87)
Specificity (summary) 0.73 (0.54 – 0.89)

Supplemental studies combined (n=3)
Sensitivity (summary) 0.49 (0.10 - 0.93)
Specificity (summary) 0.76 (0.41 – 1.0)

All studies combined (n=8)
Sensitivity (summary) 0.58 (0.38 - 0.78)
Specificity (summary) 0.74 (0.61 - 0.87)

TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
B. Combined LVFP (Simultaneous and not simultaneous measurements)

HSROC analysis

Simultaneous studies combined (n=4)
Sensitivity (summary) 0.70 (0.49 - 0.86)
Specificity (summary) 0.75 (0.58 – 0.88)
LR+ = 2.8

Not Simultaneous studies combined (n=4)
Sensitivity (summary) 0.48 (0.08 - 0.88)
Specificity (summary) 0.71 (0.39 – 0.97)
LR+ = 1.6

All studies combined (n=8)
Sensitivity (summary) 0.58 (0.38 - 0.78)
Specificity (summary) 0.74 (0.61 - 0.87)
LR+ = 2.2
C. Separate analysis for LVFP measurements

HSROC analysis

LVEDP studies combined (n=5)
Sensitivity (summary) 0.49 (0.19 - 0.80)
Specificity (summary) 0.74 (0.52 - 0.92)

All studies combined (n=8)
Sensitivity (summary) 0.58 (0.38 - 0.78)
Specificity (summary) 0.74 (0.61 - 0.87)

There are insufficient number of studies (n=2) that measured PCWP measurements to perform a meaningful analysis.
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

Primary Not Simultaneous studies (n=3)
Sensitivity (summary) 0.58 (0.18 - 0.99)
Specificity (summary) 0.63 (0.24 – 0.96)

All primary studies combined (n=5)
Sensitivity (summary) 0.64 (0.37 - 0.87)
Specificity (summary) 0.73 (0.54 – 0.89)

There are insufficient number of studies (n=2) with simultaneous measurements to perform a meaningful analysis.
### 8.2. Subgroup analysis for $E'/\text{mean}$, <8 to identify normal LVFP

**E'/\text{mean}:** Dataset for subgroup analysis (see also Tables 1 and 2)

| Study | TP | FN | FP | TN | SENS. lower | SENS. upper | SPEC. lower | SPEC. upper | Data | Timing | % HFpEF | % CAD | % HTN | % DM | Indication for cath | LR+ |
|-------|----|----|----|----|------------|------------|------------|------------|------|--------|--------|------|------|------|-------------------|-----|
| LVEDP Manouras et al, 2013 (48) EF>55% | 7  | 4  | 12 | 12 | 0.636 | 0.339 | 0.857 | 0.500 | 0.310 | 0.690 | Primary | Simultaneously | unclear | no CAD | unclear | unclear | angiography | 1.3 |
| PCWP Dokainish et al, 2004 (19) | 2  | 6  | 2  | 9  | 0.250 | 0.063 | 0.623 | 0.818 | 0.493 | 0.954 | Primary | Simultaneously | unclear | unclear | ~60% HTN | ~20% DM | ICU/CCU | 1.4 |
| PCWP Bhella et al, 2011 (39) | 2  | 3  | 1  | 4  | 0.400 | 0.100 | 0.800 | 0.800 | 0.309 | 0.973 | Primary | Simultaneously | 100% HF | no CAD | 100% HTN | ~60% DM | research | 2.0 |
| LVEDP Dokainish et al, 2010 (35) | 4  | 19 | 3  | 96 | 0.174 | 0.067 | 0.382 | 0.970 | 0.910 | 0.990 | Primary | NOT simultaneously | unclear | some CAD | ~90% HTN | ~40% DM | angiography | 5.8 |
| LVEDP Bruch et al, 2005 (22) EF>45% | 2  | 13 | 0  | 11 | 0.156 | 0.046 | 0.417 | 0.958 | 0.575 | 0.997 | Suppleme | NOT simultaneously | 100% HF | some CAD | ~80% HTN | unclear | dyspnea | 3.7 |
| LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients | 6  | 4  | 8  | 12 | 0.600 | 0.297 | 0.842 | 0.600 | 0.380 | 0.786 | Supplementary | Simultaneously | ~70% HF | no CAD | ~70% HTN | ~30% DM | dyspnea | 1.5 |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
A. Combined LVFP (primary and supplemental data)

Primary studies combined (n=4, as in Figure 4)
Sensitivity (summary) 0.36 (0.03 - 0.74)
Specificity (summary) 0.83 (0.49 – 1.0)

All studies combined (n=6)
Sensitivity (summary) 0.36 (0.10 - 0.65)
Specificity (summary) 0.84 (0.61- 1.0)

There are insufficient number of studies (n=2) with supplements data to perform a meaningful analysis.

TP= true positive; FP= false positive; FN= false negative; TN= true negative; Sens. = sensitivity; Spec. = specificity; LR+= positive likelihood ratio; HSROC = hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I² statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
B. Combined LVFP (Simultaneous and not simultaneous measurements)

Simultaneous studies combined (n=4)
Sensitivity (summary) 0.48 (0.13 - 0.80)
Specificity (summary) 0.66 (0.38 – 0.91)

All studies combined (n=6)
Sensitivity (summary) 0.36 (0.10 - 0.65)
Specificity (summary) 0.84 (0.61- 1.0)

There are insufficient number of studies (n=2) with NOT simultaneous measurements to perform a meaningful analysis.
C. Separate analysis for LVFP measurements

**HSROC analysis**

| Studies                  | Sensitivity (summary) | Specificity (summary) |
|--------------------------|-----------------------|-----------------------|
| LVEDP measurements      | 0.36 (0.05 – 1.0)     | 0.86 (0.47 – 1.0)     |
| All studies combined    | 0.36 (0.10 - 0.65)    | 0.84 (0.61 - 1.0)     |

There are insufficient number of studies (n=2) that measured PCWP measurements to perform a meaningful analysis.
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

Primary Simultaneous studies

All Primary studies

Primary Simultaneous studies (n=3)
Sensitivity (summary) 0.43 (0.01 – 0.81)
Specificity (summary) 0.69 (0.35 – 1.0)

All Primary studies (n=4)
Sensitivity (summary) 0.36 (0.03 - 0.74)
Specificity (summary) 0.83 (0.49- 1.0)

LR+ = 1.4

LR+ = 2.1
8.3. Subgroup analysis for $E/e'$ _septal_ <8 to identify normal LVFP

$E/e'$ _septal_: Dataset for subgroup analysis (see also Tables 1 and 2)

| study | TP | FN | FP | TN | SENS. | lower | upper | SPEC. | lower | upper | Data | Timing | % HFpEF | % CAD | % HTN | % DM | Indication for cath | LR+ |
|-------|----|----|----|----|-------|-------|-------|-------|-------|-------|------|--------|---------|-------|-------|------|-------------------|-----|
| LVMDP Ommen et al, 2000 (15) | 21 | 22 | 2  | 16 | 0.488 | 0.344 | 0.634 | 0.889 | 0.648 | 0.972 | Primary | Simultaneously | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 4.4 |
| PCWP Rivas-Gotz et al, 2003 (18) | 8  | 8  | 1  | 35 | 0.500 | 0.273 | 0.727 | 0.972 | 0.827 | 0.996 | Primary | Simultaneously | Unclear | Unclear | Unclear | Unclear | Unclear | ICU/Cath lab | 17.9 |
| LVMDP Rudko et al, 2008 (32) | 14 | 11 | 4  | 14 | 0.560 | 0.366 | 0.737 | 0.778 | 0.535 | 0.914 | Primary | Simultaneously | ~20% HF | ~80% CAD | ~50% HTN | Unclear | Unclear | Unclear | 2.5 |
| LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients | 6  | 4  | 8  | 12 | 0.600 | 0.297 | 0.842 | 0.600 | 0.380 | 0.786 | Supplement | Simultaneously | ~70% HF | no CAD | ~70% HTN | ~30% DM | dyspnea | 1.5 |

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.
A. Combined LVFP (primary and supplemental data)

Primary studies

- Sensitivity (summary) 0.50 (0.14 – 0.81)
- Specificity (summary) 0.89 (0.66 – 1.0)

All studies

- Sensitivity (summary) 0.54 (0.25 - 0.82)
- Specificity (summary) 0.84 (0.61 – 1.0)

**LR+ = 4.5**

**LR+ = 3.4**

TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens. = sensitivity; Spec. =specificity; LR+=positive likelihood ratio; HSROC=hierarchichal summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I² statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.
B. Combined LVFP (Simultaneous and not simultaneous measurements)

All studies are simultaneous

HSROC analysis

All studies are simultaneous (n=4)
Sensitivity (summary) 0.54 (0.25 - 0.82)
Specificity (summary) 0.84 (0.61 – 1.0)

LR+ = 3.4
C. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

All Primary studies are simultaneous

HSROC analysis

Primary studies (n=3)
Sensitivity (summary) 0.50 (0.14 – 0.81)
Specificity (summary) 0.89 (0.66 – 1.0)

LR+ = 4.5