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Cardio-Phoenix™

White Paper

CARDIO-HART™
ENABLING THE EARLY DETECTION OF CVD ONSET
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Notice to Reader.

This White Paper is a synopsis of the technical accomplishments and capabilities of Cardio-HART™, a.k.a. "CHART". It is intended to be regularly updated as and when required, with or without notice to reader.

This document was prepared with our best effort to ensure correctness and accuracy of any claims, figures, performance numbers, however, despite our best efforts, errors can occur and the reader should be aware of this possibility. Corrections will be made on a reasonable effort basis.

Last Updated:

Jan 19th, 2021 – by IK, for corrections

Jan 25th, 2021- by MB, section added for aggregate results & Performance figures were updated.

Jan 28th 2021 – by IK update performance, add external validation.

Mar 12 2021 – Update Heart Failure table, by IK

Apr 09 2021 – Update complete Heart Failure related text

 1.2.1 Heart Failure - new section introduction;

 1.5.1 Use Case #1. Primary Care perspective. according to three accepted categories of HF

 2.4 Heart Failure - the meaning for Primary Care - new

 3.5 HF performance by HART-findings - new section

 7.1.1 CHART Findings and HF indication - update CHART report example, showing HF part



CHART Whitepaper

1	What is Cardio-HART™ or CHART?	3
1.1	The intended use	3
1.2	Unmet Medical Need (UMN)	3
1.3	The CHART system, 3 Main Elements	6
1.4	Certifications and Specifications.....	7
1.5	Typical Use case.....	7
1.6	Duration and Conduct of an Examination.....	10
2	Detecting & Diagnosing Significant Heart Disease	12
2.1	Echo-findings = HART findings	13
2.2	The diagnostic capabilities of CHART.....	13
2.3	14 HART findings definition	15
2.4	Heart Failure - the meaning for Primary Care.....	16
2.5	Significant and Common Heart Diseases	21
2.6	Classification Models for HART Findings.....	24
3	HART™ Findings Performance	28
3.1	Performance evaluation for HART-findings	28
3.2	Individual Performance of HART Findings	33
3.3	HART Aggregated Performance	39
3.4	HART Performance Compared to predicate ECG.....	43
3.5	HF performance by HART-findings.....	50
4	HART™ Findings and comorbidities	53
4.1	General comorbidity analysis between heart diseases	53
4.2	Individual Comorbidity Analysis.....	57
4.3	14 HART Findings and Comorbidities.....	60
5	ECG, PCG, and MCG Finding Performance	91
5.1	Bio-signal Finding Validation.....	93
5.2	Performance Results.....	94
6	P-ECG, CPA-ECG and HART performance comparison	101
6.1	LVH/ Dilated LV	102
6.2	RVH / Dilated RV	105
6.3	LA Enlargement.....	107
6.4	RA Enlargement	109
6.5	Wall Motion Abnormality	111
7	Appendix	114
7.1	Appendix A – CHART Report Sample	114
7.2	Appendix B – CE certifications	120
7.3	Appendix D – CHART examination	121



1 What is Cardio-HART™ or CHART?

1.1 The intended use

CHART provides the practitioner with indications of early onset of CVD and also with clinical data about a patient's cardiac status that is not only of diagnostic interest, but also guides the practitioner in deciding whether to refer the patient to the Cardiologist, and provides the Cardiologist with relevant information to guide clinical decisions about testing and treatment.

It is indicated for use in clinical care situations, including Primary Care and Telehealth settings.

1.2 Unmet Medical Need (UMN)

The primary UMN addressed by CHART is

"the early detection of CVD - in Primary Care."

Primary Care is the principal contact point with the patient, where heart disease is first presented and suspected, but all too often can go unnoticed, sometimes for months, even years.

Early indication means the ability to detect and diagnose a life-threatening condition such as Heart Failure or Valve Failure immediately upon patient presentation to the clinic rather than after weeks or months clinical visits, and lab tests.

Early detection can lead to more timely access to treatment options, whether preventative or pharmacological, that can be indicated in Primary Care, when they are not only more effective but also far more cost-efficient and more accessible to patients or to secondary care as required.

The secondary UMN addressed by CHART is:

"to guide the Practitioner in deciding whether the patient should be sent, or not sent, to the Cardiologist".

Constrained by ECG's limitations and armed only with Risk Assessments, GPs find it challenging to determine when a patient needs to be referred to secondary level of care, cardiology.

Cardiology evidence, shows that this can lead to higher FP and FN rates that both strain the healthcare system, increase wait times, delaying timely access to appropriate treatment options, leading to lower patient quality of life, and higher patient morbidity and mortality. Higher rates of FP and FN directly impact overall treatment costs, not only for the patient but to the healthcare system as a whole.



For example, a patient detected with Heart Failure with Preserved EF (HFpEF), can be Normal or Mild. An indication of Mild, although Abnormal, should not warrant a referral to the Cardiologist. But Mild is also not Normal and should not be ignored, as a timely administered treatment would likely inhibit its progression to Moderate, which if left untreated it is most likely to do.

Whereas detection and diagnosis of HFrEF, both Moderate or Severe, requires referring the patient to cardiology as this level of severity is beyond the capabilities of the GP.

With CHART, GP's become first responders and gatekeepers to secondary levels of care by providing the Cardiologist with a "better patient", one that needs access to the Cardiologist.

Although technically not an UMN, but related to the previous two UMN's, CHART provides the Cardiologist with relevant information to guide clinical decisions about patient management for testing and treatment, whether the patient should remain in Primary Care or not, and assigning a triage priority for more urgent cases. This "better Patient", helps keep some patients in Primary Care, under Cardiologist direction, but also ensures and prioritizes patients on the basis of need.

These UMN's are aggravated by a technological gap in diagnostic capabilities between Primary Care and Secondary Care, which CHART can both resolve and mitigate, leading to better patient outcomes, and lower costs.

1.2.1 Heart Failure

The recent guideline for Heart Failure¹ proposed a simplified HF classification principally according to left ventricular ejection fraction (LVEF). This simplified classification includes HF with reduced EF (HFrEF): HF with an LVEF of $\leq 40\%$; HF with mildly reduced EF (HFmrEF): HF with an LVEF of 41% to 49%; HF with preserved EF (HFpEF): HF with an LVEF of $\geq 50\%$. However, the categorization of heart failure is not only relying on the type and the degree of left ventricular dysfunction, but many other conditions and pathophysiological characteristics² more accurately define

[1] ¹ Bozkurt, Biykem, et al. "Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure." Journal of cardiac failure (2021).

[2] ² Andronic, Anca Andreea, Sorina Mihaila, and Mircea Cinteza. "Heart failure with mid-range ejection fraction—a new category of heart failure or still a gray zone." Maedica 11.4 (2016): 320.



the true nature of HF, and it is that nature that warrants specificity to ensure the appropriate treatment options are selected. Its simple, LVEF is not a treatable disease in and of itself. LVEF is only one of many indications of HF, albeit a simplistic one that is easy to understand.

The recent acceptance of HFmrEF by the international HF consortiums, means there are now three major classifications for HF including HFpEF, HFmrEF, and HFrEF; each of the three have different underlying functional and morphological characteristics.

Defining HF only by LVEF is convenient and any physician can understand it. But there are three problems with this:

- 1) HFpEF cannot be separate from normal patient, since both has LVEF>50%,
- 2) LVEF measurement is not available in primary care,
- 3) the uncertainty around LVEF measurement is critical, and increases the risks. A low LVEF is not a treatable condition in Primary Care, however the underlying disease characteristics might be, which leads to different treatment options or pathways. Understanding them, gives Primary Care physicians a potential role in patient first response treatments that can complement and support Cardiology Care.

CHART as a new Breakthrough Technology from Cardio-Phoenix using novel bio-signals can construct and predict the heart abnormalities that define the underlying characteristics of all three HF categories. This breakthrough allows Primary Care to play the role of first-responder in HF patient care, and ensures that Primary Care physicians understand more clearly the diagnostic and treatment limitations of doing so in Primary Care and most critically, understanding when to send a patient to cardiology.



1.3 The CHART system

The CHART system is an AI powered diagnostic system that consists of three main elements, 1) a medical device for use at the clinical level; 2) a cloud based AI analysis system; and 3) a clinical management system to connect them.

1.3.1 The Cardio-TriTest™ (CTT)

The CTT device is a simple medical device for use in clinical practice to capture three types of bio-signals. Basically, it is 3-devices in one. First, it is a Standard 12-Lead ECG device to capture the electrical bio-signals; second, it is a 4 lead Phonocardiograph (PCG) device that captures the acoustic bio-signals from the heart; and third, it is a 4-lead device that captures the physiological or mechanical bio-signals of the heart (MCG). The signals are captured synchronously such that the 3 types of bio-signals record the same heart event at the same point in the heart cycle.

The device is interfaced through a computer by a nurse friendly UI that captures the signals and uploads them to the CHART system for AI processing. A trained ECG nurse can learn to use the device within 20 minutes. In clinical workflows, the CTT device does not change any aspect of the standard of care.

Signal capture can be done in any safe-testing center and the results of the test sent for Telehealth access directly to the patient's HCP.

The UI includes an option for the nurse to conduct a short 7 answer or long 22 answer questionnaire related to the patient's heart risk factors. Prior to each test, the nurse must record a patients blood pressure, height, waist size, hip size (girth), and weight. The CPA uses this information to normalize (index) the measurements by the patients body size, mitigating racial and ethnic differences³, thereby increasing diagnostic accuracy.

1.3.2 The CHART Processing Algorithm (CPA)

The CPA is a cloud based AI powered algorithmic processing and analysis system to assess the incoming bio-signals and provides endpoint outputs in the form of 14 x HART-findings (equivalent to ECHO-findings), 14 x ECG group findings with 33 endpoints, 7 MCG and 12 PCG specific findings. This software medical device is not accessible to users directly, it is only a

³ Poppe, K. K., et al. "Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: the EchoNoRMAL Study." JACC: Cardiovascular Imaging 8.6 (2015): 656-665.



service. Output is via PDF report, or PDF enCPAulated HL7 report, shown in [Appendix A](#) - section 7.1.

1.3.3 The Clinical Management System (CMS).

The CMS connects the CTT device to the CPA, provides clinical management of the patient, and connects the HCP with the test results. The system is a closed environment that is entirely encrypted, for cybersecurity reasons. It supports the uploading of files, the downloading of test results and their processing by the CPA server. The CMS is not a medical device.

1.4 Certifications and Specifications

1.4.1 Cardio-Phoenix Inc.

- ISO13485:2016 since 2018.

1.4.2 Cardio-TriTest™ (CTT)

- CE Mark certified, as a Class IIa device. Appendix B
- FDA cleared, Class II device, K182970

1.4.3 CHART Processing Algorithm (CPA)

- CE Mark certified, as a class IIa device, Appendix C

1.5 Typical Use case

1.5.1 Use Case #1. Primary Care perspective.

Patient presents in Primary Care complaining of shortness of breath. GP suspects several potential conditions, including HF. But there is insufficient evidence for a clinical decision for any heart disease condition, much less for HF for a referral to Cardiology.

Current practice is for GP to initiate a series of lab-tests, including an ECG examination. The tests will likely be inclusive and require patient to attend Primary Care for each and for subsequent testing. At the end of 2-3 months, the typical timeline for this, the GP will suspect HF and make a referral to the Cardiologist. There is a hard cost to this regimen, that will depend on number of consultation visits and tests undertaken, and a soft cost, in the form of additional morbidity suffered by the patient.

The CHART difference. GP prescribes a CHART examination, conducted on site or at a remote testing center. The CHART report is presented to the GP within minutes of the examination, who can then immediately confirm HF and schedule, with an appropriate priority, a referral to cardiology.



Consultation with the Cardiologists, can also help triage the patient based on severity.

The patient was given a CHART examination within the hour/same day. The results are telehealth available to the GP, for immediate follow-up.

If they indicate:

- HART summary is absence of HF, severity = “Normal”. No referral to cardiology. Next CHART examination, 2 years (as per standard of care).
- HART summary is consider HFpEF with Severity = “Normal” Systolic but abnormal HART findings associated to HFpEF, such as Atrial Fibrillation or Diastolic Dysfunction. No referral to cardiology. Next CHART examination, 1 years (as per standard of care).
- HART summary is consider HFmrEF – with severity = “Mild” Systolic Dysfunction. GP will likely not refer the patient to cardiology but put them on a regimen of preventative and pharmacological treatments and schedule a follow-up control, in either 3 or 6 months⁴.
- HART summary is consider HFrEF – with severity = Moderate or Severe, then either an immediate referral to cardiology or alternatively, dependent on the Standard of Care, the results are first shared with the Cardiologist, who can better determine if this is a patient they “need to see or not”. If yes, the patient is assigned a priority, and given an appointment based on that priority. Priorities include: Urgent (within 3-5 days), Immediate (within 14 days) or Routine, (within 90 days) as per the standard of care. If not, then a control is likely scheduled in 3 or 6 months time.
- Alternatively, if Moderate, the Cardiologist can also indicate this is not a patient they might not need to see at this time, and instead simply provide further instructions on testing and treatment, and indicate a control, e.g. that the patient be re-tested in 3 months.

CHART supports collaborative triage for the most cost efficient and most effective patient management.

From patient presentation, to appropriate patient management determination, in the above example the duration was basically “same day”. Currently, this same example regularly takes 2-3 months of various confirmation testing, evaluations and multiple clinical visits to Primary Care. Cost savings are not only related to cardiology, but also in Primary Care as

⁴ This example is in accordance with BSE diagnostic protocols. It is an example only.



there was no need for all the additional confirmation testing and clinical visits normally conducted to confirm a “suspicion” of HFdEF.

In an FDA designed and approved clinical investigation, GP's using CHART increased their diagnostic effectiveness by ~250% over their counterparts who were using a State-of-the-Art ECG device (that included Automated Algorithmic support). The protocol had ½ the GP's using CHART, the other ½ using ECG. They both attended the same patient. A direct comparison of the “effectiveness” was therefore possible.

On average, FN were reduced by 16% (from 50% to 34%) and FP by 5% (from 21% to 16%) in referral decisions.

The Study is available as a separate document, titled “Clinical Usability and Utility Study, a 3 center study of CHART”. (please send request to documents@cardiophoenix.com)

1.5.2 Use Case #2. Secondary Care perspective.

Patient was referred to Secondary care based on some minor blip in their ECG.

Current Practice, example 1. Patient is sitting in the Secondary care waiting room anxiously waiting after an appointment that was booked 3 months previously. The GP suspected HF but the clinical evidence was not conclusive. Patient is given an Expensive Echocardiography examination and there was no presence of heart disease at all. Patient was a True Negative and cardiologist just confirmed it, promptly sending the patient home. The examination took 40 minutes as the cardiologist had to do a cold start Echo, hunting for possible heart disease condition. The visit and examination has a high cost that the system absorbed.

CHART protocol, example 1. Patient was referred to secondary care on dubious results. Cardiologist prescribes a CHART examination through the local testing center or in their clinic. Results show patient is negative or Normal. The CHART report's NPV confirms the patient has no abnormality that warrants a secondary care appointment for Echocardiography. Patient is sent back to Primary Care with report. Cardiologists orders a control for the patient to be CHART examined in 12 months. Patient did not take an appointment time slot from a CHART confirmed patient. The waiting list was not prolonged. Cardiologist time used, none! All the above was virtually nil, as most was done by cardiologists trusted assistant.

Current Practice, example 2. Patient is same as above. However the blip was real and patient is a True Positive. But the delay in getting an appointment for Echocardiograph confirmation was 3 months and patient



condition has worsened, morbidity has increased as a result. Patient will now have to undertake more onerous and expensive treatment.

Current Practice, example 3. (True Story). Same patient with blip on their ECG. Patients funeral is set for Wednesday, the day before the scheduled cardiology appointment. Patient never attended his daughters wedding, which was to be on the following Saturday.

CHART protocol. GP sent patient to Testing center and his CHART report showed heart failure with decreased EF, of severity Severe. GP shared this report with Cardiologist who immediately scheduled, triaged, an appointment within days, with priority URGENT. Patient condition was confirmed and as a result successfully treated. Medicated, patient attended his daughters wedding. No ambulance was called for. The system did what both patients and practitioners expected it to do. The costs were justified, although the ongoing treatment costs were more than the burial costs, the patients quality of life was somewhat more appreciated.

1.6 Duration and Conduct of an Examination

A CHART examination is expected to be conducted by a trained nurse or medical assistant, in less than 15 minutes. An ECG trained nurse can learn to use CHART in less than 20 min.

As the device is also a Standard 12-Lead ECG device there are 10 leads. Additionally, CHART adds 4 x PMCG leads, that are placed on the thoracic wall, in the 4 standard auscultation points. A harness is used to apply light pressure on these sensor during a test.

A typical examination lasts 6-12 minutes longer than a typical ECG. This is because each examination includes:

- a. Recording 2 x 1 minute long tests, with 15 second rest between tests.
- b. Prior to the test, taking a patients “vital signs”, Blood Pressure, weight, height, waist and hip size.
- c. Optionally, one of two risk factors questionnaires can be conducted, the quick or the long. The quick has 7 risk factors, the long 22. They are especially useful in Telehealth settings.
- d. A complete examination routine with timings is shown in [Appendix D](#)



PANDEMIC QUESTIONNAIRE

Optionally During the Pandemic, two additional questionnaires can be activated. The first is for the Medical Attendant to make their own observations about the patient. The second, conducted by the MA is for the patients answers to COVID-19 related questions.

It is very useful when used in “safe-testing” centres supported by Telehealth.



2 Detecting & Diagnosing Significant Heart Disease

CHART is a breakthrough technology that uniquely uses bio-signals, instead of images as in Echocardiography, to diagnose the same significant heart diseases.

The use of bio-signals means that CHART can be used in Primary Care situations. Echocardiography is not indicated for use in Primary Care.

Yet, CHART can detect and diagnose the same 14 significant heart diseases that typically are only detected and diagnosed by Echocardiography in Cardiology⁵.

These include:

1. Left Ventricular Hypertrophy [LVH],
2. Dilated Cardiomyopathy [DCM],
3. Right Ventricular Enlargement [RVE],
4. Left Atrial Enlargement [LAE],
5. Right Atrial Enlargement [RAE],
6. LV Systolic Dysfunction [LVSD],
7. LV Diastolic Dysfunction (Impaired Relaxation) [LVDD],
8. LV Wall Motion Abnormality (Ischemia) [WMA],
9. Aortic Valve Insufficiency [AR],
10. Aortic Stenosis [AS],
11. Mitral Valve Insufficiency [MR],
12. Mitral Valve Stenosis (Mitral Defect) [MS],
13. Tricuspid Valve Insufficiency [TR],
14. Pulmonary Hypertension [PH].

Details of their performance and safety are documented herein.

⁵ The prediction capability of ECG for these abnormalities are very limited, see section 0



2.1 Echo-findings = HART findings

Echo-findings are known in CHART as “HART-findings”⁶, they constitute 14 of the most debilitating or significant heart diseases that by prevalence represents 90% of all heart diseases diagnosable by Echocardiography in the general population.

CHART being 3 devices in one, can also diagnose 99.8% of all ECG and most all PCG diseases, which when combined with the HART-findings, means it can detect and diagnose up to 95% of all significant and common heart diseases found in Primary Care population situations⁷.

This represents a disruptive shift in diagnostic capabilities in Primary Care – it makes CHART a “first-use” medical device for heart care.

CHART is a game changer for Primary Care.

With CHART, diagnostic capabilities similar to those found using Echocardiography are now available in Primary care, but now with the added purpose of early detection of CVD onset.

CHART closes the diagnostic gap between Primary Care and Secondary levels of care ensuring more appropriate patient management triage.

CHART does not replace the Cardiologist, but rather provides the medical justification for access to Secondary care and the Cardiologist.

2.2 The diagnostic capabilities of CHART.

The difficulty of diagnosing significant heart diseases using bio-signals depends in large part on the nature of the disease itself. The genius of CHART is that it analyses the three types of bio-signals, both separately and synchronized, to identify different characteristics for each of the diseases.

ECG interpretation can reach high performance if the problem is related to the electrophysiology of the heart, such as arrhythmias, premature beats, atrioventricular blocks, bundle-branch blocks.

But ECG is less clear in the case of mechano-physiological or hemodynamical abnormalities.

The 3 types of bio-signals have their strengths:

- Electro-physiological abnormalities: arrhythmias, premature beats, atrioventricular blocks, bundle-branch blocks, etc.

⁶ FDA request change of name as although the diseases described are the same, their source are not, Echo-findings originate from Echocardiography Images, and HART findings from bio-signals.

⁷ CHART does not do rare diseases. Details in Chapter 2.5.



- Mechano-physiological abnormalities: cardiomyopathy, myocarditis, myocardial infarction, ischemia, hypertrophies, atrial enlargements, systolic or diastolic dysfunction or other wall motion problems.
- Hemodynamical diseases: valve stenosis, valve regurgitation, hypertension (pulmonary hypertension)

ECG has some known signs for the mechano-physiological diseases, typically the repolarization abnormalities, such as, abnormal T wave, ST deviation - associated to coronary artery diseases, the abnormally high QRS voltages as a symptom of ventricular hypertrophies and abnormal P wave voltages related to atrial enlargements. However, the research studies are not in agreement on their reliable diagnostic performance.

For example, the ECG criteria for LVH typically shows low sensitivity, within a wide range of between 30-50%, but with a higher (~85%) specificity. This result in a low-modest positive predictive value, leading to high numbers of false negatives, and arguably to higher levels of FP. Unfortunately this higher uncertainty leads to higher numbers of referrals to cardiology as a result. See more details in section 6.

Some recent state of the art ECG processing shows prediction capability for severe systolic dysfunction and moderate/severe aortic stenosis, but the results show that the ECG symptoms (essentially an inverted T-wave) are not sufficiently specific for any one of these diseases, and the positive predictive values are low, only 10-30%. In other words these models lead to excessive numbers of false positives.

In primary care, it is critical that FP be controlled as otherwise the higher level of care will be flooded with FP, i.e. healthy patients. But it should not be at the expense of the FN, as then it is the patient that suffers.

By combining the 3 bio-signals unique characteristics, each disease can be more easily identified, leading to less FP and few FN.



2.3 14 HART findings definition

CPA analyses and diagnoses 14 significant heart diseases⁸ that are critical in patient management.

Table 1 – List of 14 HART Findings and ECHO Criteria

	HART findings	ECHO Criteria for "Mild"	ECHO Criteria for Abnormal	Abbr.
1.	Concentric LVH	IVSd ≥ [10/11] ⁹ mm and LVMI > [100/115] g/m ²	IVSd ≥ [13/14] mm and LVMI > [115/131] g/m ²	LVH
2.	Dilated Cardiomyopathy, (Eccentric LVH)	LVIDd > [53/59] mm	LVIDd > [56/63] mm	DCM
3.	RV Enlargement	RVOT prox. > 30 mm	RVOT prox. > 36 mm	RVE
4.	LA Enlargement	LAVI > 30ml/m ²	LAVI > 40ml/m ²	LAE
5.	RA Enlargement	RAVI > 30ml/m ²	RAVI > 40ml/m ²	RAE
6.	Wall motion abnormality	Mild Hypokinesis	Hypokinesis, EF<52%	WMA
7.	LV Systolic Dysfunction	EF < [54/52] %	Akinesis, Dyskinesis, EF<40%	LVSD
8.	Diastolic Dysfunction (Impaired Relaxation)	E/A < 0.85	E/A < 0.7	LVDD
9.	Aortic Valve Stenosis	AVpV > 2.0 m/s	AVpV > 2.5 m/s	AS
10.	Mitral Valve Stenosis	MVGEm > 3.7 mmHg (E > 1.25 m/s)	MVGEm > 5.0 mmHg (E > 1.5 m/s)	MS
11.	Aortic Valve Insufficiency	AR grade ≥ I	AR grade ≥ II	AR
12.	Mitral Valve Insufficiency	MR grade ≥ I MRj/LA > 20%	MR grade ≥ II MRj/LA > 30%	MR
13.	Tricuspid Valve Insufficiency	TR grade ≥ I TRj/RA > 20%	TR grade ≥ II TRj/RA > 30%	TR
14.	Pulmonary Hypertension	RVSP > 40 mmHg	RVSP > 50 mmHg	PH

⁸ HART findings correspond directly to Echo findings (they diagnose the same diseases). The FDA requested Echo findings be reserved for imaged based diagnosis of the same diseases, whereas HART findings would present bio-signal based findings.

⁹ Different threshold for Female and Male [F/M], according to <https://asecho.org/wp-content/uploads/2018/08/WFTF-Chamber-Quantification-Summary-Doc-Final-July-18.pdf>



2.4 Heart Failure - the meaning for Primary Care

The bio-signal-based diagnostic system CHART was analyzed for the indication of the HART-findings, that create the framework for the three severity categories of heart failure (HFpEF, HFmrEF, HFrEF), now recognized internationally, by most national Cardiac-failure societies, as introduced in section 1.2.1.

Table 2 shows the HF categories and the most important associated co-morbidities that are primarily diagnosed by ECG or ECHO. The list of typical abnormalities or co-morbidities are assembled using both the literature and data gathered in CHART studies.

Table 2 – HF category and related ECHO and ECG-based abnormalities

Heart Failure category	LV Systolic Dysfunction	LVEF	Typical abnormalities ("+" denotes the disease plus the previous ones)
Absent			Non-significant or mild abnormalities – ECG+ECHO
Preserved EF [HFpEF]	Absent (Normal)	>50%	Arrhythmia (Atrial Fibrillation) - ECG Structural heart diseases (LVH, LAE) - ECHO Diastolic dysfunction (DD) - ECHO Valve diseases (AS, AR most important) – ECHO Pulmonary Hypertension – ECHO Leftward Axis - ECG
Mildly-reduced EF [HFmrEF]	Mild	40-49%	+ Systolic dysfunction - ECHO, + Wall motion abnormalities – ECHO +Coronary artery disease (CAD) – ECG+ECHO + Mild dilated cardiomyopathy - ECHO + Sinus Bradycardia – ECG
Reduced EF [HFrEF]	Moderate	30-39%	+ Dilated cardiomyopathy - ECHO + More severe valve diseases - ECHO + Right Heart Enlargement - ECHO
	Severe	<30%	

The listed abnormalities and co-morbidities of HF are typically diagnosed by a combination of ECG but especially by ECHO in Secondary Care according to the current Standard of Care. Therefore, the understanding and prediction of HF is poorly supported at the Primary Care level. This is the gap bio-signal based HF prediction is trying to fill.

2.4.1 Co-morbidity and prevalence statistics

Comorbidity for the diagnosis and prognostication of HFpEF is still widely debated, and research introduces various criteria and scoring systems¹⁰.

[3] ¹⁰ Parcha, Vibhu, et al. "Diagnostic And Prognostic Implications of Heart Failure With Preserved Ejection Fraction Scoring Systems." Journal of Cardiac Failure 26.10 (2020): S38.



Based on the Cario Phoenix database statistics the almost all the ECG and ECHO measurements and findings show more abnormal mean values for the HFrEF category. However there are some exceptions, which are interesting to understanding the HFpEF and HFmrEF categories:

- HFpEF shows highest value of Systolic BP, IVSd, RWT%, AoV Vmax, AR Grade and Jet Area, QTc, and DD Impaired Relaxation, LV Hypertrophy, AV/MV Stenosis, AV Regurgitation, Prolonged QT from findings.
- HFmrEF shows highest QT interval similarly to HFpEF and highest prevalence of Sinus Bradycardia. The prevalence of MI is similarly high as HFrEF has.
- In case of other parameters and findings the HFrEF has the worst mean values and highest deviation.

In this following co-morbidity analysis the LVEF was used as an independent variable to estimates the prevalence of ECG and ECHO abnormalities. The LVEF as continual measurement is split into 9 categories: 1) 20-33% with center is 29.4%, 2) 34-38% with center of 35.9%, 3) 39-43% with center of 40.5%, 4) 44-48% with center of 45.6%, 5) 49-53% with center of 50.7%, 6) 54-58% with center of 55.5%, 7) 59-63% with center of 60.3%, 8) 64-68% with center of 65.3%, 9) 69-80% with center of 71.1%. Along these categories the patient was grouped and the prevalence of ECHO and ECG findings are calculated. The results are plotted in Fig. 1 together with the average value of some principal ECHO measurements: LVEF, LVIDd, LVMI, LAVI, RVSP, E/A (multiplied with 100).

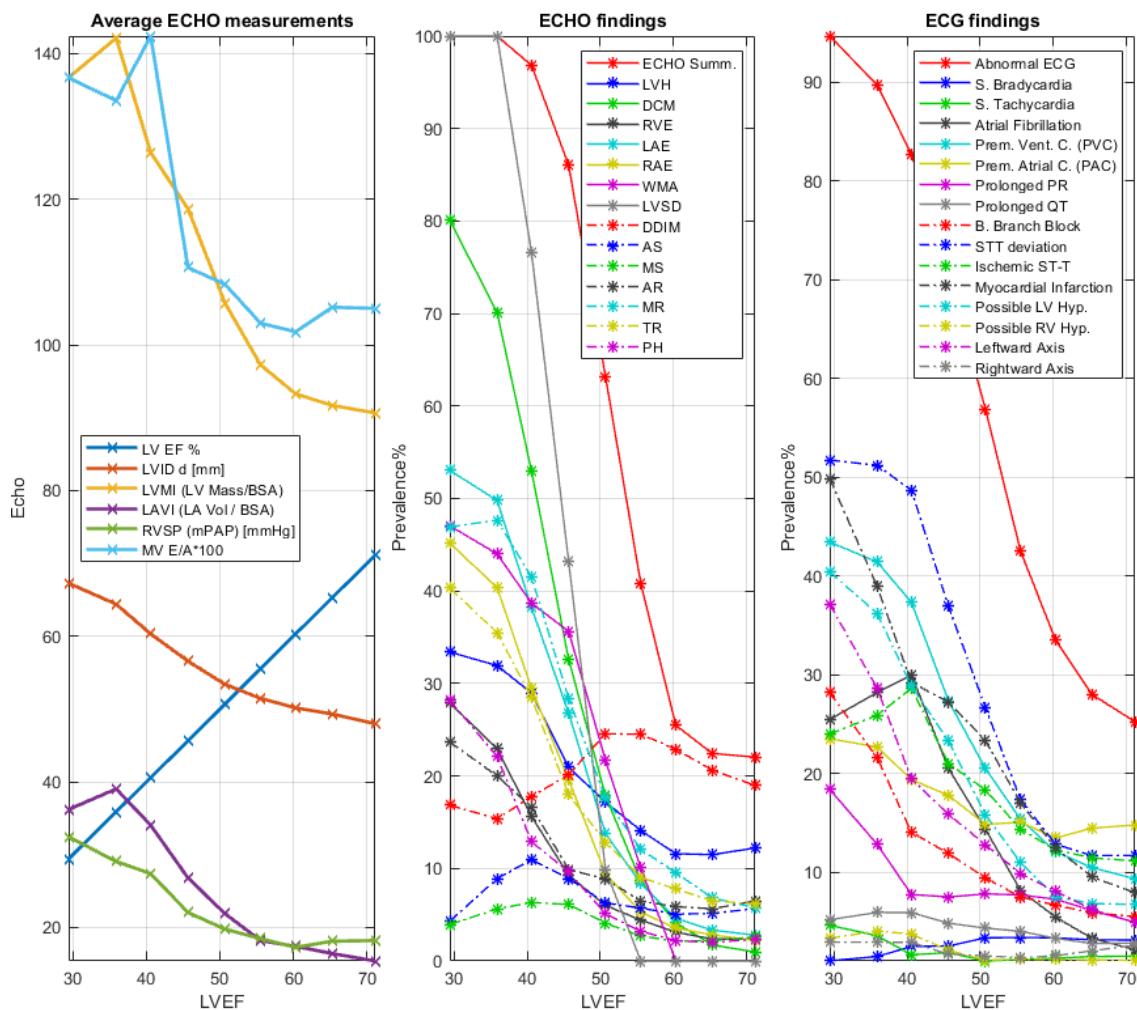


Figure 1 – Co-morbidity analysis according to LVEF categories:

1st graph - Trend of average ECHO measurements in function of LVEF categories

2nd graph - Trend of ECHO-finding prevalence in function of LVEF categories

3rd graph - Trend of ECG-finding prevalence in function of LVEF categories

Heart disease progresses with age, and the cardiac co-morbidity statistics confirm both the disease progression (severity) and the increased co-morbidity factor with increasing age. Fig. 2 shows the prevalence statistics, similarly to Fig. 1, but using patient age instead of LVEF.

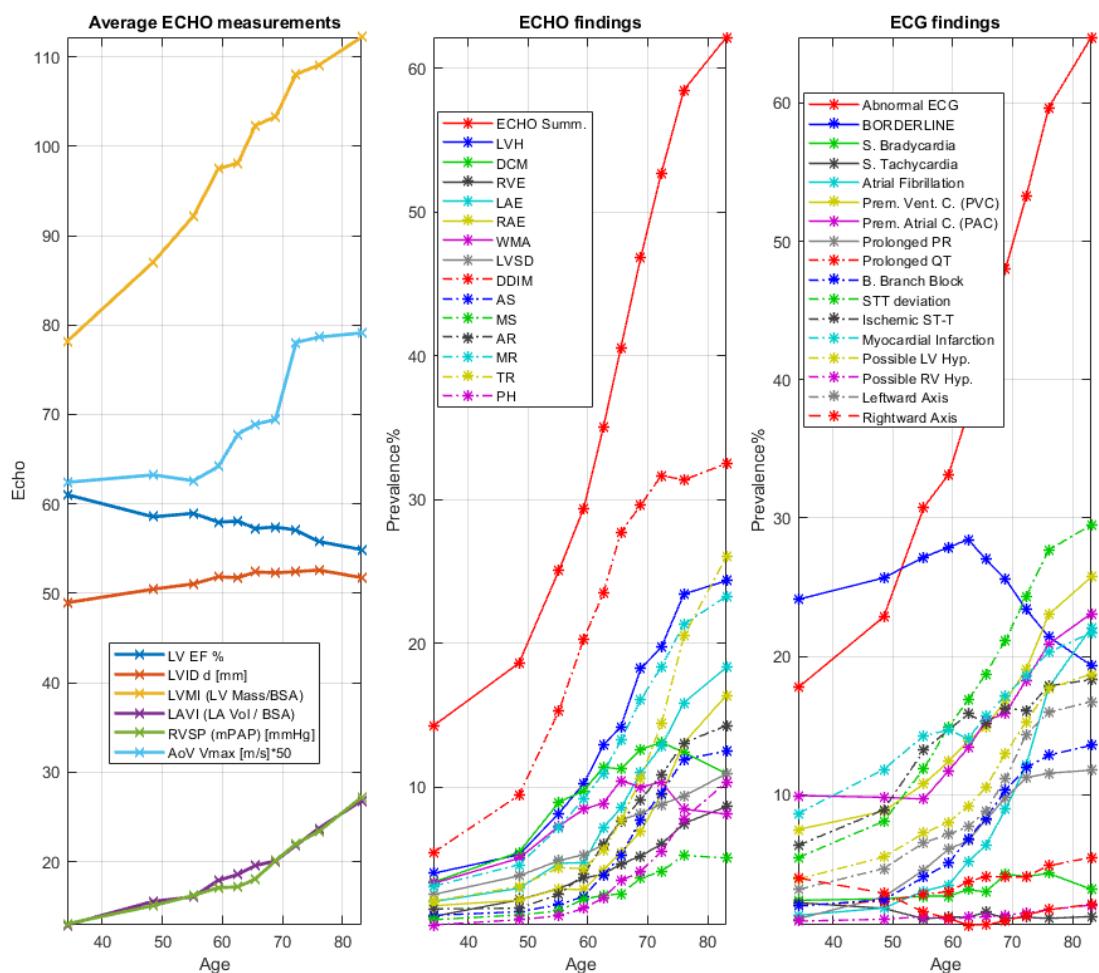


Figure 2 - Co-morbidity analysis according to AGE categories:

1st graph - Trend of average ECHO measurements in function of AGEF categories

2nd graph - Trend of ECHO-finding prevalence in function of AGE categories

3rd graph - Trend of ECG-finding prevalence in function of AGE categories

The Fig. 3 illustrate the individual binary ECHO-findings and ECG-findings. These results provide some disjunctive properties between the HF categories:

- The HFpEF from HFmrEF do not differ too much in prevalence and disease severity, but rather by disease type. HFpEF mostly includes DD, LV hypertrophy and mild/moderate valve disease patients, but HFmrEF includes patients with ischemic problems: WMA, ST-T deviation, MI.
- The HFrEF category includes the most severe abnormal patients, typically the reduce LVEF, dilated LV and enlarged right heart. These patients have the highest level of co-morbidity mixing between electrical, structural, function and valve diseases.
- The co-morbidity analysis shows that all the listed ECHO findings together indicate heart failure, more precisely the enlarged heart



with decreased myocardial contractility or general abnormal heart functioning.

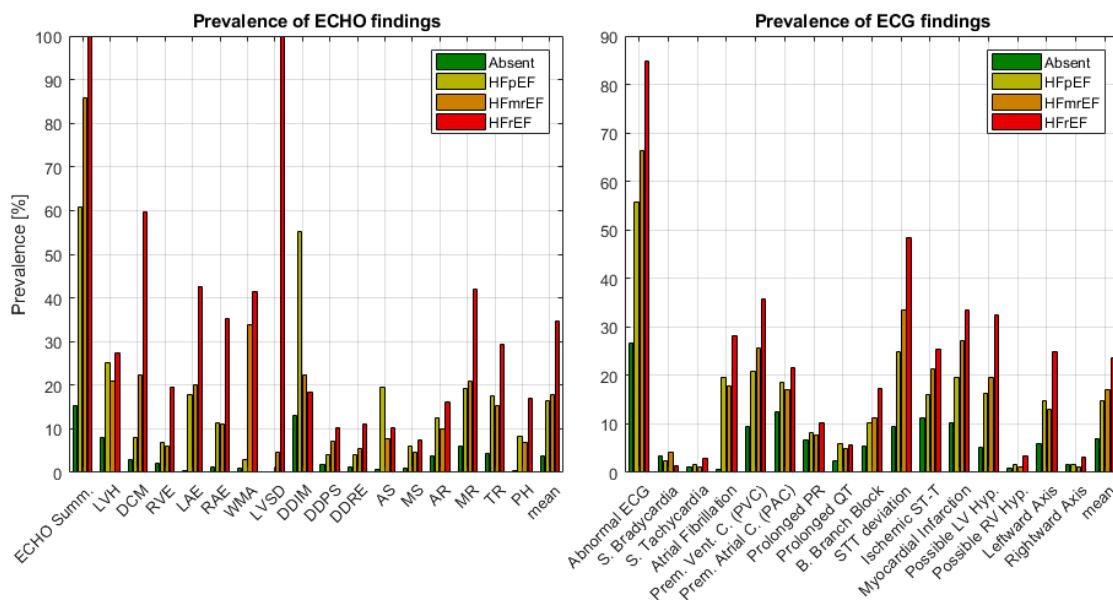


Figure 3 - Prevalence analysis of ECHO and ECG findings in four category of HF

2.4.2 HART-findings and HF indication

CHART uses state-of-the-art neural network regression techniques to extract the hidden medical information from the signals. The supervised training of these networks is trained for key ECHO measurements including LV ejection fraction, see Fig. 4. These compressed features provide the main prediction capability for the CHART-findings.

Based on the estimated LVEF and HART-findings, CHART indicate HF classes using following simple rules:

- HFrEF if LVSD is abnormal and estimated LVEF<40%
- HFmrEF if LVSD is mild and estimated LVEF is between 41-50%
- HFpEF if LVSD is normal but patient has any one abnormal or two mild abnormal from following abnormalities: AFib, DD, PH, LAE, WMA, AS, LVH (AFib is ECG finding without mild condition, the other is predicated by HART findings)
- Otherwise Absent

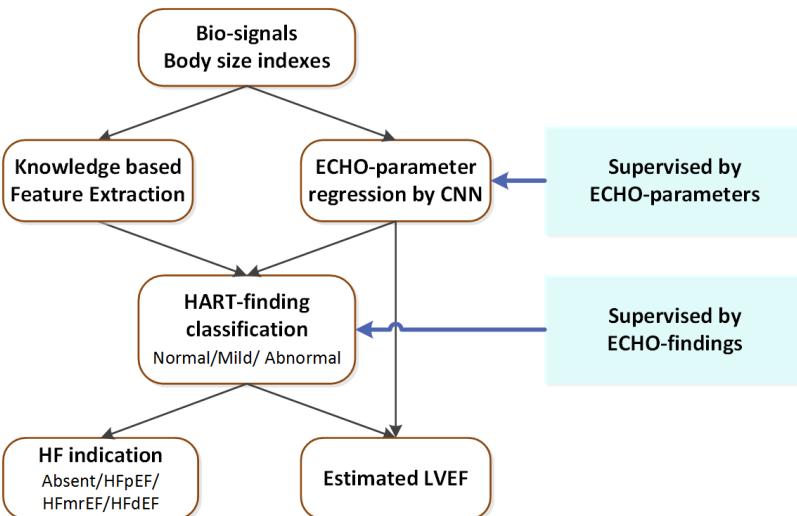


Figure 4 – CHART block diagram for indicating HF and estimated LVEF

2.5 Significant and Common Heart Diseases

Significant heart diseases are those typically indicated via Echocardiography, as Echo-findings or HART-findings¹¹, whereas Common Heart diseases are typically indicated via ECG, as ECG findings. CHART findings as defined for all available ECG and ECHO-findings are evaluated.

The diseases are defined based on a prevalence analysis of the study population, for the disease prevalence in the intended population.

The analysis lists the ECG and ECHO findings that represent the diagnosed diseases. The following basic truth underlie these findings:

- All the standard ECG statements are supported by various State-of-the-Art ECG automated algorithmic analyzers.
- All the available ECHO findings are detected and checked during the echocardiographic analysis in clinical studies.
- Excluded: known cardiac interventions (from list of ECHO-findings), not intended to be diagnosed by this diagnostic device, and so are excluded include: Pacemaker, ICD, CABG, PCI, Artificial valve
- Excluded: non-diagnostic ECHO-findings, such as Spontaneous echo contrast, and other image quality related findings
- Excluded: ECG summary findings, because those are fully redundant findings: Normal ECG, Borderline ECG, Abnormal ECG. Only the Uninterpretable ECG is kept, because in that case no other findings are detected.

¹¹ ECHO-findings and HART-findings denote the same heart diseases. They were differentiated by their means of diagnosis, Echo is imaged based, whereas CHART is bio-signal based. The FDA requested this change to differentiate not the disease but the method of diagnose that same disease.



- Excluded: Sinus Rhythm from ECG findings, because it is normal and is not considered as a disease per se.

In case of ECHO-findings, the prevalence is calculated for all severity of abnormal, including mild, moderate and severe.

In case of ECG findings, the prevalence is calculated including following modalities: prominent, frequent, multiple, marked, probable, possible, borderline.

We can categorize ECG and ECHO-finding prevalence into the following classes:

- Significant and Common heart diseases – prevalence > 1%
- Rare heart diseases – prevalence between 0.1% and 1%
- Very rare heart diseases – prevalence < 0.1%

2.5.1 CHART findings coverage

CPA predicts the HART-, ECG-, PCG- and MCG-findings, which is a selected subset of the analyzed ECG and ECHO findings. (In the CHART system the ECHO-findings are represented by the HART findings.)

The figure below illustrates the prevalence graphically.

Green background color represents findings that the CHART system predicts. Yellow colour, findings it does not predict. Purple represents ECHO findings, it predicts and Orange, ECG findings it predicts. Blue are the integrated findings, a group finding - that are combined to reduce system complexity to the HCP. (in accordance with Intended Use)

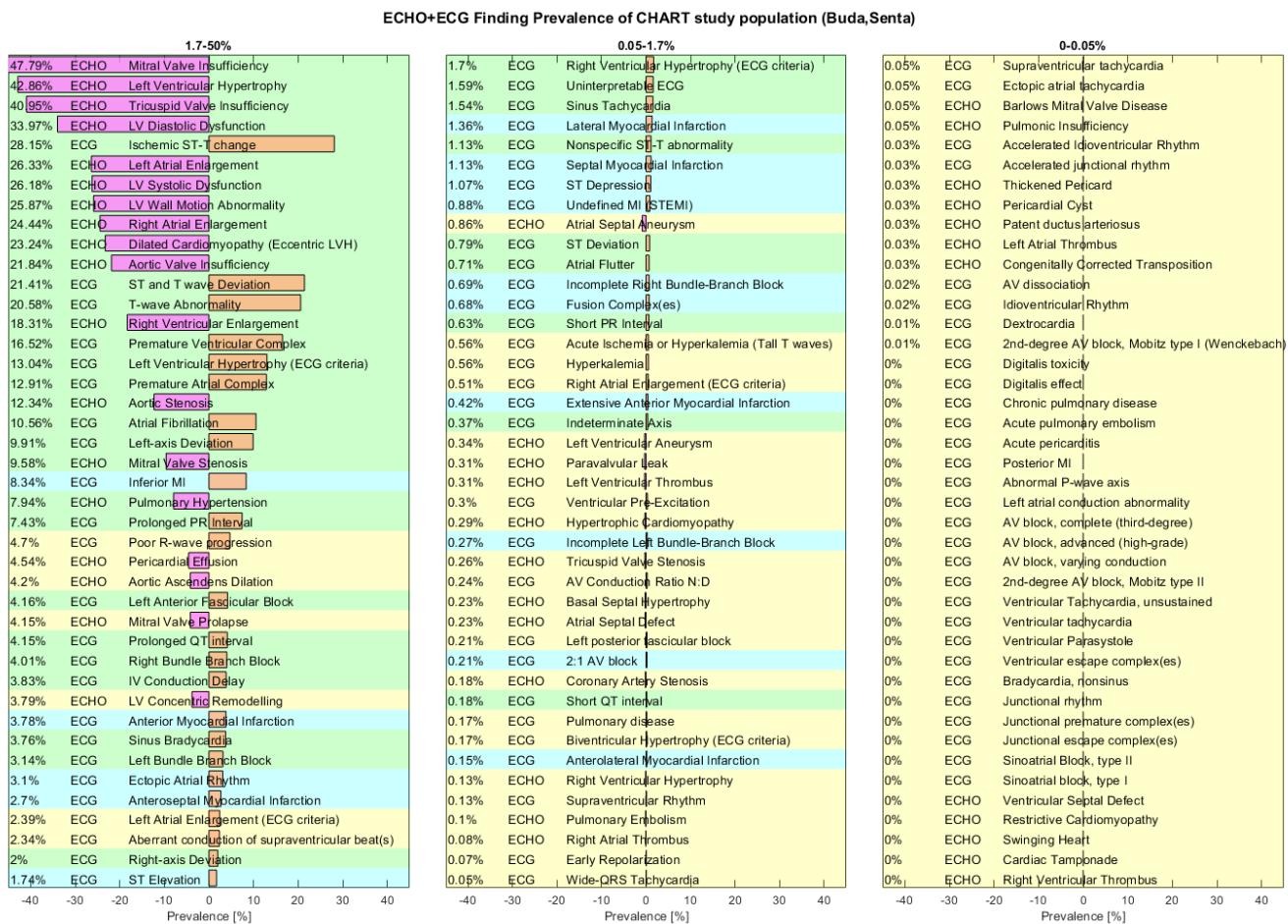


Figure 2-5 - ECG and ECHO-findings prevalence analysis of CHART study population



2.5.2 Conclusions

- ECHO-findings show higher prevalence (64%) compared to ECG-findings (36%).
- **Most significant heart diseases are detected by ECHO, not ECG.**
- CHART system predicts most of the significant heart diseases (prevalence > 1%)
- CHART system does not predict the very rare heart diseases (prevalence < 0.1%)
- CHART system predicts 95% of occurred heart diseases according to the available 25 ECG and 14 ECHO-findings
- This analysis does not include the PCG and MCG findings, which is also provided by CHART report. However, PCG and MCG findings are integrated into HART findings and provide critical morphological information about the hearts functioning.

2.6 Classification Models for HART Findings

CPA classification models use medical features extracted from each of the bio-signals, all synchronized to each other.

CPA AI analysis and interpretation algorithms consists of four main phases:

1. Preparation Phase – is a signal quality phase where signals are processed to ensure noise is reduced and the signals are valid. This ensures high performance in the remainder in the processing.
2. Knowledge Phase – knowledge and physics driven feature generation producing more than 2000 physiological and statistical features.
3. Predictor Phase - produces strong compressed predictor features through supervised learning using the processed, segmented and aligned bio-signals.
4. Classification Phase – Hybrid Machine Learning classification using the knowledge and compressed features. Processing is in 3 distinct NN Steps:
 - a. Step 1, the focus is on FN capture, for highest possible sensitivity, but this generates a high number of FP¹².

¹² This methodology means that the true sensitivity rate for each finding is much higher than what is officially reported after Step 3. In Step 1, the average sensitivity is actually in the mid-90's percentile. This however results in a very high number of FP, which is then controlled in Step 2.



- b. Step 2, using the previous results, focus is on FP reduction, for highest specificity, however, without compromising the previously captured FN;
- c. Step 3, focus is on disease severity, for diagnosing Normal, Mild, Moderate and Severe.

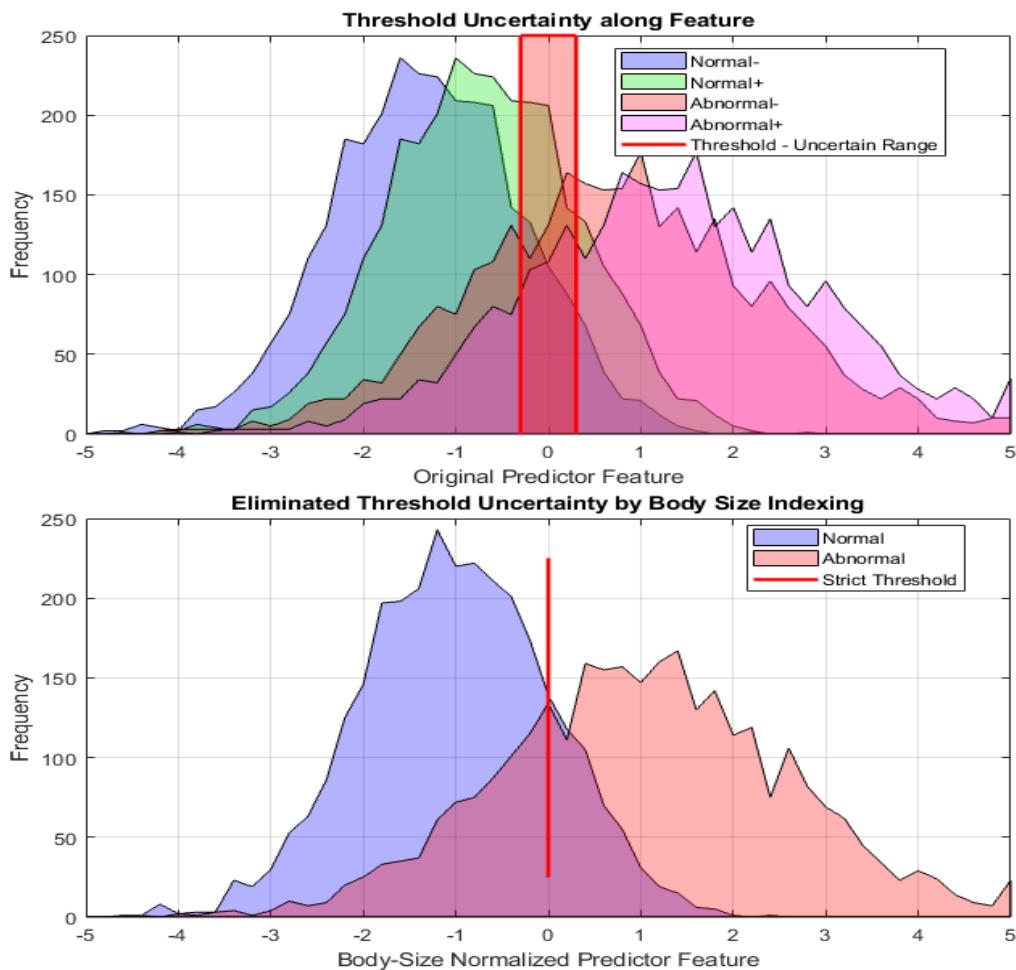
This innovative approach does not redefine disease thresholds, but rather ensures the highest possible sensitivity and specificity, based on prevalence, for each disease, to ensure the highest possible PPV and NPV rates.

2.6.1 Understanding Thresholds in Deep Learning.

CHART's AI, is based on CRS knowledge base, and validated for ground truth, and as such it does not learn new "thresholds", but rather learns to recognize how to apply thresholds to individual patients, making for more accurate diagnostic results.

For example:

Figure 2-6



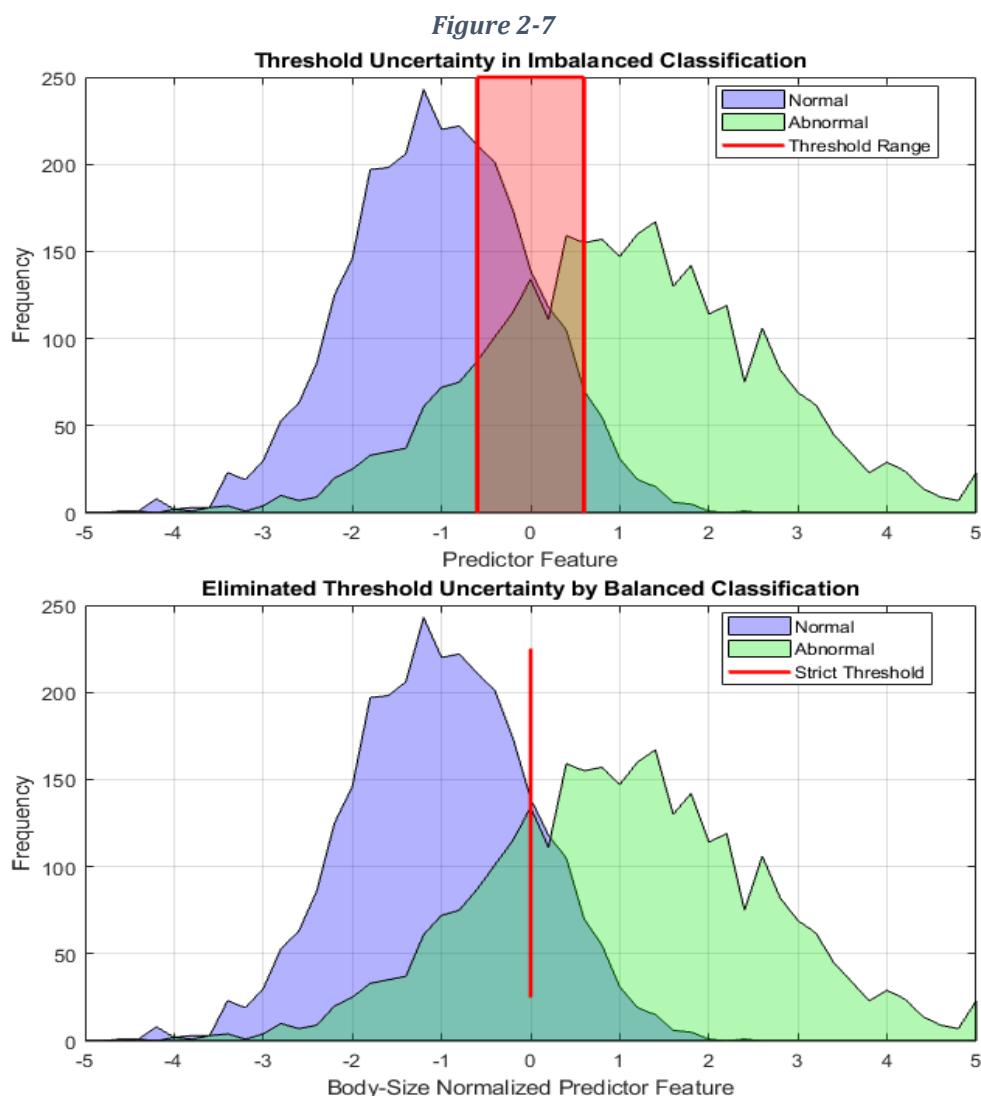


In figure 1, top graph, an AI based on a 1-d CNN, has a wide threshold uncertainty range within the generated features which leads to a higher number of FPs and FNs.

In figure 1, bottom graph, CHART, does not learn a new threshold range because it is based both a threshold preservation mechanism within the algorithm and learning was done on a validated ground truth dataset to establish a stricter threshold range. CHART uses indexing, by body size, such that the thresholds are adapted to the specific patient context, leading to far fewer FP and FN.

A second problem with 1d-CNN's, is their use of unbalanced data that can further increase threshold range bias, further increasing FPs and FNs.

CHART however, uses a strategy of "Balanced Classification" where FN and FP are balanced, defined as $\text{FN} \sim \text{FP} = 1$.



A balanced classification mitigates threshold range bias uncertainty and greatly reduces the FN and FP from unbalanced data.



In figure 2, top graph, the typical 1d CNN would have a wider range of threshold bias uncertainty resulting from the use of unbalanced data. In the bottom graph, CHART's Classification strategy means CHART does not learn new threshold ranges, but instead learns to apply the CRS ranges to the individual patient based on prevalence. This results in higher PPV and NPV rates.

Note: a recent trend by researchers is to use 1d-CNNs and feed ECG signals into them to discover the target "disease". CNN's however are not aware of the thresholds that define that disease as a disease as defined by the Clinical Reference Standards (CRS) committees and regulatory bodies. So the 1-d CNN "learns" new one from the data, including all the biases that are contained in that data. This produces high FP rates and low PPV. The use of non-ground truth validated ECHO data can result in significant threshold variability and bias, which the CNN will learn. It is well known by the ASE¹, including the BSE, CSE, and ESE, that inter Cardiologist measurement variability is as high as 25%. As such, hospital data based on 1 cardiologist's diagnosis does not make for a validated ground truth. It is convenient for research purposes but not valid, much less practical, for clinical use in patient care settings.



3 HART™ Findings Performance

3.1 Performance evaluation for HART-findings

The HART classification models are trained and validated on databases having echocardiographic confirmed ground truth, established by typically 5 Cardiologist in consensus.

The validation database contains the ECG, PCG and MCG bio-signals and the ECHO images, measurements, and findings for each patient. All the patients have echocardiographic assessment after bio-signal recording within 10 days.

The ground truth of ECHO findings was established by Cardiologist consensus and confirmed with ECHO measurements (list is not exhaustive):

- IVSd - End-diastolic Interventricular Septum Thickness [mm]
- LVmass - Left Ventricular Mass [g]
- LVMI = LVmass / BSA - Left Ventricular Mass Index [g/m²]
- LVIDd - End-diastolic Left Ventricular Diameter (internal) [mm]
- RVOT - Right Ventricular Outflow Tract Proximal [mm]
- LAVI - Left Atrial Volume Index [mL/m²]
- RAVI - Right Atrial Volume Index [mL/m²]
- EF - Ejection Fraction [%]
- E/A - E/A Wave Velocity [1/1]
- AVpV - Aortic maximum Velocity [m/s]
- E - Mitral Inflow E Wave Velocity [m/s]
- ARgr - Rate of Aortic Regurgitation [grade]
- MRgr - Rate of Mitral Regurgitation [grade]
- TRgr - Rate of Tricuspid Regurgitation [grade]
- RVSP - Right Ventricular Systolic Pressure [mmHg]

Patient records are collected in five clinical investigations over several years, including 24000 records with 10-30 second length:

- Training and Testing dataset – used for training & internal testing
 - Senta 1 and Buda 5
- External Validation dataset - not used for training
 - Senta 2 and Buda 6
- Independent External Validation database – not used for training
 - CUUS

All the records were separated into unique and separate datasets, without any patient sharing: the training dataset includes 14000 tests, whereas the validation dataset includes 10000 tests. From the sets ~3%



were removed because of unacceptable signal quality or uncertain ground truth; finally, 6882 samples were used for external validation (EV), and 2878 samples for independent external validation (IV).

The Senta 1 and Buda 5 datasets were collected from different population groups, in different centers, located in different countries, using different doctors and cardiologist.

The Senta 2 and Buda 6 dataset were also collected from different groups, locations, doctors, but in separate years.

All the tests, were validated through a year long Ground Truth Consensus Study, consisting of 15 cardiologists, with any 5 randomly assigned to any one test, for concensus review in 3 steps. All tests were validated for ground truth based on Echocardiography and ECG based on the Clinical Reference Standards.

The CUUS dataset is from an FDA designed and approved pivotal prospective clinical study that created an Independent External Validation Dataset from 3 different centers, using different doctors on different patient populations, as part of normal clinical practice, conducted 18 months after the original datasets (Senta 1, Buda 5, Senta 2 and Buda 6 were collected). It consists of independent patients, device, nurses, doctors, from 3 different locations and was evaluated for ground truth by not less than 3 cardiologists, from different centers. Each test included and Echocardiography and ECG confirmation tests.



3.1.1 Performance metric definition

The following performance metrics are calculated on binary classification, where ground truth are compared to CPA (HART) predictions providing true negative (TN), false positive (FP), false negative (FN) and true positive (TP).

Table 3 - Performance metrics

Metric	Description	Symbol and Formulae
Sensitivity	True positive rate compared to positive samples	$SE = \frac{TP}{TP + FN}$
Specificity	True negative rate compared to negative samples	$SP = \frac{TN}{TN + FP}$
Overall Accuracy	Rate of correct decision compared to all samples	$ACC = \frac{TN + TP}{N}$
Positive Predictive Value	provide useful insight into how to interpret positive test results	$PPV = \frac{TP}{TP + FP}$
Negative predictive Value	provide useful insight into how to interpret negative test results	$NPV = \frac{TN}{TN + FN}$
Positive Likelihood Ratio	likelihood ratio for positive results	$LR+ = \frac{SE}{1 - SP}$
Negative Likelihood Ratio	likelihood ratio for negative results	$LR- = \frac{1 - SE}{SP}$
Diagnostic Odds Ratio	measure of the effectiveness of a diagnostic test	$DOR = \frac{LR+}{LR-}$
Positive Percent Agreement	Positive agreement is the proportion of comparative method positive results in which the test method result is positive ¹³	$PPA \equiv SE$
Negative Percent Agreement	Negative agreement is the proportion of comparative method negative results in which the test method result is negative.	$NPA \equiv SP$
Positive rate	Rate of positive cases by algorithm	$PR = \frac{FP + TP}{N}$
Prevalence	Rate of positive decision from reference (consensus ground truth)	$PREV = \frac{FN + TP}{N}$

¹³ <https://analyse-it.com/blog/2020/4/diagnostic-accuracy-sensitivity-specificity-versus-agreement-ppa-npa-statistics>



Cohens Kappa	Kappa ¹⁴ a more robust measure than simple percent agreement (ACC), since it takes into account the possibility of the agreement occurring by chance	$K = \kappa = \frac{p_o - p_e}{1 - p_e}$ $\text{observed agreement } p_o = \frac{TN + TP}{N} = ACC$ $\text{hypothetical probability of chance agreement } p_e$ $= \frac{p_- + p_+}{N} = \frac{TN + FP}{N} * \frac{TN + FN}{N} + \frac{FN + TP}{N} * \frac{FN + TP}{N}$
Correlation	Pearson correlation coefficient calculated only for detailed decision to express the similarity in details – when e.g. Watch3 more similar to Watch12 than Urgent	$r(x, y) = \frac{\sum_{i=1}^N (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^N (x_i - \bar{x})^2} \sqrt{\sum_{i=1}^N (y_i - \bar{y})^2}}$
Area Under Curve	Area under ROC curve.	<i>AUC</i>
ni2:PPV%	modified (increased) PPV for two positive sequential test	$\rho(\phi) = \frac{a^n \phi}{a^n \phi + (1 - b)^n (1 - \phi)}$ ¹⁵
ni2:NPV%	modified (increased) NPV for two negative sequential test	
PPV95:ni	the number of required sequential positive test that has minimum PPV=95%	$n = \frac{\ln \left[\frac{\phi \rho(\phi) - \rho(\phi)}{\phi \rho(\phi) - \phi} \right]}{\ln \left[\frac{a}{1-b} \right]}$ ¹⁶

3.1.2 Performance requirements for HART-findings

The binary performance is expressed with Sensitivity (SE%), Specificity (SP%), positive predictive value (PPV%) and negative predictive value (NPV%). The prevalence (PREV%) supplements the performance and makes it more interpretable.

HART diseases are not the typical electrophysiological problems, which is why the ECG features are not enough, adequate or sufficient.

CPA models using MCG and PCG features together with ECG can reach higher diagnostic performance compared to the best performance possible with ECG findings

ECG findings including LVH criteria (the best one), Atrial Fibrillation, Inverted T-wave (ischemia criteria), ST-T deviation shows 25-50%

¹⁴ Chmura Kraemer, Helena, Vyjeyanthi S. Periyakoil, and Art Noda. "Kappa coefficients in medical research." Statistics in medicine 21.14 (2002): 2109-2129.

¹⁵ See (16) in: Bayala, Jacques. "Bayesian updating and sequential testing: Overcoming inferential limitations of screening tests." arXiv preprint arXiv:2006.11641 (2020).

¹⁶ See (24) in: Bayala, Jacques. "Bayesian updating and sequential testing: Overcoming inferential limitations of screening tests." arXiv preprint arXiv:2006.11641 (2020).



sensitivity with 85-95% specificity and NPV, and a 10-50% PPV for the 14 significant heart diseases.

The performance requirements for CPA models are significantly higher compared to this ECG findings performance, this means: 60-80% sensitivity with 90-95% specificity and NPV, 50-70% for PPV. The following table shows the exact performance criteria separately for prevalence categories:

Table 4 – Performance requirements for HART findings

prevalence category	prevalence criteria	SE	SP	PPV	NPV
balanced	prev ~ 50%	>80%	>80%	>80%	>80%
more common	40% > prev >25%	>70%	>80%	>60%	>80%
imbalanced	25% > prev > 5%	>60%	>90%	>50%	>90%
less frequent	prev < 5%	>50%	>98%	>40%	>98%



3.2 Individual Performance of HART Findings

3.2.1 External Validation

Table 5 – External validation performance of 14 HART findings with performance requirements

HART Finding	SE%		SP%		PPV%		NPV%		PREV%	Prevalence category
	EV	Req.	EV	Req.	EV	Req.	EV	Req.		
LVH	80.9	>70%	81.1	>80%	60.6	>60%	92.2	>80%	26.5	more common
DCM	78.1	>60%	90.4	>90%	61.5	>50%	95.4	>90%	16.4	imbalanced
RVE	67.1	>60%	94.9	>90%	49.4	>50%	97.5	>90%	6.9	imbalanced
LAE	97.2	>60%	92.4	>90%	64.7	>50%	99.6	>90%	12.5	imbalanced
RAE	85.9	>60%	92.6	>90%	50.4	>50%	98.7	>90%	8.0	imbalanced
WMA	87.4	>60%	90.0	>90%	49.8	>50%	98.4	>90%	10.2	imbalanced
LVSD	93.9	>60%	86.0	>90%	55.7	>50%	98.7	>90%	15.8	imbalanced
LVDD	74.8	>60%	80.4	>80%	61.3	>60%	88.5	>80%	29.3	more common
AS	89.5	>60%	97.3	>90%	70.1	>50%	99.2	>90%	6.6	imbalanced
MS	64.9	>60%	98.0	>98%	48.5	>40%	99.0	>98%	2.8	less frequent
AR	64.0	>60%	86.9	>90%	57.1	>50%	89.9	>90%	21.4	imbalanced
MR	70.3	>70%	84.6	>80%	60.7	>60%	89.4	>80%	25.3	more common
TR	72.5	>60%	89.7	>90%	61.6	>50%	93.5	>90%	18.5	imbalanced
PH	67.0	>60%	95.9	>90%	52.4	>50%	97.8	>90%	6.2	imbalanced
Average	78.1		90.0		57.4		95.6		14.7	



3.2.2 Confidence intervals and Performance

Table 6 - External performance metrics of the 14 HART findings with confidence intervals

HART Finding	Performance with confidence interval (95% CI)	
LVH	SE = 80.9% (95% CI: 79-82.7) SP = 81.1% (95% CI: 80-82.1)	PPV = 60.6% (95% CI: 58.7-62.6) NPV = 92.2% (95% CI: 91.3-92.9)
DCM	SE = 78.1% (95% CI: 75.5-80.4) SP = 90.4% (95% CI: 89.6-91.2)	PPV = 61.5% (95% CI: 58.9-64) NPV = 95.4% (95% CI: 94.9-96)
RVE	SE = 67.1% (95% CI: 62.7-71.3) SP = 94.9% (95% CI: 94.3-95.4)	PPV = 49.4% (95% CI: 45.5-53.3) NPV = 97.5% (95% CI: 97.1-97.9)
LAE	SE = 97.2% (95% CI: 95.9-98.2) SP = 92.4% (95% CI: 91.7-93)	PPV = 64.7% (95% CI: 62-67.3) NPV = 99.6% (95% CI: 99.4-99.7)
RAE	SE = 85.9% (95% CI: 82.7-88.7) SP = 92.6% (95% CI: 91.9-93.2)	PPV = 50.4% (95% CI: 47.2-53.7) NPV = 98.7% (95% CI: 98.4-99)
WMA	SE = 87.4% (95% CI: 84.7-89.8) SP = 90% (95% CI: 89.3-90.8)	PPV = 49.8% (95% CI: 47-52.7) NPV = 98.4% (95% CI: 98.1-98.7)
LVSD	SE = 93.9% (95% CI: 92.3-95.3) SP = 86% (95% CI: 85-86.8)	PPV = 55.7% (95% CI: 53.4-58) NPV = 98.7% (95% CI: 98.3-99)
LVDD	SE = 74.8% (95% CI: 72.8-76.7) SP = 80.4% (95% CI: 79.3-81.5)	PPV = 61.3% (95% CI: 59.3-63.2) NPV = 88.5% (95% CI: 87.5-89.4)
AS	SE = 89.5% (95% CI: 86.3-92.1) SP = 97.3% (95% CI: 96.9-97.7)	PPV = 70.1% (95% CI: 66.2-73.8) NPV = 99.2% (95% CI: 99-99.4)
MS	SE = 64.9% (95% CI: 57.8-71.6) SP = 98% (95% CI: 97.6-98.3)	PPV = 48.5% (95% CI: 42.2-54.7) NPV = 99% (95% CI: 98.7-99.2)
AR	SE = 64% (95% CI: 61.5-66.5) SP = 86.9% (95% CI: 86-87.8)	PPV = 57.1% (95% CI: 54.7-59.5) NPV = 89.9% (95% CI: 89-90.7)
MR	SE = 70.3% (95% CI: 68.1-72.5) SP = 84.6% (95% CI: 83.6-85.6)	PPV = 60.7% (95% CI: 58.6-62.9) NPV = 89.4% (95% CI: 88.5-90.3)
TR	SE = 72.5% (95% CI: 70-75) SP = 89.7% (95% CI: 88.9-90.5)	PPV = 61.6% (95% CI: 59.1-64.1) NPV = 93.5% (95% CI: 92.8-94.1)
PH	SE = 67% (95% CI: 62.3-71.4) SP = 95.9% (95% CI: 95.4-96.4)	PPV = 52.4% (95% CI: 48.1-56.6) NPV = 97.8% (95% CI: 97.4-98.1)



3.2.3 Likelihood and Other Performances

Table 7 – Additional metrics for External performance of the 14 HART findings

HART Finding	K %	LR+	LR-	PR %	DOR	PPV95:ni	ni2:PPV* %
LVH	56.0	4.3	0.24	35.4	18.2	2.7	86.8
DCM	61.8	8.1	0.24	20.8	33.5	2.2	92.9
RVE	53.2	13.2	0.35	9.4	38.0	2.2	92.8
LAE	73.7	12.8	0.03	18.8	424.0	1.9	95.9
RAE	59.4	11.6	0.15	13.7	76.4	2.2	92.2
WMA	58.1	8.8	0.14	17.8	62.8	2.4	89.7
LVSD	62.4	6.7	0.07	26.7	94.7	2.4	89.4
LVDD	51.9	3.8	0.31	35.7	12.2	2.9	85.8
AS	76.9	33.0	0.11	8.5	305.4	1.6	98.7
MS	54.0	32.4	0.36	3.8	90.6	1.9	96.8
AR	48.8	4.9	0.41	24.0	11.8	2.7	86.7
MR	52.2	4.6	0.35	29.2	13.1	2.6	87.6
TR	58.3	7.1	0.31	21.8	23.1	2.3	91.9
PH	55.7	16.5	0.34	8.0	47.9	2.0	94.8
<i>average</i>	<i>58.7</i>	<i>12.0</i>	<i>0.24</i>	<i>19.5</i>	<i>89.4</i>	<i>2.3</i>	<i>91.6</i>

*ni2:PPV indicates the change in PPV when the CHART examination is repeated 2x, over a period of 2-3 days with same results.

3.2.3.1 Likelihood Ratios

Likelihood Ratios are an indication to further help interpret diagnostic tests. of what is the probability that the diagnosis result is likely for an individual patient and help the clinician determine whether a positive result is a TP or a FP; or whether the negative result is a TN or a FN, independent of disease prevalence.

Likelihood ratios have a number of useful properties:

- because they are based on a ratio of sensitivity and specificity, they do not vary in different populations or settings
- they can be used directly at the individual patient level
- they allow the clinician to quantitate the probability of disease for any individual patient.



The interpretation of likelihood ratios is intuitive: the larger the positive likelihood ratio, the greater the likelihood of disease; the smaller the negative likelihood ratio, the lesser the likelihood of disease.

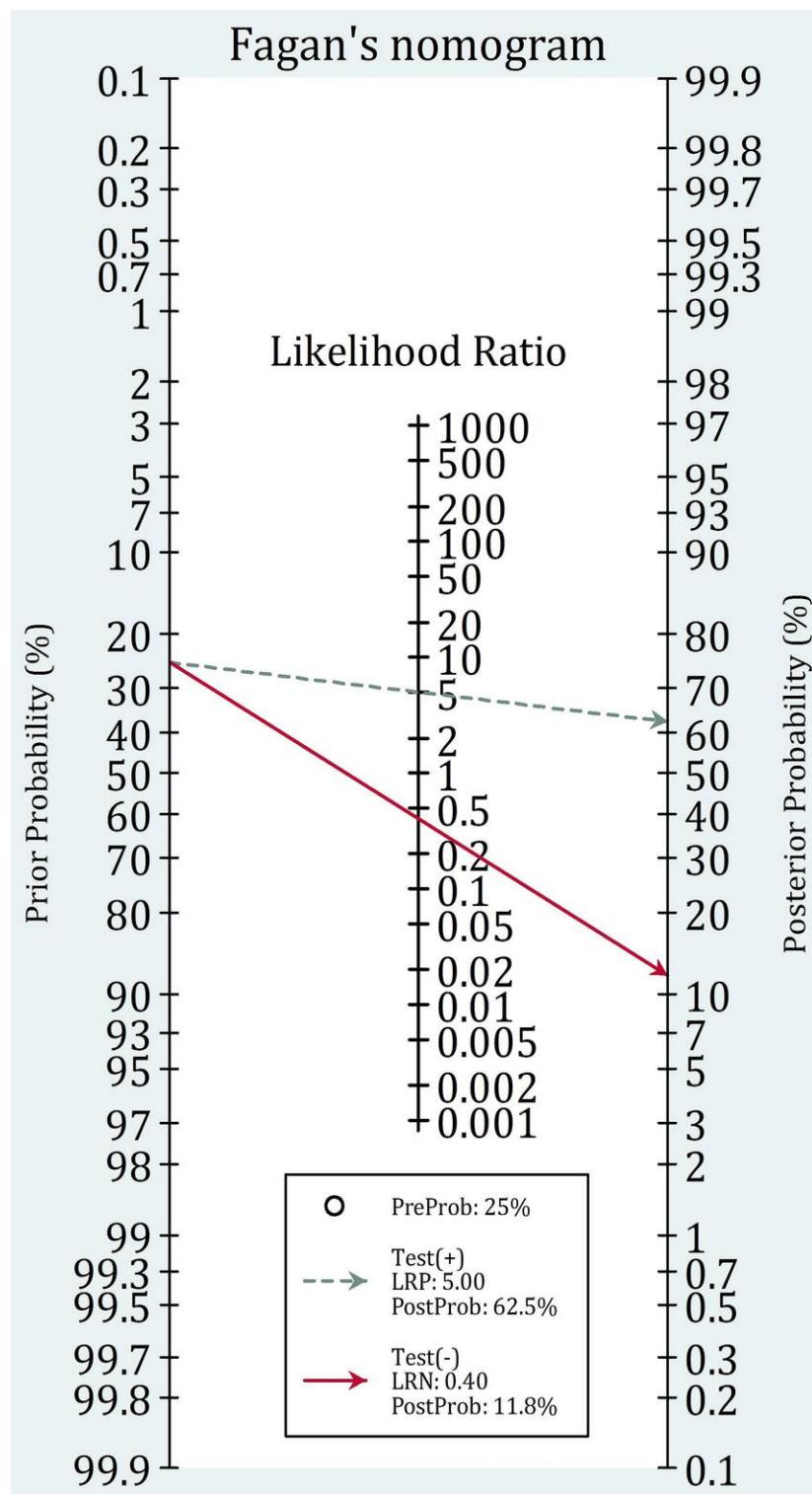


Figure 8 - Fagan's Nomogram Example

For example. See figure Fagan's Nomogram.



A pre-test probability of 25% for a disease was fixed, which was estimated by the number of symptomatic cases in a selected study, ie, with an estimated prevalence of 20%, with LR+ (LRP) is 5.00, and LR- (LRN) is 0.4.

If this patient tests positive, the post-test probability that patient truly has the disease would be 62.5% (Green dotted line). On the other hand, if patient tests negative, the post-test probability that patient truly has disease would be 11.8% (solid red line).

The results were obtained by the following calculations: pretest odds=prevalence/1-prevalence; post-test odds=pretest odds x LR- (LR+); post-test probability=post-test odds/1+post-test odds. LR, likelihood ratio.

The larger the spread between the two post probability numbers, the more likely the results are accurate.



3.2.4 Independent Validation

The independent validation (IV) results are compared to external validation (EV) results in the following table.

Table 8 – Independent validation performance of 14 HART findings compared to External validation performance

HART Finding	SE%		SP%		PPV%		NPV%		PREV%	
	EV	IV	EV	IV	EV	IV	EV	IV	EV	IV
LVH	80.9	77.2	81.1	95.7	60.6	77.9	92.2	95.5	26.5	16.5
DCM	78.1	70.7	90.4	98.2	61.5	81.9	95.4	96.7	16.4	10.2
RVE	67.1	69.7	94.9	97.9	49.4	44.2	97.5	99.3	6.9	2.3
LAE	97.2	95.9	92.4	97.5	64.7	73.8	99.6	99.7	12.5	6.7
RAE	85.9	61.8	92.6	96.9	50.4	50.0	98.7	98.1	8.0	4.7
WMA	87.4	81.8	90.0	95.6	49.8	69.9	98.4	97.7	10.2	11.0
LVSD	93.9	89.7	86.0	93.7	55.7	69.0	98.7	98.3	15.8	13.5
LVDD	74.8	77.5	80.4	78.6	61.3	72.8	88.5	82.5	29.3	42.5
AS	89.5	85.4	97.3	98.3	70.1	63.1	99.2	99.5	6.6	3.3
MS	64.9	NA*	98.0	NA*	48.5	NA*	99.0	NA*	2.8	0*
AR	64.0	69.9	86.9	94.5	57.1	62.4	89.9	96.0	21.4	11.5
MR	70.3	83.3	84.6	97.2	60.7	70.9	89.4	98.6	25.3	7.5
TR	72.5	64.0	89.7	96.6	61.6	58.7	93.5	97.3	18.5	6.9
PH	67.0	79.5	95.9	99.0	52.4	71.4	97.8	99.4	6.2	3.1
Average	78.1	77.4	90.0	95.4	57.4	66.6	95.6	96.8	14.7	10.7

* EV database has not sufficient positive for MS

3.2.5 Conclusions

- The performance meets with the predefined requirements.
- The average negative predictive value is high (NPV ~ 95%), the positive predictive value PPV is robust, between 50 and 70% (average PPV ~ 60%).
- The performance deviation between external and independent validation is acceptable, and the balance deviation between sensitivity and specificity is expected according to the prevalence difference between two validation set.



- The positive prediction has an increased probability with repeated tests, if a test shows consistently positive results. Two sequential positive tests can achieve a ~95% positive probability, see **ni2:PPV%** metric.
- This means one negative test has strong probability for true negative, but two positive sequential tests reaches 95% probability for true positive on average.
 - Note: At 95% PPV, the results highly likely to be the same as Echocardiography confirmation; where Echocardiography might not yet be available, these results can be relied upon allowing for immediate patient management decisions.

3.3 HART Aggregated Performance

3.3.1 Binary Format - FP and FN Analysis

The Aggregated Performance is provided to better understand the overall performance when the HART assessment is considered as a whole, as related to the balance between false positives and false negatives and specificity and sensitivity.

The overall performance of the aggregated HART findings including the 13 significant heart diseases¹⁷ - called as HART summary.

The overall binary statistics is based on the aggregated ground truth (GT) and aggregated CPA prediction:

- Abnormal reference = [abnormal LVH] or [abnormal DCM] or ... [abnormal PH] – when abnormal is defined by GT.
- Positive prediction = [positive LVH] or [positive DCM] or ... [positive PH] – when positive abnormal is classified by CPA

This classification is balanced (the number of positives similar to number of negative), therefore the performance requirements are also based on balanced classification, when the sensitivity proportional to specificity and PPV is proportional to NPV.

This overall statistic should not be used as an indication for any specific disease, but rather to better understand the overall performance when the

¹⁷ In the aggregated heart disease does not include Diastolic Dysfunction of Impaired Relaxation, because this condition is considered as a mild problem, compared to others.



HART assessment is considered as a whole, as related to the balance between false positives and false negatives and specificity and sensitivity.

Table 9 – Aggregated Diagnostic Performance of HART findings

Performance Metric	EV+IV*	Req.**
Sensitivity, SE	80.2%	> 80%
Specificity, SP	86%	> 80%
Positive Predictive Value, PPV	85.3%	> 80%
Negative Predictive Value, NPV	81.1%	> 80%
F-Score, F1	82.7%	-
Accuracy, ACC	83.1%	-
Kappa, K	66.2%	-
Prevalence, PREV	50.3%	-
Positive Rate, PR	47.3%	-
Positive Likelihood Ratio, LR+	5.73	-
Negative Likelihood Ratio, LR-	0.23	-
Diagnostic Odds Ratio, DOR	24.9	-
PPV in case of two positive sequential test, ni2:PPV	97.1%	-
NPV in case of two negative sequential test, ni2:NPV	94.9%	-

* The performance is calculated on joined external and independent validation data, that has balanced property.

** Requirement is based on balanced classification, PREV~50%

3.3.2 Triple format

The triple format of the aggregated HART findings take into account the middle category between Normal and Abnormal, called “Mild” by the various Echocardiography Societies. “Mild” means patient have one or a few mild abnormality, typically moderate/severe diastolic dysfunction with preserve EF and/or some asymptomatic heart enlargement or non significant valve insufficiency.

The ECG summary with its triple outcome is provided in statistics for comparison purpose. The ECG middle category is “borderline” in accordance



with the standard, but it meets the “Mild” condition by ECHO and HART assessment.

The overall triple statistics is based on the aggregated ground truth (GT) and aggregated CPA prediction:

- Mild condition = minimum one mild ECHO finding, but in case of impaired relaxation the severity is minimum moderate.
- Abnormal condition = minimum one moderate/severe abnormal ECHO finding or more than three mild condition – when abnormal is defined by GT.

Table 10 – Confusion matrix of Triple Aggregated Diagnostic of HART Summary and P-ECG Summary

		HART summary prediction			Sum
		Negative	Positive / Mild	Positive / Abnormal	
Reference - GT	Normal	1916	974	60	2950
	Mild	632	1426	386	3444
	Abnormal	68	1288	2010	3366
					9760
		P-ECG summary			
		Normal	Borderline	Abnormal	Sum
Reference - GT	Normal	1654	670	626	2950
	Mild	1282	1074	1088	3444
	Abnormal	426	534	2406	3366
					9760

The Negative HART summary has high negative predictive value for the Abnormal patient, while the Positive/Abnormal HART summary has high positive predictive value for the non-Normal patients. See following table:



Table 11 – Probability evaluation of HART and ECG summary compared to ECHO-based ground truth

Outcome	by HART Summary	by ECG Summary
Negative	Patient predicted as Negative by HART is not Abnormal in 97.4% probability (NPV = 97.4%)	Patient predicted as Normal by ECG is not Abnormal in 87.3% probability (NPV = 87.3%)
	Patient predicted as Negative by HART is Mild with 24.1% probability	Patient predicted as Normal by ECG is Mild with 38.1% probability
	Patient predicted as Negative by HART is Abnormal only in 2.6% probability (100%-NPV)	Patient predicted as Normal by ECG is Abnormal only in 12.7% probability (100%-NPV)
Mild	Patient predicted as Positive/Mild by HART is Mild in 52% probability	Patient predicted as Borderline by ECG is Mild in 47% probability
Positive	Patient predicted as Positive/Abnormal by HART is not Normal in 97.6% probability (PPV = 97.6%)	Patient predicted as Abnormal by ECG is not Normal in 84.8% probability (PPV = 84.8%)
	Patient predicted as Positive/Abnormal by HART is Mild in 15.7% probability	Patient predicted as Abnormal by ECG is Mild in 26.4% probability
	Patient predicted as Positive/Abnormal by HART is Normal only in 2.4% probability (100%-PPV)	Patient predicted as Abnormal by ECG is Normal in 15.2% probability (100%-PPV)

3.3.3 Conclusion

- When the HART assessment is Negative (normal), then the moderate/severe abnormality can be rule out, patient would be normal by echocardiography with high probability. The discussion can be only between normal and mild.
- When the HART assessment is Positive/Abnormal, then patient has some moderate/severe condition with high probability, and incitates to refer patient to cardiology for a detailed and more certain diagnosis. The discussion rather the type and severity of disease: mild, moderate or severe.
- When the HART assessment is Positive /Mild, then patient condition is less certain, and advised to carefully take into account the ECG, PCG and MCG findings together with patient symptoms and history for the appropriate referral and treatment options.



3.4 HART Performance Compared to predicate ECG

This analysis compares the HART findings of two different versions of CHART, CPA (HART2018) and CPA (HART2021), when compared to a State-of-the-Art ECG automated diagnosis algorithm currently used by many ECG devices¹⁸.

The three algorithms are compared for their capabilities in the prediction of Significant and Common heart diseases.

This will highlight the benefit of using HART findings over using ECG only findings to diagnose Significant Heart diseases.

The Significant heart diseases are the referenced HART findings, which are the same as the consensus-based ECHO findings – the ground truth.

As there are no Clinical Reference Standards (CRS) for the ECG criteria for all 14 Significant heart diseases, we selected the most appropriate CRS based ECG-findings and paired them to each ECHO-finding, partly based on the associated disease, and, partly based on a cross-information analysis

Note: this is similar to what an Overreading Cardiologists, ORC, does to determine if Echocardiography should be

between ECG and ECHO findings.

The following Table lists the pairs selected for the analysis.

¹⁸ There were several devices used as comparators. They shall remain nameless as their performances are all similar and based on the Standards. There are no clinically meaningful differences between them such that a comparison to one, is a comparison to all.



Table 12 – Paired ECG and HART findings in relative performance comparison

Abbreviation	ECG-finding(s)	ECHO-findings (ground truth) HART-finding	Description
ECGsumm/ HARTsumm	ECG Summary (Abnormal ECG)	HART Summary (Abnormal HART)	The ECG summary is associated to HART summary. Both are conclusive for whether the heart has normal or abnormal condition.
LVH/LVH	Left Ventricular Hypertrophy (ECG criteria)	Left Ventricular Hypertrophy	LVH by ECG is direct to ECHO-based LVH
LVH/DCM	Left Ventricular Hypertrophy (ECG criteria)	Dilated Cardiomyopathy	Eccentric hypertrophy is associated to Dilated LV, moreover ECG LVH show higher coincidence to DCM as LVH diagnosed by ECHO.
STTdev/DCM	ST Deviation with T-wave change	Dilated Cardiomyopathy	ST-T deviation shows good correlation with DCM
LAE/LAE	Left Atrial Enlargement (ECG criteria)	Left Atrial Enlargement	LAE by ECG is direct to ECHO-based LAE
PVC/LAE	Premature Ventricular Complex	Left Atrial Enlargement	PVC shows good correlation with ECHO-based LAE
RAE/RAE	Right Atrial Enlargement (ECG criteria)	Right Atrial Enlargement	RAE by ECG is direct to ECHO-based RAE
AFib/RAE	Atrial Fibrillation	Right Atrial Enlargement	AFib show good correlation with ECHO-based right heart enlargement.
RVH/RVE	Right Ventricular Hypertrophy (ECG criteria)	Right Ventricular Enlargement	ECG has no RVE, but has RVH similarly ECG has no DCM but has LVH for left ventricle. However, ECG criteria for hypertrophy is not strictly for concentric, it covers eccentric enlargement.
AFib/RVE	Atrial Fibrillation	Right Ventricular Enlargement	AFib show good correlation with ECHO-based right heart enlargement.
STTdev/LVSD	ST Deviation with T-wave change	LV Systolic Dysfunction	ST-T deviation is associated to reduced heart function due to any CAD related problem.
LAX/LVDD	Left-axis Deviation	LV Diastolic Dysfunction	Left Axis deviation shows the highest correlation to the ECHO-based diastolic dysfunction
Isch/WMA	Ischemia	LV Wall Motion Abnormality	Ischemia by ECG is direct to ECHO-based ischemic cardiomyopathy, and is diagnosed through wall motion abnormalities.
STTdev/WMA	ST Deviation with T-wave change	LV Wall Motion Abnormality	ST-T deviation are associated to wall motion abnormalities due to CAD related problem.
MI/WMA	Myocardial Infarction (ECG criteria)	LV Wall Motion Abnormality	MI is associated to wall motion abnormalities due to CAD related problem.



LVH/AS	Left Ventricular Hypertrophy (ECG criteria)	Aortic Stenosis	LVH by ECG shows the highest correlation to the ECHO-based aortic stenosis
LVH/AR	Left Ventricular Hypertrophy (ECG criteria)	Aortic Valve Insufficiency	LVH by ECG shows the highest correlation to the ECHO-based aortic insufficiency
Isch/MR	Ischemia	Mitral Valve Insufficiency	Ischemia by ECG shows the highest correlation to the ECHO-based mitral insufficiency
AFib/MS	Atrial Fibrillation	Mitral Valve Stenosis	Atrial Fibrillation shows the highest correlation to the ECHO-based mitral stenosis
AFib/TR	Atrial Fibrillation	Tricuspid Valve Insufficiency	Atrial Fibrillation shows the highest correlation to the ECHO-based tricuspid insufficiency
AFib/PH	Atrial Fibrillation	Pulmonary Hypertension	Atrial Fibrillation shows the highest correlation to the ECHO-based pulmonary hypertension

The results are plotted in the following two figures, where the

- first graph shows the performance metrics: SE - sensitivity, SP – specificity, PPV – positive predictive value, PR – positive rate
- second graph shows the relative performance increase by 14 HART findings compared to select ECG findings in a ROC analysis. Both the CPA (2018a) and the latest CPA (2021) HART models are tested and plotted.

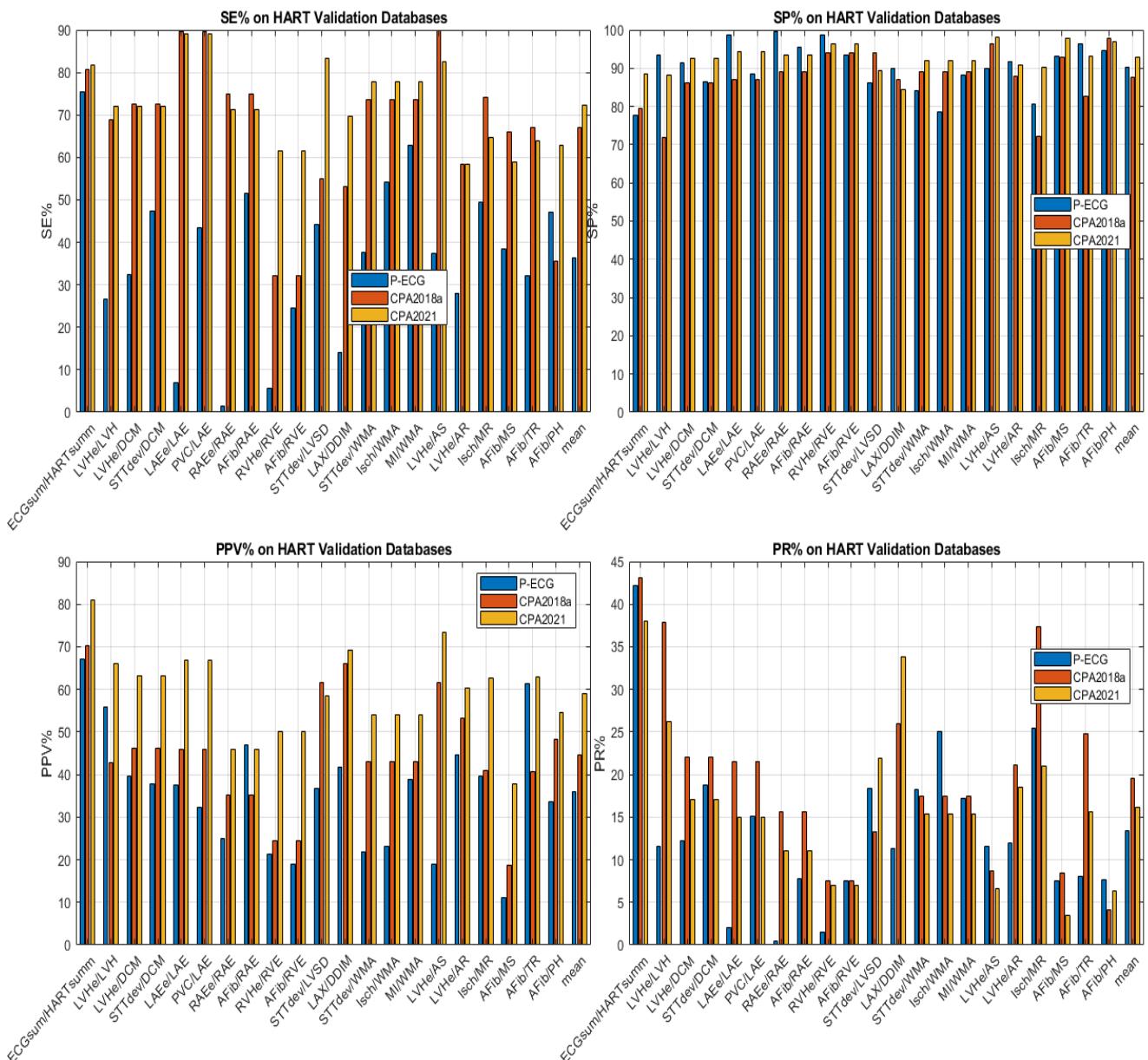


Figure 3-2 – HART finding (2018a and 2021 versions) performance compared to P-ECG

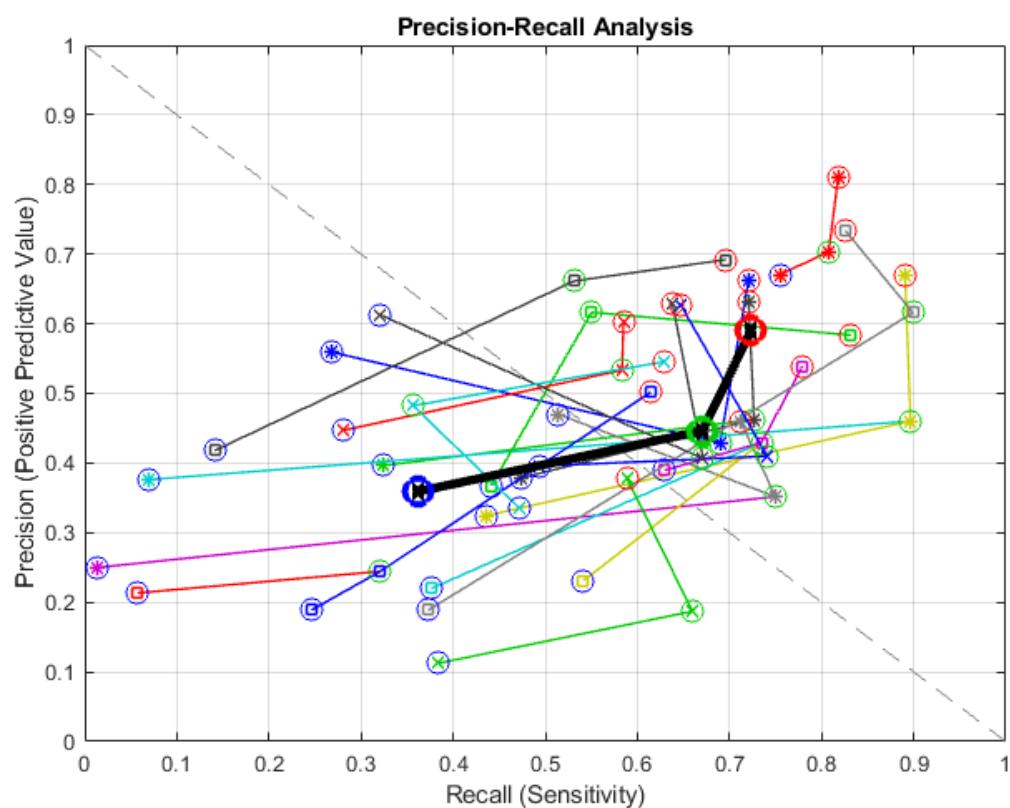
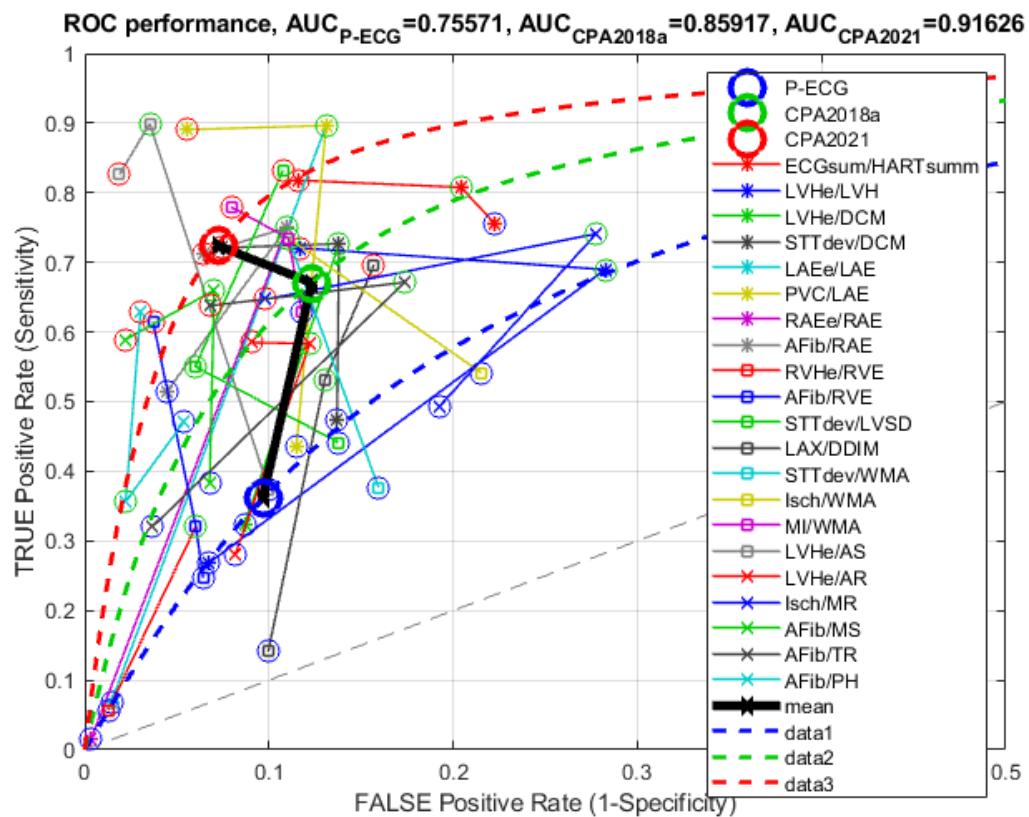


Figure 3-3 – HART finding (2018a and 2021) ROC and PRC performance compared to P-ECG

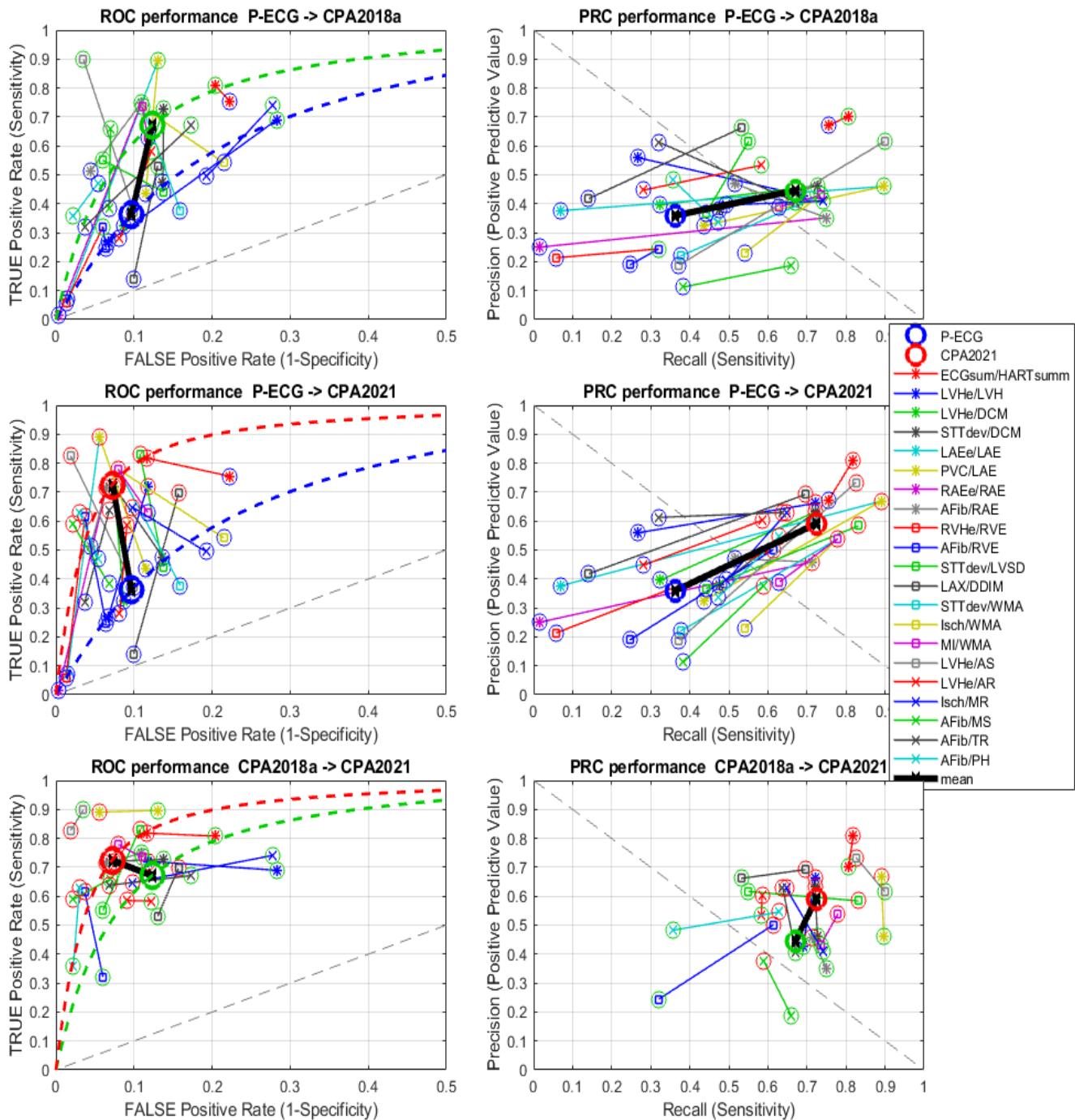


Figure 3-4 - HART finding (2018a and 2021) ROC and PRC performance compared to P-ECG – compared pairwisely



3.4.1 Conclusions: P-ECG findings and the HART findings by CPA2021 models

- The average SE and SP on this list of diagnostic pairs shows both SE and SP increase in the HART models: SE from 36% to 72%, SP from 90% to 93%

Note: this averaging does not take into account the prevalence and uniqueness of the 14 significant heart diseases.

- The average positive predictive value is increased by HART findings compared to ECG diagnosis: PPV nearly doubled from 36% to 60%
- In all the 14 diseases, the HART findings provide better classification results compared to ECG findings. In clinical practice, this means:
 - Earlier detection of CVD onset.
 - Identification of disease comorbidities
 - the reductions in both FN and FP outcomes leads to much less morbidity or mortality,
 - enables more timely access to appropriate treatment options, whether preventative or pharmacological, and
 - less delay in accessing these options, or
 - leads to a medically justified referral to a Cardiologist and access to higher level of care.
- When the ECG-findings are compared to the reference ECHO-findings they show significant differences.
- It proves on the one hand the incompleteness of both these diagnostic methods in and of themselves.
- On the other hand, it also proves that when ECG+ECHO are combined, together they can create a more comprehensive diagnosis of a broader and wider range of heart diseases, do it earlier and most critically, in a manner that is more understandable by Primary Care physicians (they get it more easily).
- With respect to CPA intended use, CPA ensures that physician's diagnostic effectiveness will be highly effective in a very meaningful way, not simply marginally, thereby resulting in far more positive patient outcomes.



3.4.2 Conclusions between 2018a and 2021 models

- In the case of CPA2021 the binary model outputs are analyzed, which provides positive outcome for a specific CRS thresholds between mild and moderate condition of the diseases.
- The average SE and SP on this list of diagnostic pairs shows both SE and SP increase with the new CPA2021 models: SE from 67% to 72%, SP from 88% to 92% and PPV from 45% to 60% on average.
- The new CPA2021 models significantly helps reduce false positives without creating more false negatives.

3.5 HF performance by HART-findings

The prediction of HF categories by HART findings are evaluated with the help of ground truth ECHO-based HF categories. The two-validation set of Cardio Phoenix database was used to estimate the performance. These data were not used in the training of HART-findings AI models.

Table 13 shows HF quad-format confusion matrix on independent validation (IVA) and external validation (EVA) database.

Table 13 - Confusion matrix on HF classification by CHART system

IVA		HF indication by signal-based HART findings				
		Absent	HFpEF	HFmrEF	HFrEF	Summa
Reference HF by consensus ECHO- and ECG-finding	Absent	3728	370	284	40	4422
	HFpEF	266	442	296	70	1074
	HFmrEF	230	36	542	156	964
	HFrEF	32	14	90	286	422
	Summa	4256	862	1212	552	6882
EVA		HF indication by signal-based HART findings				
		Absent	HFpEF	HFmrEF	HFrEF	Summa
Reference HF by consensus ECHO- and ECG-finding	Absent	2004	50	52	0	2106
	HFpEF	90	132	78	16	316
	HFmrEF	158	24	90	32	304
	HFrEF	22	4	72	54	152
	Summa	2274	210	292	102	2878

Table 14 shows HF binary performance on independent validation (IVA) and external validation (EVA) database compare to ECG summary performance.



Table 14 – Binary Performance Evaluation of HF classification by CHART system compared to Abnormal ECG summary

	CHART HF prediction			Abnormal ECG summary		
	IVA	EVA	IVA+EVA	IVA	EVA	IVA+EVA
Sensitivity %	78.5	65.0	75.3	70.5	64.0	68.9
Specificity %	84.3	95.2	87.8	67.3	86.1	73.4
Positive Predictive Value %	73.6	83.1	75.4	54.5	62.8	56.1
Negative Predictive Value %	87.6	88.1	87.8	80.4	86.7	82.7
F1 score %	76.0	73.0	75.3	61.5	63.4	61.9
HF Prevalence %	35.7	26.8	33.1	35.7	26.8	33.1

The HART finding approach by CHART system reach significantly higher performance in prediction of HF estimated by the overall validation set: the sensitivity increased from 69% to 75%, the specificity from 73% to 88%, the positive predictive value from 56% to 75%, the negative predictive value from 83% to 88%, and the F1 score from 62% to 75%.

To better understand why HART-findings are strong for HF, we can compare the distribution of HART summary to ECG and ECHO summaries in sense of HF categories. Fig. 12 shows the distribution of ECHO-, ECG- and HART-summary for the four type of HF patients, where all the summary has triple class form which means there is a middle class between normal and abnormal.

Both the false positive and false negatives by ECHO summary is smaller compared to ECG summary: the abnormal ECHO for Absent HF is much less than the abnormal ECG; there is no normal ECHO, but there are some normal ECG for HF categories. The HART-summary is very similar to ECHO-summary; thus, HART-summary provides the ECHO power in HART diagnosis and HF prediction.

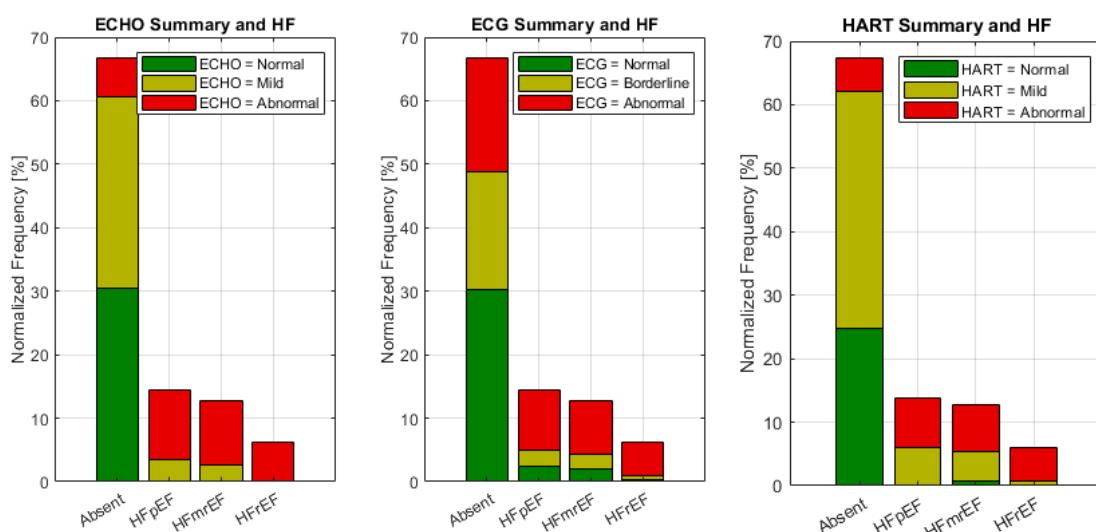


Figure 5 – ECHO-, ECG- and HART-summary distribution for HF categories



3.5.1 Conclusion

The early detection of HF is important, and can reduce the risk of mortality. The typical early phase of HF is the HFpEF category, which is a complex diversified condition, that cannot be classified as only diastolic HF or valve disease. HFpEF detection includes the arrhythmias, structural heart diseases (LVH, LAE), valve diseases (most prevalent are AR, AS, MR, TR) and diastolic dysfunction (DD).

CHART interpretation with HART and ECG-findings can strongly indicating Pre-Heart Failure stage that is a useful aid to suspect HF in primary care level. Pre-Heart Failure stage include patients without current or prior symptoms or signs of heart failure but evidence of structural heart diseases or abnormal cardiac systolic or diastolic function (Stage B)¹⁹.

CHART covers all these abnormalities and currently seems the best tool to indicates early stage of HF in primary care level.

The abnormalities associated to right side of the heart are very indicative for the HFrEF, especially the right atrial and ventricular enlargement. CHART provide RAE and RVE findings, that are more sensitive compared to ECG RVH criteria, thus, not left the physician blind for right side heart problems.

The HART-findings based HF indication reach significantly higher performance, both the false negative and false positives are lower, compared to abnormal ECG finding. This benefit over ECG is confirm and show same trend as the Clinical Usability Study of CHART report, according to which the GP referral decision to cardiology care is more accurate based on CHART findings compared to ECG alone finding. In this case the reference referral decision is defined by cardiologist consensus based on risk factors, ECG and ECHO interpretation.

[4] ¹⁹ Bozkurt, Biykem, et al. "Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure." Journal of cardiac failure (2021).



4 HART™ Findings and comorbidities

The 14 HART findings predict fourteen (14) of the most significant heart diseases prevalent in the “@risk”²⁰ patient population for cardiac diseases.

This comorbidity analysis shows two critical elements in the use of the 14 HART findings when used together:

1. It shows the relationship between any one disease and the others.
2. It shows evidence that early detection of CVS is critical to averting and or deferring moderate and severe outcomes.
3. It is in the mild phase that much of the disease progression happens and, when left untreated, results in higher severity, very quickly.
4. The conclusion is that when the condition is mild, there are many pathways to prevention and pharmacological treatment options that can keep a patient out of, or delay need for higher levels of care.

4.1 General comorbidity analysis between heart diseases

In this analysis we include the 14 significant heart diseases as diagnosed by echocardiography with a severity of moderate or severe cases.

We also include 13 main echo measurements that are used to express the continuity between normal-mild-moderate and severe categories of these diseases. The four severity conditions are defined by the American Society of Echocardiography (ASE), the BSE, the ESE and others.

In Figure 4-1 below, four graphs are plotted that indicate the relationship between diseases and echo findings or parameters. It shows the degree of co-morbidity that exists between the various 14 significant heart diseases:

- Top-left graph illustrates the sensitivity matrix calculated between the 14 ECHO findings plus the “Abnormal ECG finding”²¹. The number means the percentages of patients having a positive predictor finding has a positive target finding. Th Matrix shows all the pairwise comorbidity

²⁰ The @Risk patient population, “at-risk”, is a patient with a known cardiac risk as per the standard of care, including but not limited to, hypertension, diabetes, smoking, family history, lack of physical activity, alcohol abuse, etc... by age and gender.

²¹ Abnormal ECG finding, is a typical finding from ECG that is a summary of ECG findings. Here it is used to represent ECG abnormalities and to compare the relative sensitivity and specificity to each disease. Note, that sensitivity is high, but specificity to target is low.



between these diseases. The typical sensitivity is between 15 - 60%, the average is 28%.

- Top-right graph illustrates the correlation coefficient between the included 13 ECHO measurements. The numbers are the known Pearson type correlation coefficient, where 0% means independency, and 100% means the maximum correlation. The typical correlation is between 10 - 50%, the average is 25%.
- Bottom-left graph shows the number of abnormal common diseases of all the patients. Half of patient (53%) have no moderate or severe heart diseases. 20% of patient has one abnormality, 10% has two abnormality, 6% has three, 4% has four, etc.
- Bottom-middle graph shows how the ECHO measurements participate in the principal component of the 13 ECHO parameters, calculated by PCA.
 - Roughly all the ECHO parameters play a role in the principal variance of this multi-dimensional data.
 - The ejection fraction (%) is negative, because its abnormality trend is opposite the others, the lower the worse the condition. The LA volume index (LAVI) has the highest weights, which means the severity of LA enlargement is a good predictor of the general severity of a patient's heart problems.
- Bottom-right graph shows the 2D plot of first and second PCA component of ECHO parameters as a cloud, where the colors represent the number of positive significant heart diseases. The correlation between 1st PCA component and number of diseases is really high ($r = 0.86$).

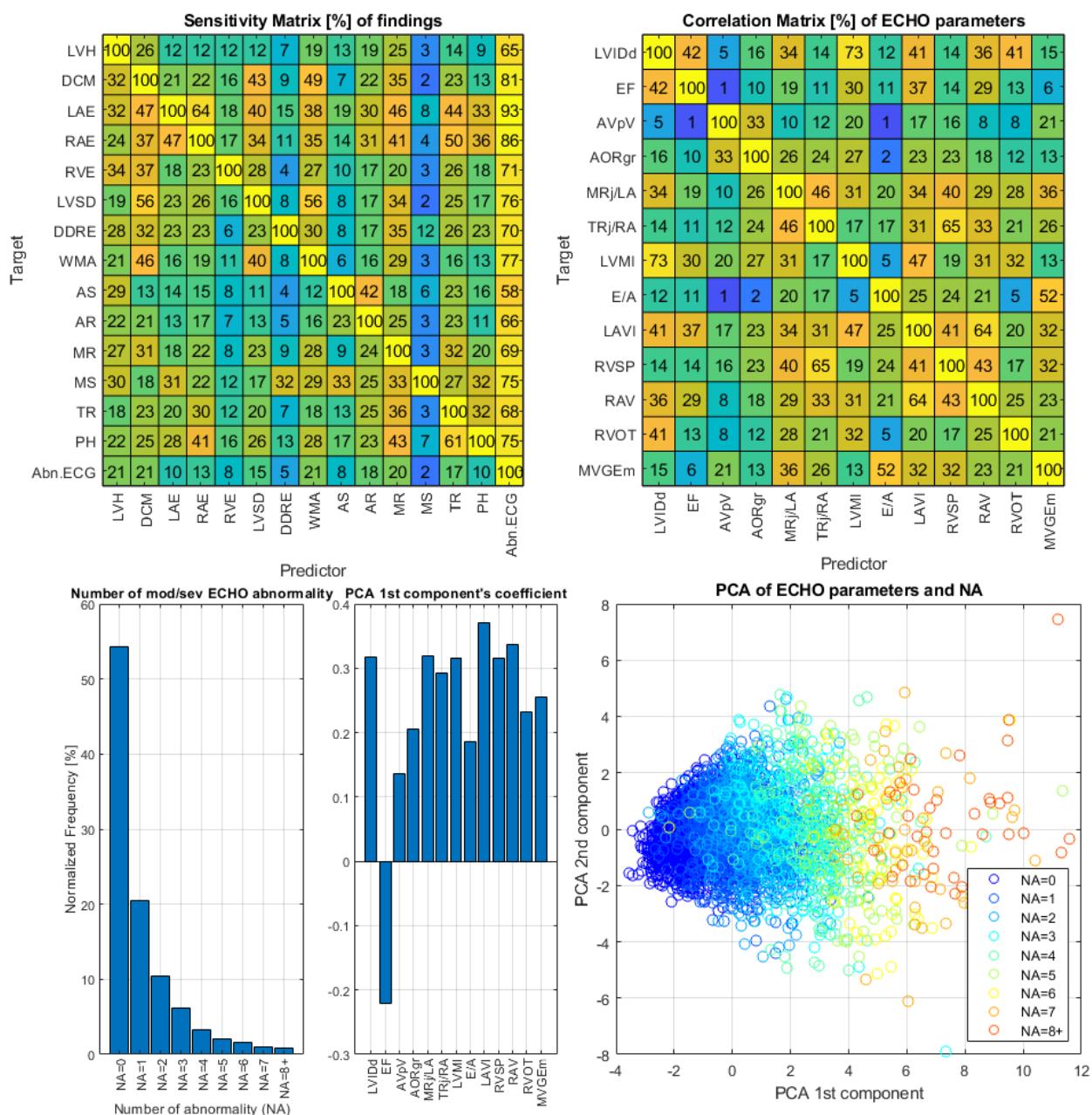


Figure 4-1 General comorbidity analysis on CPA validation database



4.1.1 Conclusions

More than half of the abnormal patients have more than one heart disease.

Based on the analysis, 26% of patients have a minimum of two moderate/severe diseases, and 20% of patient have one moderate/severe disease, altogether abnormal patients is 46%.

The principal component analysis reduces the number of variables of a data set, while preserving as much information as possible. The principal component of 13 echo measurements transform the main variability in the multidimensional space into one dimension, or one scale. This can be considered as one super echo-parameter, that includes most of the information.

The correlation between number of diseases and this super parameter (principal component of echo measurements) is really high, the Pearson correlation coefficient is $r=0.86$.

In other words the echo measurements move together to some extent from normal to severe abnormal scale, due to the connection between them. This means ***from a co-morbidity aspect the progression of the severity of one disease implies other diseases.***

Heart disease is never just a single disease²².

The general comorbidity factor increases with the progression of the severity of the heart diseases. If the patient's heart condition deteriorates - as the values of the echo measurements deteriorate, then the probability increases that the heart gets another moderate / severe abnormality(s).

²² Dr. Sandor Khoor, Chief of Cardiology, St. Istvan Hospital, Budapest, Hungary.



4.2 Individual Comorbidity Analysis

This section provides an explanation for the individual comorbidity analysis reports in the next subsections.

In these analysis, one disease and its primary ECHO measurement is selected.

The prevalence trend of significant heart diseases (ECHO findings) and ECG abnormality is evaluated by a subset of patients, where the subset is based on the increased threshold along with the primary ECHO measurements.

In the example in Figure 4-2, the DCM abnormality and its primary ECHO parameter, LVIDd is selected.

The first prevalence point evaluated on a patient set is LVIDd < 46mm, when the 46mm is derived from the average of patients having no DCM. The second point evaluated on the patient set is LVIDd < 49 mm. This is continued up to the abnormal LVIDd domain (LVIDd < 78mm), and finally we reach the original prevalence level that is observed on the whole available patient data set.

The top row in Figure 4-2, plots the prevalence trend of the 14 significant heart diseases (ECHO findings or HART findings).

The middle row in Figure 4-2 plots the prevalence trend of the most important ECG findings.

On the right side of first two rows, the magnitude of prevalence trend is expressed and plotted with vertical bars, where the higher value means higher correlation and co-morbidity factor. The negative values means the opposite situation, when the prevalence is decreased by increasing the inclusion threshold of the selected echo parameter.

The bottom graph shows the distribution of the selected primary ECHO parameter, where the colors represent the normal (absence), mild and moderate-severe categories derived from the ground truth (which is not only based on the primary parameter). The vertical dotted lines, show the center of these three-color category.

The light yellow section in each graph highlights the rise of morbidity in the early stages of any disease, including comorbidities. What is absolutely incredible is that the early onset of disease is where the greatest change, highest morbidity rate, happens.

This is the range where preventative and early care can be most effective.

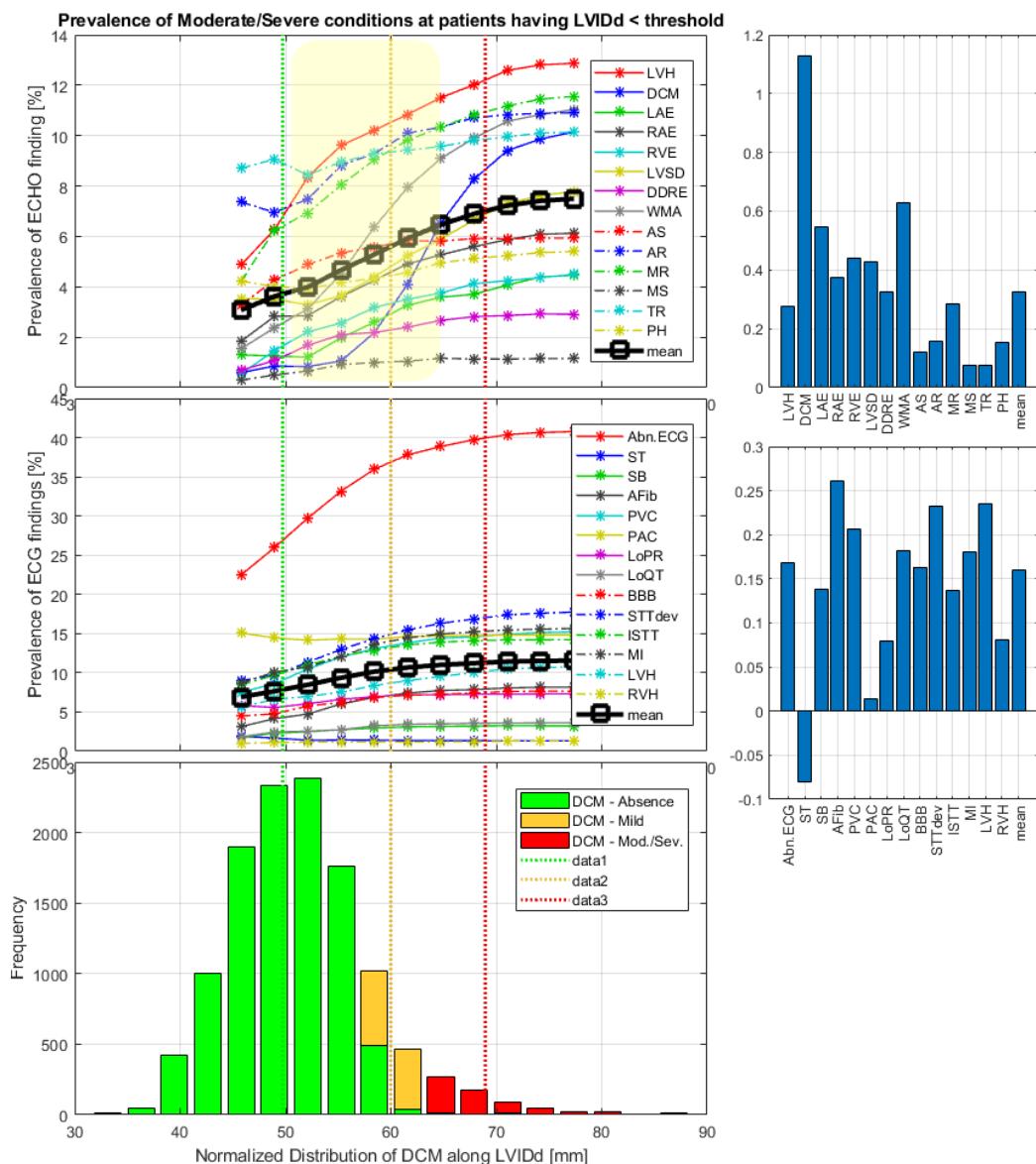


Figure 4-2 Example of individual comorbidity analysis

4.2.1 Conclusion from DCM example

Conclusion from DCM graph on Figure 4-2.

- Most of the non-DCM ECHO and ECG diseases show an increased prevalence trend when the DCM ECHO parameter criteria increases.
- ECHO co-morbidity
 - The average increase of co-morbidity prevalence is ~2% points (from 4% to 6%) by including mildly abnormal LVIDd beside the normal LVIDd patients.



- Similarly, the average increase of co-morbidity prevalence is ~2% points (from 6% to 8%) by including moderate-severe abnormal LVIDd beside the normal-mild LVIDd patients.
- ECG co-morbidity
 - The increase of abnormal ECG co-morbidity prevalence is ~11% points (from 26% to 37%) by including mildly abnormal LVIDd beside the normal LVIDd patients.
 - The increase of abnormal ECG co-morbidity prevalence is ~4% point (from 37% to 41%) by including moderate-severe abnormal LVIDd beside the normal-mild LVIDd patients.
- The average prevalence increase between normal and mild category is similarly high as between mild and moderate-severe categories.
- The higher the value of LVIDd shows a higher co-morbidity prevalence even within the normal domain.
- **This indicates the importance of early detection of DCM, since the co-morbidity is growing drastically along the normal-mild domain.**



4.3 14 HART Findings and Comorbidities

4.3.1 Concentric LV Hypertrophy

Abbreviation	LVH
Description	Concentric Left Ventricular Hypertrophy
ICD10 code	I51.7 Cardiomegaly
Echo criteria	LVMI (LVmass/BSA)> {125/110}g/m ² and IVSd (Septum diameter) > 12mm
Cardiovascular Risk	Left ventricular hypertrophy is a maladaptive response to chronic pressure overload and an important risk factor for atrial fibrillation (AFib), diastolic heart failure, systolic heart failure, and sudden death in patients with hypertension. ²³ LVH can cause congestive HF and cardiac arrhythmias as life-threatening cardiovascular complications. ²⁴
Morbidity	The frequency of echocardiographic LVH was 32%, substantially higher than that detected by ECG (9%). ²⁵ - Calculated on unhealthy patient population occurs in health care systems.
Co-Morbidity	LVH is an abnormal increase in left ventricular mass, which is a marker for and contributes to coronary events, stroke, heart failure, peripheral arterial disease, and cardiovascular mortality in patients with hypertension. Factors influencing left ventricular geometry in persons with hypertension include comorbidities such as coronary artery disease, diabetes mellitus, obesity, and valvular heart disease ²⁶ The Co-Morbidity analysis on CPA database (Figure 4-3) shows strong co-morbidities for almost all the significant heart diseases, including DCM, LAE, RAE, RVE, LVSD, WMA, MR, TR, PH, Abnormal ECG, ST-T deviation.
Mortality	The mortality rate was 5.40 per 100 patient-years in men with LVH and 2.58 in men without LVH (crude relative risk

²³ Katholi, Richard E., and Daniel M. Couris. "Left ventricular hypertrophy: major risk factor in patients with hypertension: update and practical clinical applications." International journal of hypertension 2011 (2011).

²⁴ <https://www.vascularhealthclinics.org/institutes-divisions/cardiology/left-ventricular-hypertrophy-enlarged-heart/>

²⁵ Martinez, María A., et al. "Prevalence of left ventricular hypertrophy in patients with mild hypertension in primary care: impact of echocardiography on cardiovascular risk stratification." American journal of hypertension 16.7 (2003): 556-563.

²⁶ Aronow, Wilbert S. "Hypertension and left ventricular hypertrophy." Annals of translational medicine 5.15 (2017).



	[RR]=2.09) and 3.21 and 0.66, respectively, in women (RR=4.87). ²⁷ Left ventricular (LV) mass index has Hazard Ratio = 1.4. ²⁸
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The analysis on figure shows how the prevalence of 14 significant heart diseases and abnormal ECG findings are increasing in the function of LVMI parameters, which represent the severity of LVH.

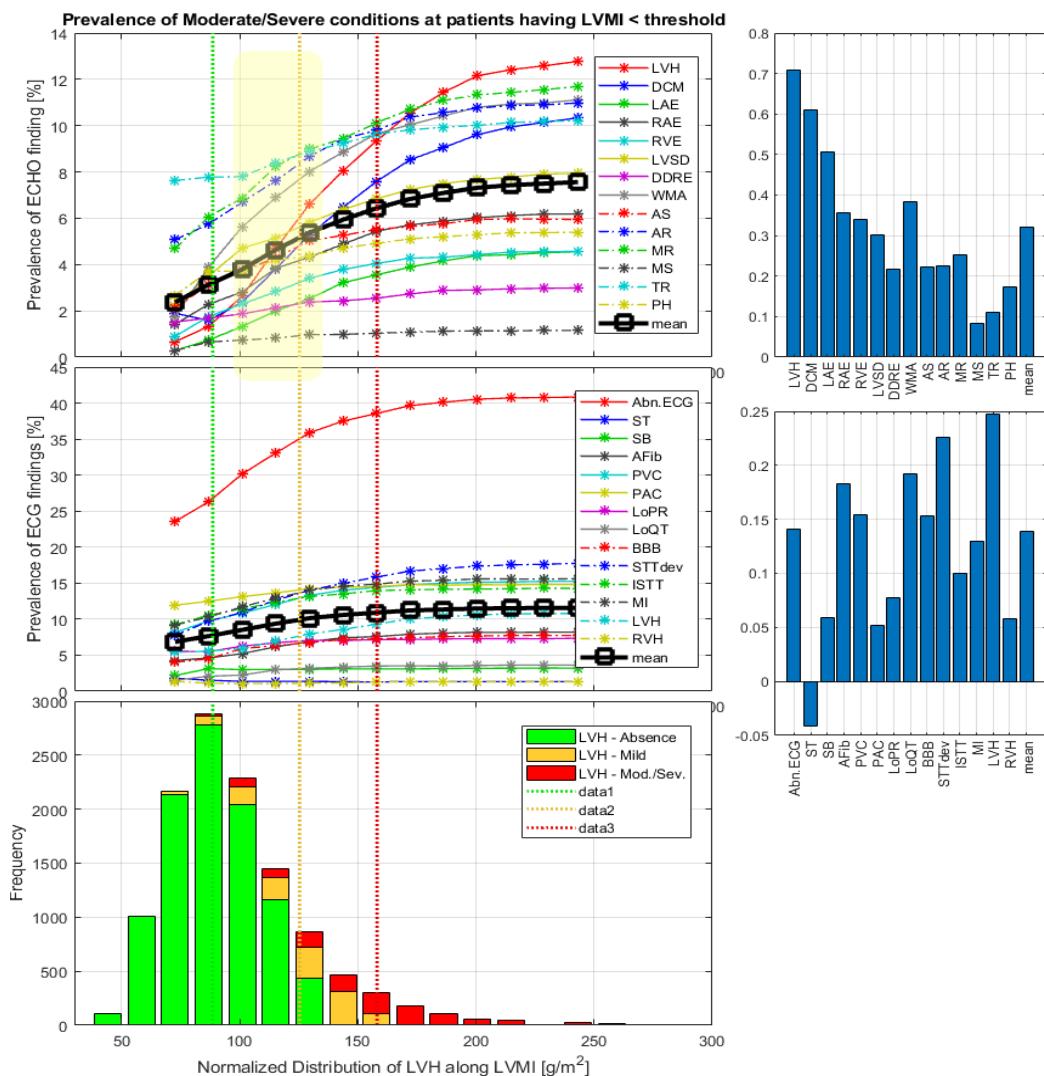


Figure 4-3 Co-morbidity analysis of LVH along continual LVMI, using CPA database

²⁷ Liao, Youlian, et al. "Left ventricular hypertrophy has a greater impact on survival in women than in men." Circulation 92.4 (1995): 805-810.

²⁸ Elhendy, Abdou, et al. "Prediction of mortality in patients with left ventricular hypertrophy by clinical, exercise stress, and echocardiographic data." Journal of the American College of Cardiology 41.1 (2003): 129-135.



4.3.2 Dilated Cardiomyopathy

Abbreviation	DCM
Description	Dilated Cardiomyopathy, known as Eccentric LVH or LV Enlargement
ICD10 code	I42.0 Dilated cardiomyopathy
Echo criteria	LVIDd (Diastolic LV diameter) > [57/63]mm Confirmed by non-ischemic impaired LV systolic function, EF<45%
Cardiovascular Risk	As DCM eventually leads to impaired contractility, standard approaches to prevent or treat heart failure are the first-line treatment for patients with DCM. Most causes of heart failure arising from DCM occur from pump failure (70%) due to dilatation. ²⁹ DCM is a major risk factor for developing heart failure (HF) as the presence of reduced systolic function does not imply symptoms. ³⁰ The WHO defines DCM as a serious cardiac disorder in which structural or functional abnormalities of the heart muscle can lead to substantial morbidity and mortality owing to complications such as heart failure and arrhythmia ³¹
Morbidity	More recently, Hershberger et al ³² used a different approach to estimate DCM prevalence, based on the known ratio of idiopathic DCM to HCM of ≈2:1, prevalence estimates of HF, and prevalence estimates of LV dysfunction as a surrogate for DCM. With this approach, a much higher prevalence of DCM is estimated, in the range of 1:250 (0.4%). – Calculated on general population.
Co-Morbidity	DCM complications includes: Congestive heart failure, Cerebrovascular accident, Valvular heart disease, Abnormal cardiac rhythms, Sudden cardiac death, Thromboembolism. ³³ The Co-Morbidity analysis on CPA database (Figure 4-4) shows strong co-morbidities for many heart diseases, including LVH, LAE, RAE, RVE, LVSD, DDRE, WMA, MR, PH, Abnormal ECG, ST-T deviation and AFib.

²⁹ Heinz-Peter Schultheiss, DeLisa Fairweather, Alida L. P. Caforio, Felicitas Escher, Ray E. Hershberger, Steven E. Lipshultz, Peter P. Liu, Akira Matsumori, Andrea Mazzanti, John McMurray, Silvia G. Priori, Dilated cardiomyopathy, Nat Rev Dis Primers. 2019; 5(1): 32. Published online 2019 May 9. doi:10.1038/s41572-019-0084-1

³⁰ McNally, Elizabeth M., and Luisa Mestroni. "Dilated cardiomyopathy: genetic determinants and mechanisms." Circulation research 121.7 (2017): 731-748.

³¹ Richardson P, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation. 1996;93:841-842. doi: 10.1161/01.CIR.93.5.841.

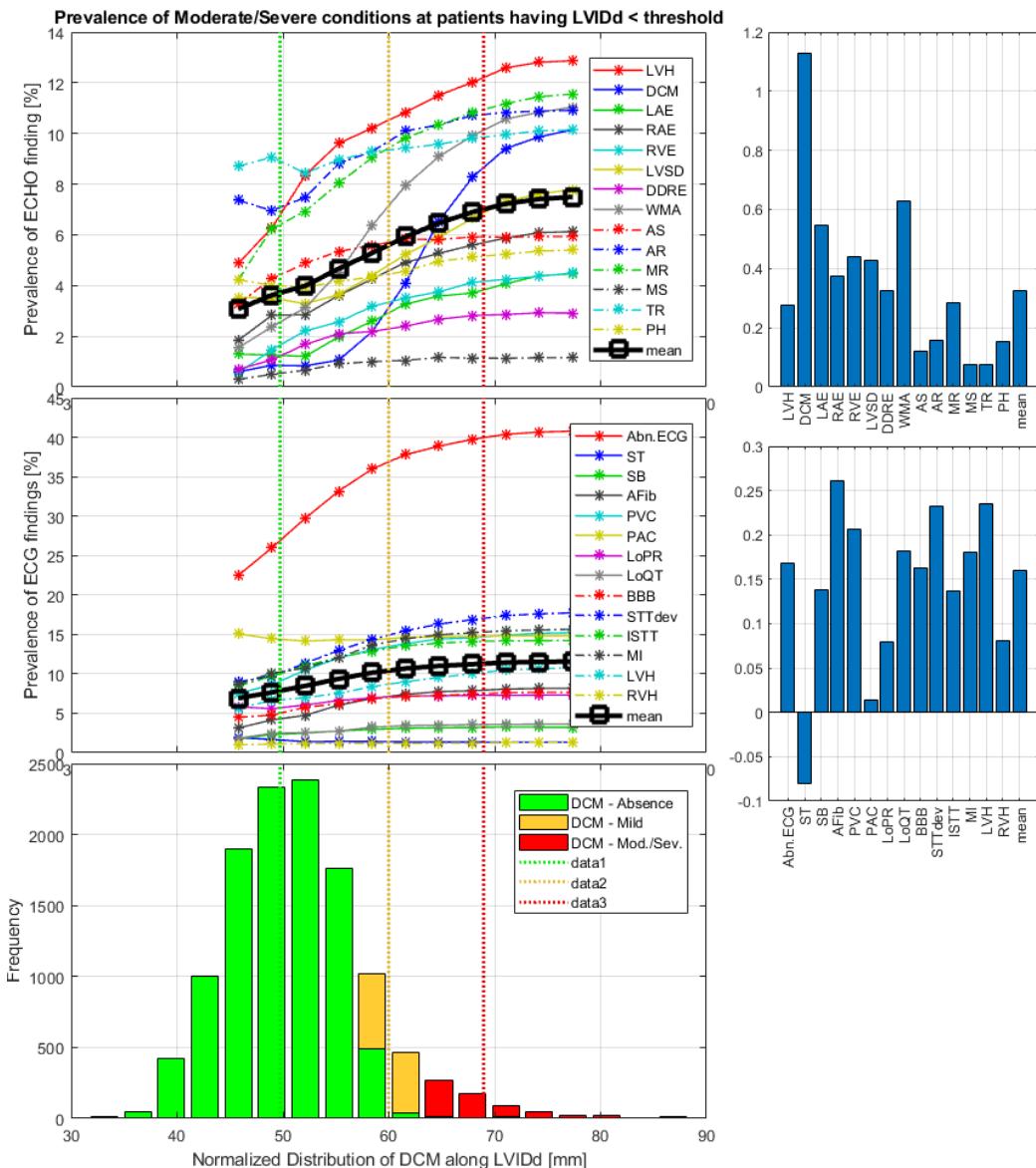
³² Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. Nat Rev Cardiol. 2013; 10:531-547. doi: 10.1038/nrcardio.2013.105.

³³ Mahmaljy, Hadi, Varun S. Yelamanchili, and Mayank Singhal. "Dilated cardiomyopathy." StatPearls [Internet] (2020).



Mortality	The estimated mortality associated with cardiomyopathy was 5.9 per 100,000 global population ³⁴ Several studies report a relative risk of mortality from DCM of 1.2–1.5 for black compared with age-matched white people ³⁵
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Figure 4-4 Co-morbidity analysis of DCM along continual LVIDd, using CPA database



³⁴ Lozano R, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0.

³⁵ Heinz-Peter Schultheiss, DeLisa Fairweather, Alida L. P. Caforio, Felicitas Escher, Ray E. Hershberger, Steven E. Lipshultz, Peter P. Liu, Akira Matsumori, Andrea Mazzanti, John McMurray, Silvia G. Priori, Dilated cardiomyopathy, Nat Rev Dis Primers. 2019; 5(1): 32. Published online 2019 May 9. doi:10.1038/s41572-019-0084-1



4.3.3 RV Enlargement

Abbreviation	RVE
Description	Right ventricular Enlargement, known as Right ventricular dilation, and associated to Right ventricular hypertrophy
ICD10 code	I51.7 Cardiomegaly
Echo Criteria	RVOT (RV Outflow Track Diameter) > 28mm or RVDd-basal>40mm, RVDd-mid>35mm, RVDd-long>86mm ³⁶
Cardiovascular Risk	Right ventricular hypertrophy (also called right ventricular enlargement) happens when the muscle on the right side of your heart becomes thickened and enlarged. Right ventricular hypertrophy is usually caused by a problem in your lungs. ³⁷
Morbidity	RV dilation was present in 31% patients in hospitalized patients with coronavirus disease-2019 (COVID-19). ³⁸
Co-Morbidity	The most common etiology of right ventricular hypertrophy is severe lung disease. The disorders that induce pulmonary hypertension and secondary right ventricular hypertrophy include the following: Pulmonary arterial hypertension (PAH), Pulmonary hypertension owing to left heart disease, Pulmonary hypertension from lung disease and/or hypoxia, Chronic thromboembolic pulmonary hypertension (CTEPH), Pulmonary hypertension with unclear multifactorial mechanisms, TR ³⁹ The Co-Morbidity analysis on CPA database (Figure 4-5) shows strong co-morbidities some significant heart diseases, including LVH, DCM, RAE, LAE, AS, PH, Sinus Bradycardia and AFib.
Mortality	The presence of signs and/or symptoms resulting from RV failure identifies a subgroup of patients with an extremely unfavourable prognosis, and survival is usually less than two years. ⁴⁰ This study provides important evidence associating right heart strain with adverse outcomes in hospitalized patients with COVID-19 infection: Right ventricular enlargement was

³⁶ Partington, Sara L., and Philip J. Kilner. "How to image the dilated right ventricle." Circulation: Cardiovascular Imaging 10.5 (2017): e004688.

³⁷ <https://www.healthline.com/health/right-ventricular-hypertrophy>

³⁸ Argulian, Edgar, et al. "Right ventricular dilation in hospitalized patients with COVID-19 infection." JACC: Cardiovascular Imaging (2020).

³⁹ Bhattacharya, Priyanka T., and Sandeep Sharma. "Right Ventricular Hypertrophy." StatPearls [Internet]. StatPearls Publishing, 2020.

⁴⁰ Bussani, Rossana, et al. "Right ventricular dilatation after left ventricular acute myocardial infarction is predictive of extremely high peri-infarctual apoptosis at postmortem examination in humans." Journal of clinical pathology 56.9 (2003): 672-676.



	<p>the only variable significantly associated with mortality in a multivariable analysis (odds ratio, 4.5).⁴¹</p> <p>In patients with acute pulmonary embolism, RV enlargement on reconstructed CT 4-CH view helps predict early death.⁴²</p>
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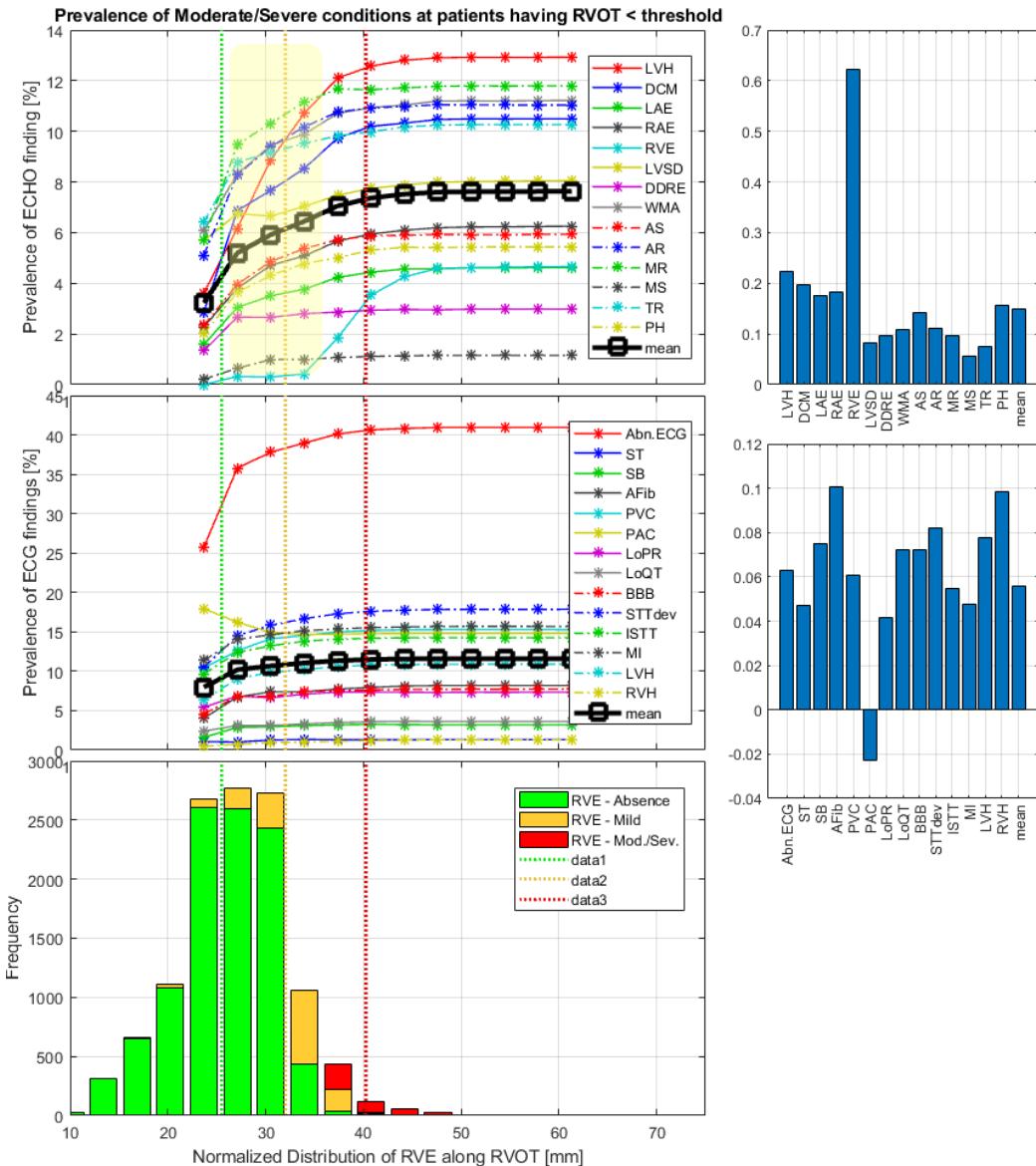


Figure 4-5 Co-morbidity analysis of RVE along continual RVOT, using CPA database

4.3.4 LA Enlargement

Abbreviation	LAE
Description	Left Atrial Enlargement or Left Atrial Dilation
ICD10 code	I51.7 Cardiomegaly

⁴¹ <https://medicalxpress.com/news/2020-05-ventricular-dilation-linked-mortality-covid-.html>

⁴² Schoepf, U. Joseph, et al. "Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism." Circulation 110.20 (2004): 3276-3280.



Echo Criteria	LAVI (LA volume / BSA)> 40ml/m2
Cardiovascular Risk	<p>Echocardiographically determined left atrial size has been shown to be a significant predictor of cardiovascular outcomes.</p> <p>With worsening LV compliance, LA pressure increases to maintain adequate LV filling, which results in LA enlargement. Therefore, LA volume may reflect the severity of diastolic dysfunction.⁴³</p> <p>Thus, like LVH, LA enlargement is an independent long-term predictor of cardiovascular events. The cardiovascular risk, however, is not further increased when LA enlargement is superimposed on an increase of LV mass.⁴⁴</p> <p>Our meta-analysis demonstrated that LAE is associated with an increased and graded risk of stroke.⁴⁵</p>
Morbidity	LAE was defined according to 11 different criteria (4 studies applied two or three criteria), and its prevalence consistently varied among studies, from 16.0–83.0%, with a prevalence in the pooled hypertensive population of 32%. ⁴⁶
Co-morbidity	<p>Atrial fibrillation (AFib) is a frequently encountered arrhythmia associated with increased morbidity and mortality. Several large population-based prospective studies have shown a strong association between M-mode anteroposterior LA diameter and the risk of new onset AF⁴⁷ left-ventricular hypertrophy as being significantly higher in patients with LAE⁴⁸.</p> <p>The Co-Morbidity analysis on CPA database (Figure 4-6) shows strong co-morbidities for almost all the significant heart diseases, including LVH, DCM, RAE, RVE, LVSD, DDRE, WMA, AS, AR, MR, TR, PH, ST-T deviation and AFib.</p>
Mortality	Left atrial enlargement may predispose to atrial fibrillation, which in turn may increase the risk of embolic events, heart failure and death. Left atrial diameter has a graded and

⁴³ Patel, Dharmendrakumar A., et al. "Clinical implications of left atrial enlargement: a review." Ochsner Journal 9.4 (2009): 191-196.

⁴⁴ Bombelli, Michele, et al. "Prognostic significance of left atrial enlargement in a general population: results of the PAMELA study." Hypertension 64.6 (2014): 1205-1211.

⁴⁵ Xu, Yicheng, et al. "Left Atrial Enlargement and the Risk of Stroke: A Meta-Analysis of Prospective Cohort Studies." Frontiers in Neurology 11 (2020).

⁴⁶ Cuspídi, Cesare, Marta Rescaldani, and Carla Sala. "Prevalence of echocardiographic left-atrial enlargement in hypertension: a systematic review of recent clinical studies." American journal of hypertension 26.4 (2013): 456-464.

⁴⁷ Patel, Dharmendrakumar A., et al. "Clinical implications of left atrial enlargement: a review." Ochsner Journal 9.4 (2009): 191-196.

⁴⁸ Cuspídi, Cesare, Marta Rescaldani, and Carla Sala. "Prevalence of echocardiographic left-atrial enlargement in hypertension: a systematic review of recent clinical studies." American journal of hypertension 26.4 (2013): 456-464.



	independent association with all-cause mortality in both sexes and with ischemic stroke in women. ⁴⁹
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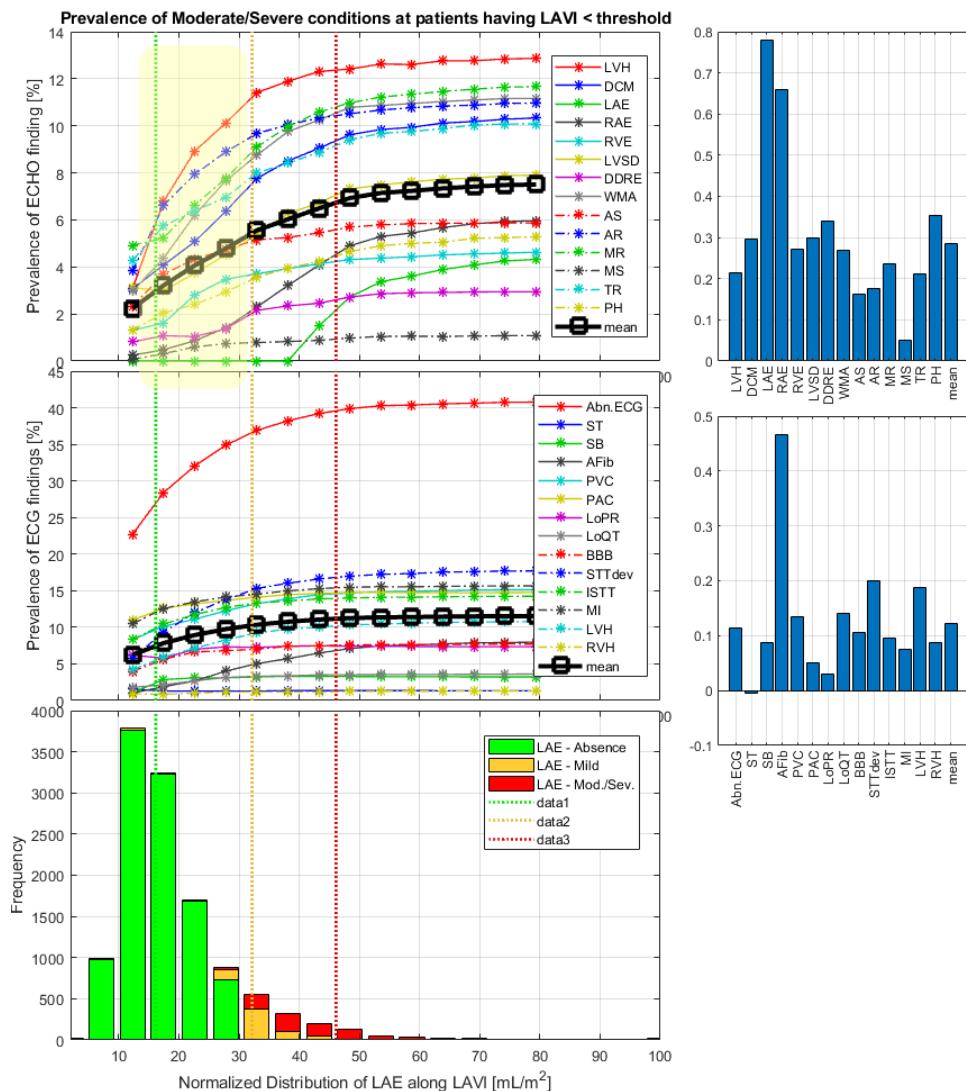


Figure 4-6 Co-morbidity analysis of LAE along continual LAVI, using CPA database

⁴⁹ Bouzas-Mosquera, Alberto, et al. "Left atrial size and risk for all-cause mortality and ischemic stroke." Cmaj 183.10 (2011): E657-E664.



4.3.5 RA Enlargement

Abbreviation	RAE
Description	Right Atrial Enlargement
ICD10 code	I51.7 Cardiomegaly
Echo Criteria	RAVI (RA volume / BSA) > 40ml/m ²
Cardiovascular Risk	Right atrial enlargement is associated with increased risk for congestive heart failure and increased mortality in patients with primary pulmonary hypertension. ⁵⁰
Morbidity	The prevalence of cardiovascular magnetic resonance (CMR) LAE and RAE was 28% and 11%, respectively, and by any ECG criteria was 82% and 5%, respectively. – Calculated for referred to CMR unhealthy patients. Subjects with AF have a significantly higher prevalence of left (LAE) but not right atrial enlargement (RAE), compared with subjects in SR. ⁵¹
Co-Morbidity	The Co-Morbidity analysis on CPA database (Figure 4-7) shows strong co-morbidities for many heart diseases, including DCM, LAE, RVE, LVSD, DDRE, WMA, MR, TR, PH, ST-T deviation and AFib.
Mortality	The risk of all-cause mortality in patients with pulmonary arterial hypertension (PAH) was found to statistically increase by 50% for every 5-unit increase in right atrial area (RAA) ⁵²

⁵⁰ Tsao, Connie W., et al. "Accuracy of electrocardiographic criteria for atrial enlargement: validation with cardiovascular magnetic resonance." Journal of Cardiovascular Magnetic Resonance 10.1 (2008): 7.

⁵¹ Tsao, Connie W., et al. "Accuracy of electrocardiographic criteria for atrial enlargement: validation with cardiovascular magnetic resonance." Journal of Cardiovascular Magnetic Resonance 10.1 (2008): 7.

⁵² Liu, Ke, et al. "Association between right atrial area measured by echocardiography and prognosis among pulmonary arterial hypertension: a systematic review and meta-analysis." BMJ open 10.9 (2020): e031316.

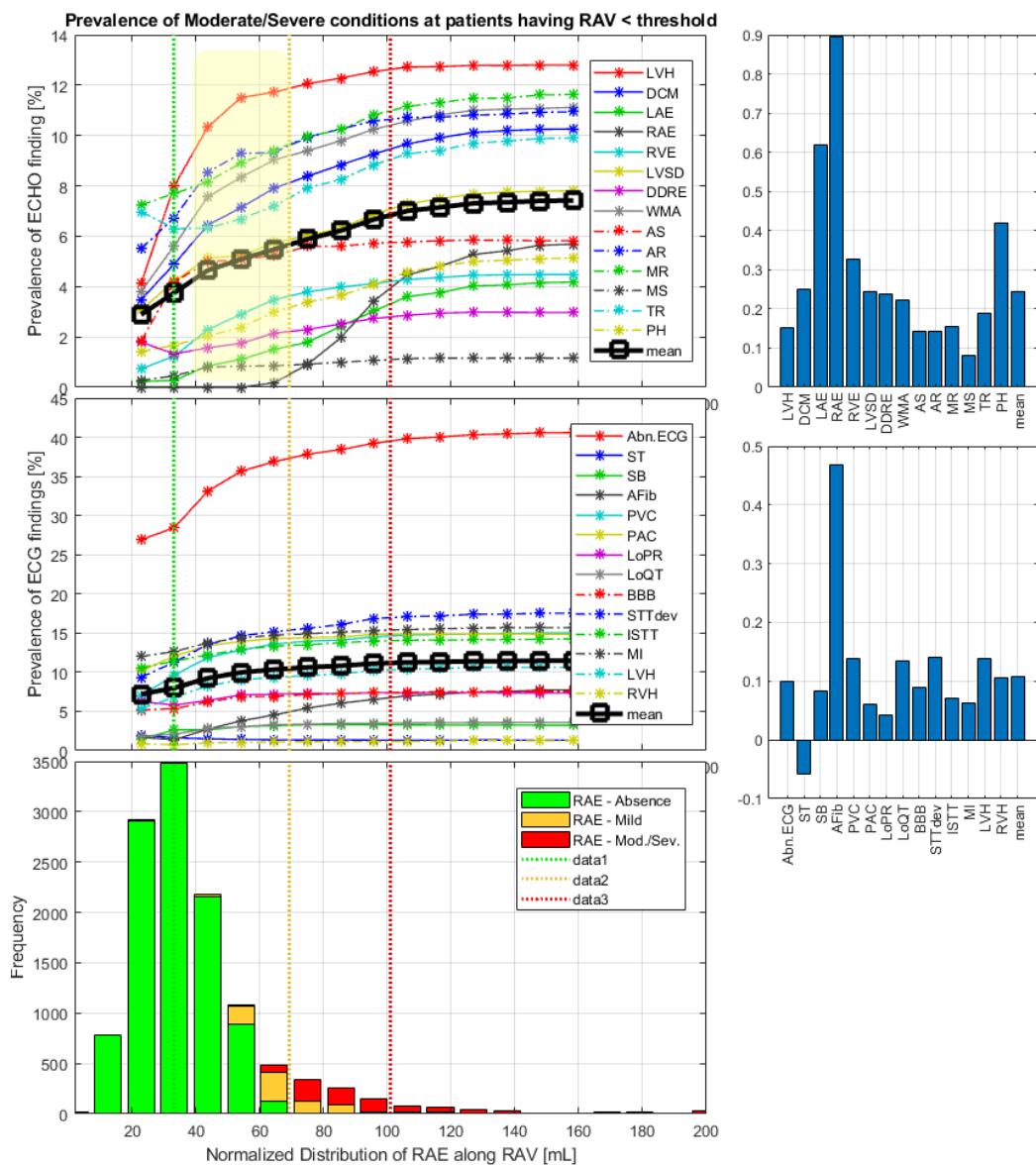


Figure 4-7 Co-morbidity analysis of RAE along continual RAVI, using CPA database



4.3.6 Wall Motion Abnormality

Abbreviation	WMA
Description	Wall Motion Abnormality - Ischemic Function with mildly abnormal EF
ICD10 code	I25.5
Echo Criteria	Hypokinesis on any part of LV EF (ejection fraction) = 40 - 50%
Cardiovascular Risk	Echocardiographic left ventricular WM abnormalities in adults without overt cardiovascular disease are associated with 2.4- to 3.4-fold higher risks of cardiovascular morbidity and mortality, independent of established risk factors. The present population-based study of adults without clinically evident CVD demonstrates a strong relationship between the presence of WM abnormalities and cardiovascular events and death. These findings suggest that echocardiographic assessment of regional LV dysfunction can identify adults without known CVD who are at increased risk of future cardiovascular events. ⁵³ Abnormal ventricular wall motion is a strong clinical predictor of sudden, arrhythmic, cardiac death. ⁵⁴
Morbidity	Echocardiographic assessment revealed that 5% of participants (n=140) had focal hypokinesia, and 1.5% (n=42) had wall motion abnormalities – calculated on participants without clinically evident cardiovascular disease in the second Strong Heart Study examination ⁵⁵ .
Co-Morbidity	The Co-Morbidity analysis on CPA database (Figure 4-9Figure 4-7) related to LVSD indirectly shows the co-morbidities for WMA: DCM, LAE, RVE, MR, Abnormal ECG and AFib. Left ventricular mass and geometry are also related with stroke incidence, with concentric hypertrophy carrying the greatest risk. ⁵⁶
Mortality	HF and ischemic stroke (IS) share vascular risk factors such as age, hypertension, diabetes mellitus, coronary artery disease and atrial fibrillation. Persons with HF have higher incidence of IS, varying from 1.7% to 10.4% per year across various cohort studies. Reduced EF, independent of severity, is associated with higher risk of stroke. Stroke in patients with HF is more severe and is associated with a higher rate of

⁵³ <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.652149>

⁵⁴ <https://www.frontiersin.org/articles/10.3389/fphys.2012.00235/full>

⁵⁵ Cicala, Silvana, et al. "Prevalence and Prognostic Significance of Wall Motion Abnormalities in Adults without Recognized Cardiovascular disease: The Strong Heart Study." (2006): II_478-II_479.

⁵⁶ Cuadrado-Godia E, Ois A, Roquer J. Heart failure in acute ischemic stroke. Curr Cardiol Rev. 2010;6(3):202-213. doi:10.2174/157340310791658776



	<p>recurrence, dependency, and short term and long term mortality. Cardiac morbidity and mortality is also high in these patients.⁵⁷</p> <p>8% with no wall motion abnormality (WMA) died compared to 18% in patients with a WMA. In patients with moderate/severe ischemia, the presence of a resting WMA was associated with a higher mortality rate. In a multivariable model, LVEF (< 50%) was associated with a hazard ratio of 2.2 however, WMA and number of abnormal segments did not reach statistical significance. Calculated on study population: 49% patients underwent revascularization, 13% patients died, 73% patients had a normal left ventricular ejection fraction, 48% patients had a resting wall motion abnormality (WMA).⁵⁸</p>
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⁵⁷ Cuadrado-Godia E, Ois A, Roquer J. Heart failure in acute ischemic stroke. *Curr Cardiol Rev.* 2010;6(3):202-213. doi:10.2174/157340310791658776

⁵⁸ Kilcullen, Niamh M., et al. "The prognostic significance of resting regional left ventricular function in patients with varying degrees of myocardial ischemia." *Cardiology research* 4.6 (2013): 178.

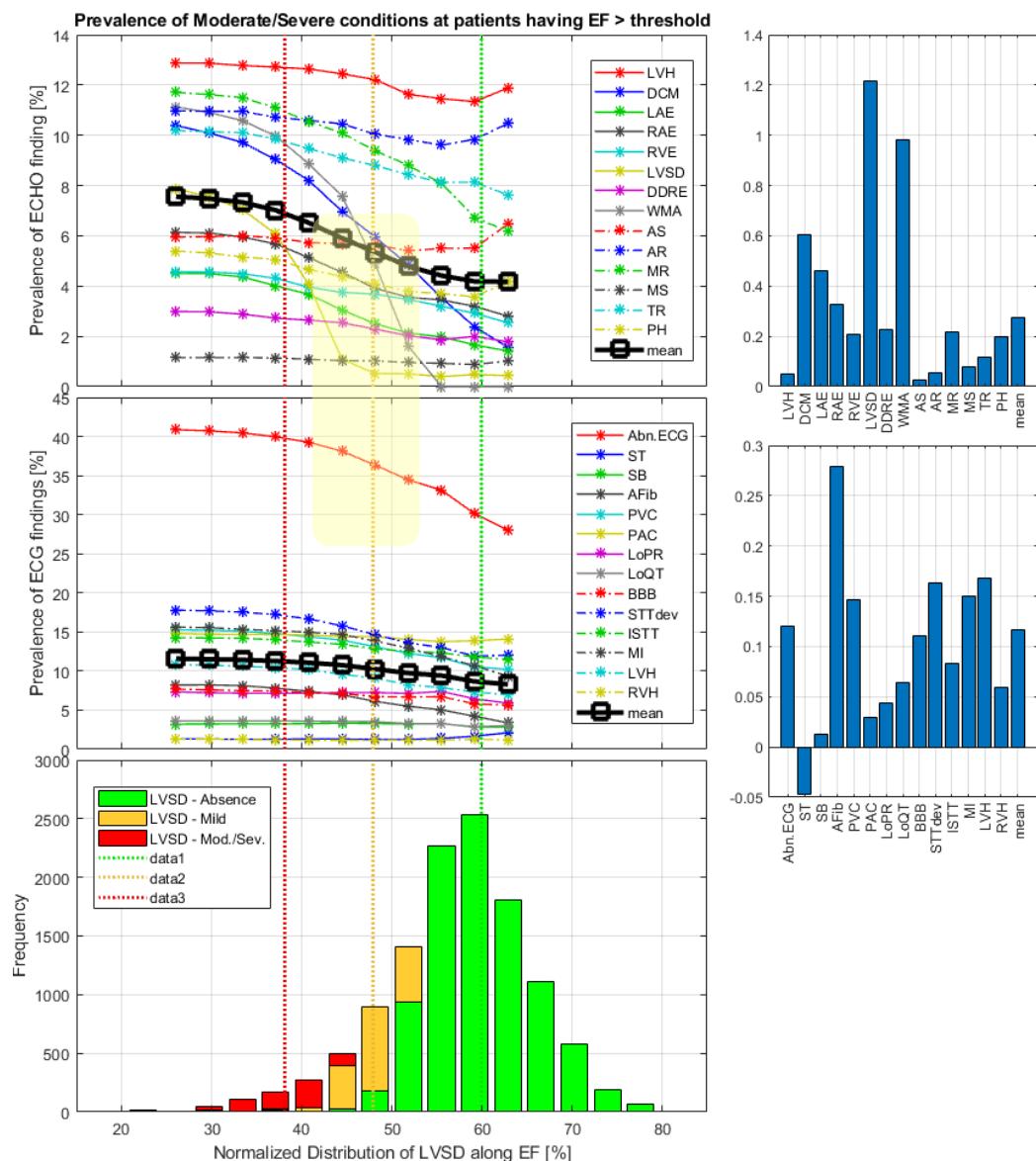


Figure 4-8 Co-morbidity analysis of WMA along continual EF, using CPA database



4.3.7 Systolic Dysfunction with moderate/severe EF

Abbreviation	LVSD
Description	LV Systolic Dysfunction with moderate/severely decreased EF
ICD10 code	I50.2
Echo Criteria	EF (ejection fraction) <40% or extensive akinesis, dyskinesis in LV wall motion
Cardiovascular Risk	<p>Left ventricular dysfunction (LVD) is associated with cardiovascular mortality. Its association with ischemic stroke has been mainly documented after myocardial infarction. The stroke risk associated with LVD, especially of mild degree, in the general population is unclear. The purpose of this study was to evaluate the relationship between LVD and ischemic stroke in a multiethnic cohort. LVD, even of mild degree, is independently associated with an increased risk of ischemic stroke. The assessment of LV function should be considered in the assessment of the stroke risk.⁵⁹</p> <p>Heart failure due to left ventricular systolic dysfunction (LVSD) is a common, costly, disabling and life-threatening condition.⁶⁰</p>
Morbidity	0.56% of Participants Free of Heart Failure Who Underwent Routine Framingham Study has EF<40% ⁶¹
Co-Morbidity	The Co-Morbidity analysis on CPA database (Figure 4-9Figure 4-7) shows some significant co-morbidities for LVSD progression: DCM, LAE, RVE, WMA, MR, PH, Abnormal ECG, ST-T deviation, MI and AFib.
Mortality	<p>Patients with LVSD (with/without HF) had a higher risk of stroke or systemic embolism (SSE) or death (but similar rate of SSE) compared with patients with HF but preserved LV systolic function; both had a greater risk than patients without either HF or LVSD.⁶²</p> <p>Increasing LVSD is associated with elevated risk of Sudden death (SD)⁶³</p>

⁵⁹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2677017/>

⁶⁰ Fahey, T., et al. "Diagnosis of left ventricular systolic dysfunction (LVSD): development and validation of a clinical prediction rule in primary care." Family practice 24.6 (2007): 628-635.

⁶¹ Vasan, Ramachandran S., et al. "Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades." JACC: Cardiovascular Imaging 11.1 (2018): 1-11.

⁶² McMurray, John JV, et al. "Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial." Circulation: Heart Failure 6.3 (2013): 451-460.

⁶³ Macchia, Alejandro, et al. "Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids." European journal of heart failure 7.5 (2005): 904-909.

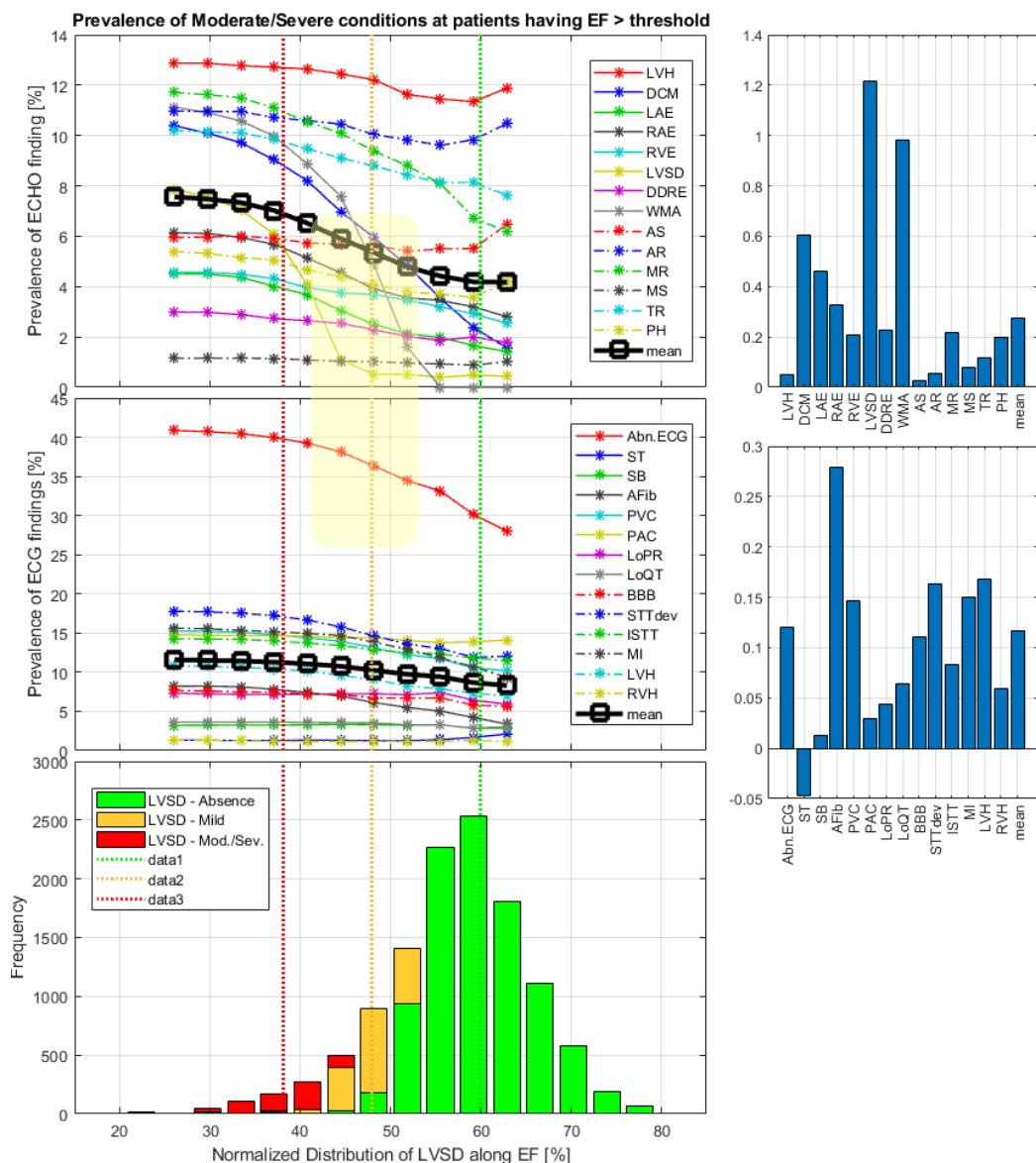


Figure 4-9 Co-morbidity analysis of LVSD along continual EF, using CPA database



4.3.8 Diastolic Dysfunction

Abbreviation	LVDD
Description	Diastolic dysfunction: Impaired Relaxation, Pseudonormal and Restrictive Filling
ICD10 code	I50.3
Echo criteria	Impaired Relaxation: E/A < 0.8 Restrictive Filling: E/A > 2.0
Cardiovascular Risk	Three million Americans have congestive heart failure (CHF), and 500,000 new cases are diagnosed each year. The condition is the most common discharge diagnosis for patients older than 65 years ⁶⁴ and is the most expensive disease for Medicare. ² Systolic and diastolic dysfunction can cause CHF. ⁶⁵ All patients with systolic dysfunction have concomitant diastolic dysfunction; therefore, a patient cannot have pure systolic heart failure. ⁶⁶ In contrast, certain cardiovascular diseases such as hypertension may lead to diastolic dysfunction without concomitant systolic dysfunction. ⁶⁷ Although diastolic heart failure accounts for approximately 40 to 60 percent of patients with CHF, these patients have a better prognosis than those with systolic heart failure. ⁶⁸
Morbidity	The overall prevalence of LV diastolic dysfunction in a random sample of a general population, as estimated from echocardiographic measurements, was as high as 27.3% ⁶⁹
Co-Morbidity	The Co-Morbidity analysis on CPA database (Figure 4-10Figure 4-7) shows there is few co-morbidities, like LAE and AFib for the increased E/A as indicator of restrictive filling. However, there are some prevalence increase at E/A<1 as indicator of impaired relaxation.
Mortality	Only moderate and severe DD were associated with an increased mortality risk (hazard ratio = 1.58) ⁷⁰

⁶⁴ Tecce MA, Pennington JA, Segal BL, Jessup ML. Heart failure: clinical implications of systolic and diastolic dysfunction. *Geriatrics*. 1999;54:24–8,31–3.

⁶⁵ Litwin SE, Grossman W. Diastolic dysfunction as a cause of heart failure. *J Am Coll Cardiol*. 1993;22(4 suppl A):49A-55A.

⁶⁶ Brutsaert DL, Sys SU. Diastolic dysfunction in heart failure. *J Card Fail*. 1997;3:225–42.

⁶⁷ Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol*. 1999;33:1948–55.

⁶⁸ Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history?. *J Am Coll Cardiol*. 2001;38:1277–82.

⁶⁹ Kuznetsova, Tatiana, et al. "Prevalence of left ventricular diastolic dysfunction in a general population." *Circulation: Heart Failure* 2.2 (2009): 105-112.

⁷⁰ Halley, Carmel M., et al. "Mortality rate in patients with diastolic dysfunction and normal systolic function." *Archives of internal medicine* 171.12 (2011): 1082-1087.

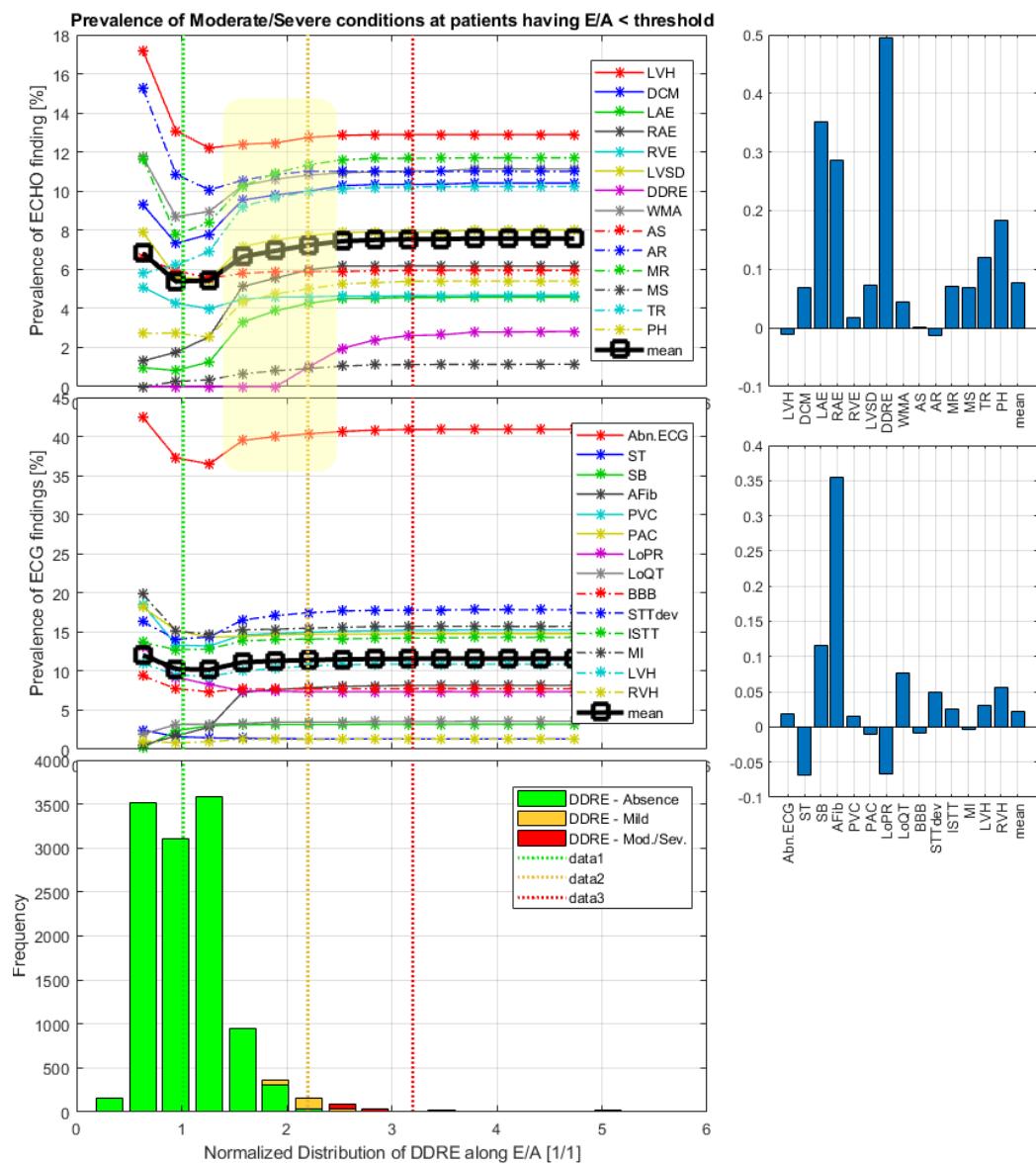


Figure 4-10 Co-morbidity analysis of LVDD along continual E/A, using CPA database



4.3.9 Aortic Stenosis

Abbreviation	AS
Description	Aortic stenosis
ICD10 code	I35.0
Echo criteria	AVpV (AV peak velocity) > 2.3 m/s
Cardiovascular Risk	echocardiographic measures consistent with severe aortic stenosis, symptoms must be presumed to be a result of aortic stenosis, even if other potentially causative conditions, such as CAD, are present. ⁷¹ Survival in patients with aortic stenosis that is managed with watchful waiting is comparable to that in patients without aortic stenosis. It is important to distinguish patients who are truly asymptomatic from those who have a routine activity level that has decreased to below their symptom threshold. This is especially important in older patients who may attribute their symptoms to normal aging or concurrent illness. ⁷²
Morbidity	Aortic valve stenosis affects 3 percent of persons older than 65 years and leads to greater morbidity and mortality than other cardiac valve diseases. ⁷³ The pathology of aortic stenosis includes processes similar to those in atherosclerosis, including lipid accumulation, inflammation, and calcification. ⁷⁴ The development of significant aortic stenosis tends to occur earlier in those with congenital bicuspid aortic valves. ⁷⁵ Although the survival rate in asymptomatic patients is comparable to that in age-and sex-matched control patients, survival notably worsens after symptoms appear.
Co-Morbidity	Echocardiography also provides useful information about LV function, left ventricular filling pressure, and coexisting

⁷¹ American College of Cardiology/American Heart Association algorithm for the management of severe aortic stenosis. (CABG = coronary artery bypass graft.) Adapted from Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in Circulation. 2007;115(15): e409]. Circulation. 2006;114(5):e108.

⁷² Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in Circulation. 2007;115(15):e409]. Circulation. 2006;114(5):e84–e231.

⁷³ Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993;21(5):1220–1225.

⁷⁴ Otto CM, Knusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of “degenerative” valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation.* 1994;90(2):844–853.

⁷⁵ Lewin MB, Otto CM. The bicuspid aortic valve: adverse outcomes from infancy to old age. *Circulation.* 2005;111(7):832–834.



	<p>abnormalities of other valves⁷⁶ aortic stenosis accompanied by LV systolic dysfunction (i.e., ejection fraction of less than 50 percent, aortic valve replacement is a lifesaving therapy and improves LV function.^{77 78 79}</p> <p>at moderate risk for development of endocarditis⁸⁰ Hypertension.</p> <p>The Co-Morbidity analysis on CPA database (Figure 4-11) shows weaker co-morbidities for AR.</p>
Mortality	Mortality dramatically increases after aortic stenosis becomes symptomatic. The average overall survival rate is two to three years in symptomatic patients without surgical treatment. Among older members of this population, one- and three-year mortality rates of 44 and 75 percent, respectively, have been reported. ⁸¹

⁷⁶ Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2007;115(15):e409]. *Circulation*. 2006;114(5):e84–e231.

⁷⁷ Otto CM, Pearlman AS. Doppler echocardiography in adults with symptomatic aortic stenosis. Diagnostic utility and cost-effectiveness. *Arch Intern Med*. 1988;148(12):2553–2560.

⁷⁸ Otto CM. Valvular aortic stenosis: disease severity and timing of intervention. *J Am Coll Cardiol*. 2006;47(11):2141–2151.

⁷⁹ Paquette B, Corbineau H, Laurent M, et al. Valve replacement in patients with critical aortic stenosis and depressed left ventricular function: predictors of operative risk, left ventricular function recovery, and long term outcome. *Heart*. 2005;91(10):1324–1329.

⁸⁰ Bonow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation*. 1998;98:1949–84....

⁸¹ Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111(24):3290–3295.

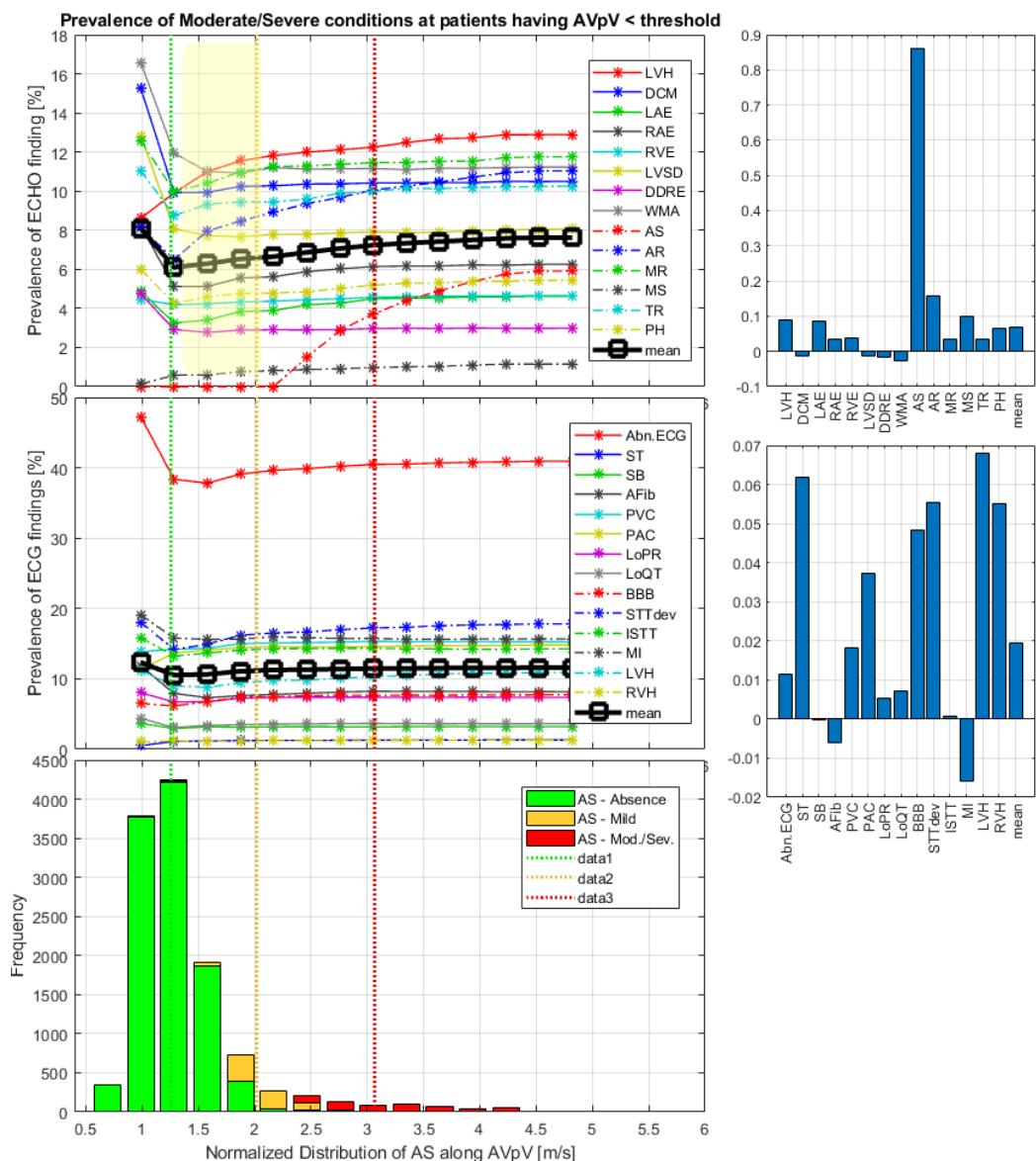


Figure 4-11 Co-morbidity analysis of AS along continual AVpV, using CPA database



4.3.10 Mitral Stenosis

Abbreviation	MS
Description	Mitral Stenosis, including Degenerative Mitral Stenosis (DMS) and Rheumatic Mitral Stenosis (RMS)
ICD10 code	I34.2, I05.0
Echo Criteria	MVGEm (Mean gradient) > 5mmHg DT (Deceleration Time) > 500ms MVA (Mitral valve area) < 1.5cm ²
Cardiovascular Risk	primarily affecting women ⁸² . rapid acceleration later in life ⁸³ patients with regurgitant valvular lesions require careful echocardiography monitoring for left ventricular function and may require surgery even if no symptoms are present. ⁸⁴ asymptomatic until atrial fibrillation develops
Morbidity	Leads to degenerative mitral stenosis (DMS). Leads to AF decrease left ventricular filling, reduce cardiac output and increase left atrial pressure, pulmonary hypertension, ⁸⁵
Co-morbidity	most MS lesions can cause left ventricular dysfunction even in the absence of symptoms. ⁸⁶ Leads to atrial fibrillation, DMS (degenerative mitral stenosis) and left-sided heart failure: dyspnea on exertion, orthopnea and paroxysmal nocturnal dyspnea. Patients may also present with hemoptysis and signs of right-sided heart failure. ⁸⁷ The Co-Morbidity analysis on CPA database (Figure 4-12) shows weaker co-morbidities for LAE, RAE, DDRE, PH and AFib.

⁸² Carabello BA, Crawford FA. Valvular heart disease. *N Engl J Med*. 1997;337(1):32-41 [published erratum appears in N Engl J Med 1997;337:507].

⁸³ Bonow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation*. 1998;98:1949-84.

⁸⁴ [B Shipton](#), [H Wahba](#) Valvular heart disease: review and update, *Am Fam Physician*. 2001 Jun 1;63(11):2201-8.

⁸⁵ Carabello BA, Crawford FA. Valvular heart disease. *N Engl J Med*. 1997;337(1):32-41 [published erratum appears in N Engl J Med 1997;337:507].

⁸⁶ Shipton, B., & Wahba, H. (2001). Valvular heart disease: review and update. *American family physician*, 63(11), 2201-2208.

⁸⁷ Shipton B, Wahba H. Valvular heart disease: review and update. *Am Fam Physician*. 2001 Jun 1;63(11):2201-8. PMID: 11417772.



Mortality	The 1- and 5-year survival rates were 78% and 47%, respectively, and were slightly worse with higher grades ($P = .02$). ⁸⁸
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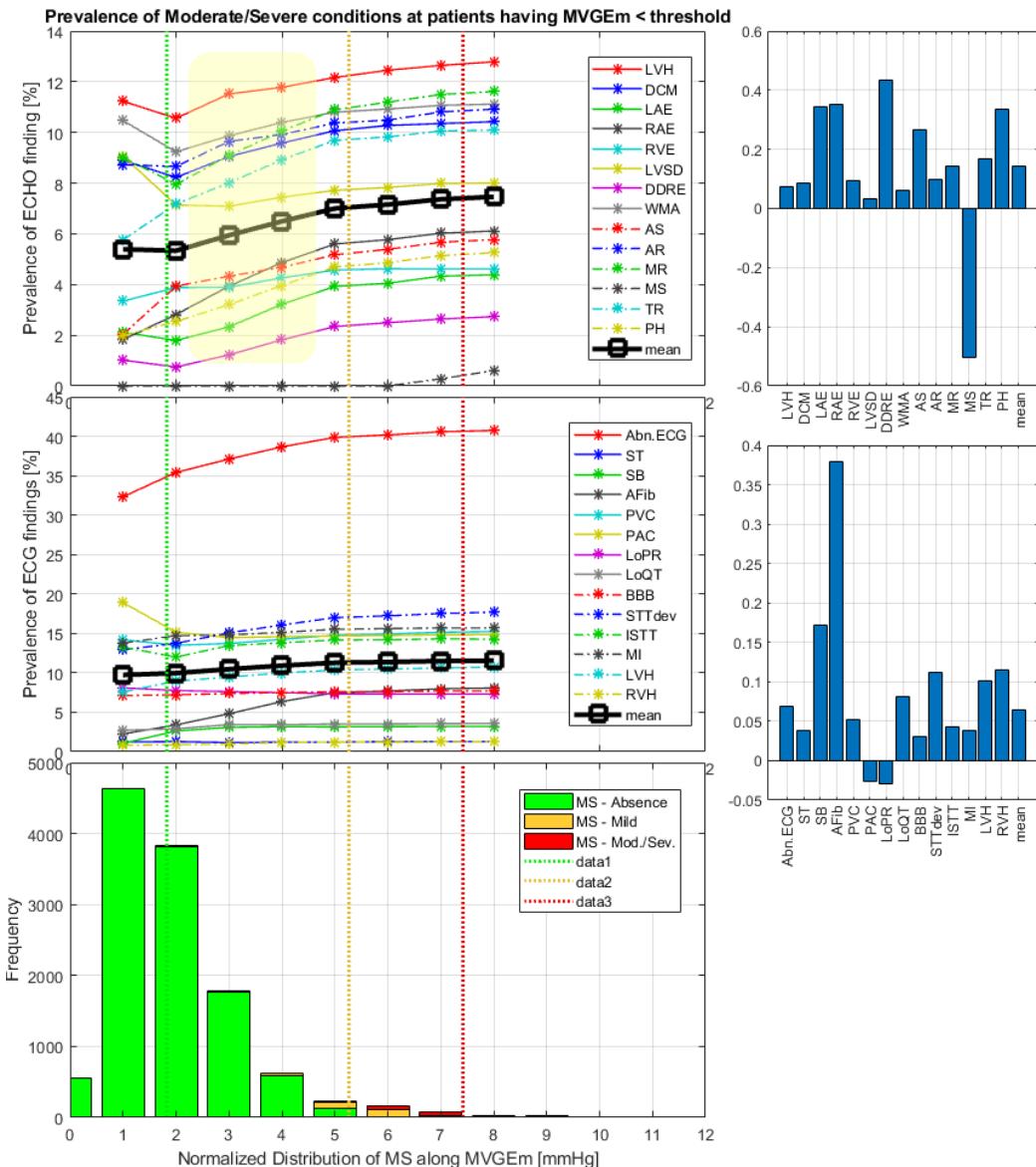


Figure 4-12 Co-morbidity analysis of MS along continual MVGEm, using CPA database

⁸⁸ Oktay AA, Gilliland YE, Lavie CJ, et al. Echocardiographic Assessment of Degenerative Mitral Stenosis: A Diagnostic Challenge of an Emerging Cardiac Disease. *Curr Probl Cardiol*. 2017;42(3):71-100. doi:10.1016/j.cpcardiol.2017.01.002



4.3.11 Aortic Regurgitation

Abbreviation	AR
Description	Aortic Regurgitation
ICD10 code	I35.1
Echo Criteria	ARgr (AR grade) ≥ II
Cardiovascular Risk	causes of aortic regurgitation include endocarditis, rheumatic fever, collagen vascular disease, aortic dissection and syphilis ⁸⁹ the stroke volume is increased, which in turn causes systolic hypertension, high pulse pressure and increased afterload. ⁹⁰ asymptomatic until severe left ventricular dysfunction has developed
Morbidity	Left-sided heart failure: orthopnea, dyspnea and fatigue. progressive chamber enlargement with decreased contractility make recovery of left ventricular function and improved survival impossible, even with surgery. ⁹¹ Compelling evidence supports surgical correction before the onset of permanent left ventricular damage, even in asymptomatic patients. In patients with chronic aortic regurgitation, surgery should be performed before the ejection fraction falls below 55 percent or the end-systolic dimension exceeds 55 mm. ⁹² ¹³
Co-Morbidity	The Co-Morbidity analysis on CPA database (Figure 4-13) shows weaker co-morbidities for AS and AFib.
Mortality	AR of mild or greater severity was seen in 13% of men and 8.5% of women in the Framingham Offspring Study. Moderate or more severe AR was estimated to be prevalent in approximately 0.5% of the total USA population. ⁹³

⁸⁹ Carabello BA, Crawford FA. Valvular heart disease. *N Engl J Med.* 1997;337(1):32–41 [published erratum appears in N Engl J Med 1997;337:507].

⁹⁰ Bonow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation.* 1998;98:1949–84.

⁹¹ Bonow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation.* 1998;98:1949–84.

⁹² Carabello BA, Crawford FA. Valvular heart disease. *N Engl J Med.* 1997;337(1):32–41 [published erratum appears in N Engl J Med 1997;337:507].

⁹³ Ancona, R., and S. Comenale. "Epidemiology of aortic valve stenosis (AS) and aortic valve incompetence (AI): is the prevalence of AS/AI similar in different parts of the world." *Eur Soc Cardiol* 18.10 (2020).

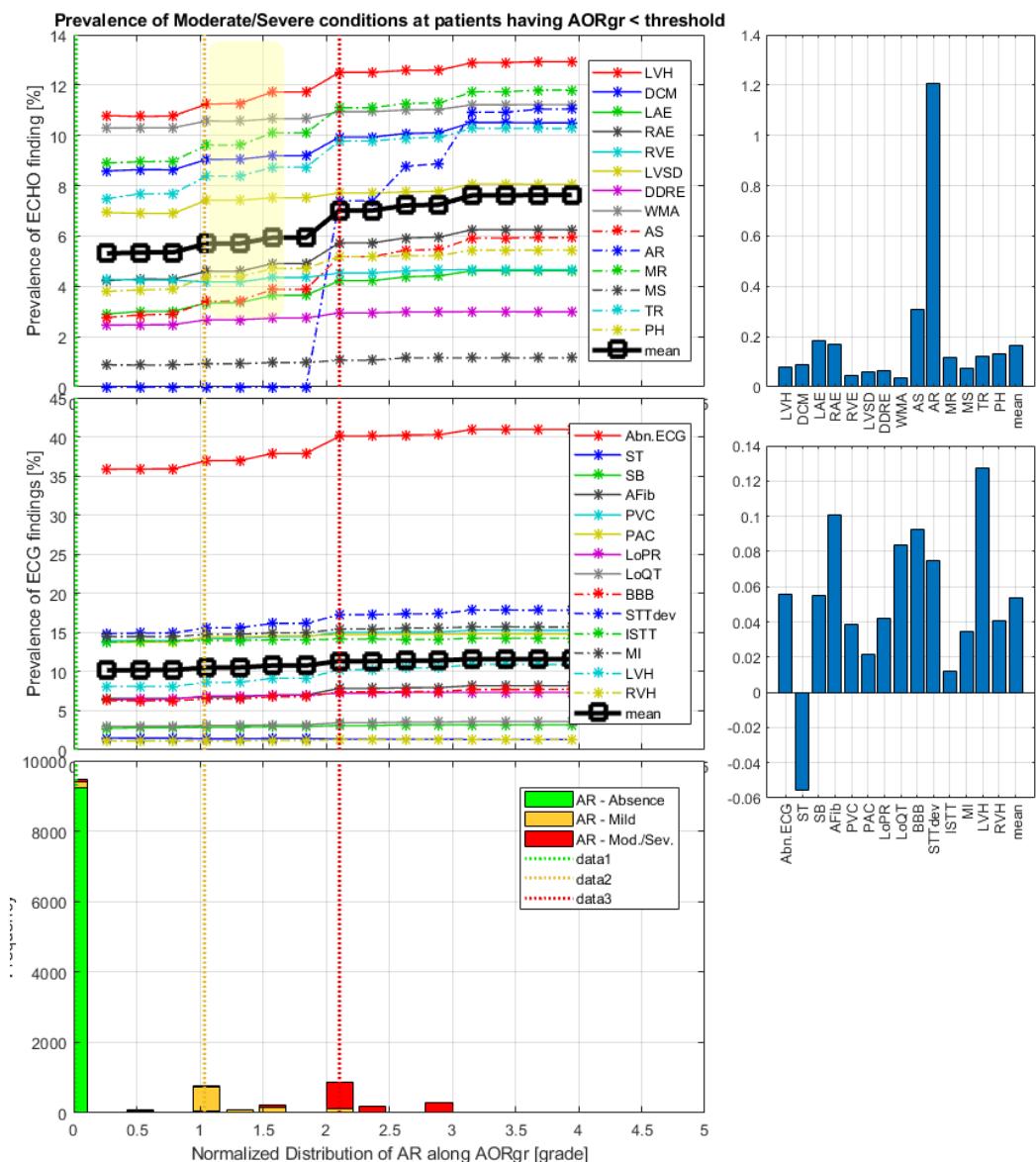


Figure 4-13 Co-morbidity analysis of AR along graded $AORgr$ estimated parameter, using CPA database



4.3.12 Mitral Regurgitation

Abbreviation	MR
Description	Mitral Regurgitation
ICD10 code	I34.0, I05.1
Echo Criteria	MRgr (MR grade) \geq II
Cardiovascular Risk	Severe MR patients should be referred for surgery if symptoms are moderate to severe, if the ejection fraction is less than 60 percent or if the end-systolic dimension approaches 45 mm, even in the absence of symptoms ^{94 95}
Morbidity	Acute and chronic mitral regurgitation (MR) affect approximately 5 in 10,000 people. With the aid of color Doppler echocardiography, mild MR can be detected in as many as 20% of middle-aged and older adults. ⁹⁶
Co-Morbidity	Mitral Valve Prolapse The Co-Morbidity analysis on CPA database (Figure 4-14Figure 4-16) shows significant co-morbidities for most of significant heart diseases: DCM, LAE, RAE, LVSD, DDRE, WMA, AR, TR, PH, Abnormal ECG, Sinus Bradycardia, ST-T deviation, Long QT and AFib.
Mortality	No studies have demonstrated successful use of medical therapy, other than as prophylaxis against endocarditis, in the treatment of chronic mitral regurgitation. ^{97 98}

⁹⁴ Bonow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation*. 1998;98:1949-84.

⁹⁵ Carabello BA, Crawford FA. Valvular heart disease. *N Engl J Med*. 1997;337(1):32-41 [published erratum appears in N Engl J Med 1997;337:507].

⁹⁶ <https://www.medscape.com/answers/155618-166199/what-is-the-prevalence-of-mitral-regurgitation-mr-in-the-us>

⁹⁷ Bonow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation*. 1998;98:1949-84.

⁹⁸ Carabello BA, Crawford FA. Valvular heart disease. *N Engl J Med*. 1997;337(1):32-41 [published erratum appears in N Engl J Med 1997;337:507].

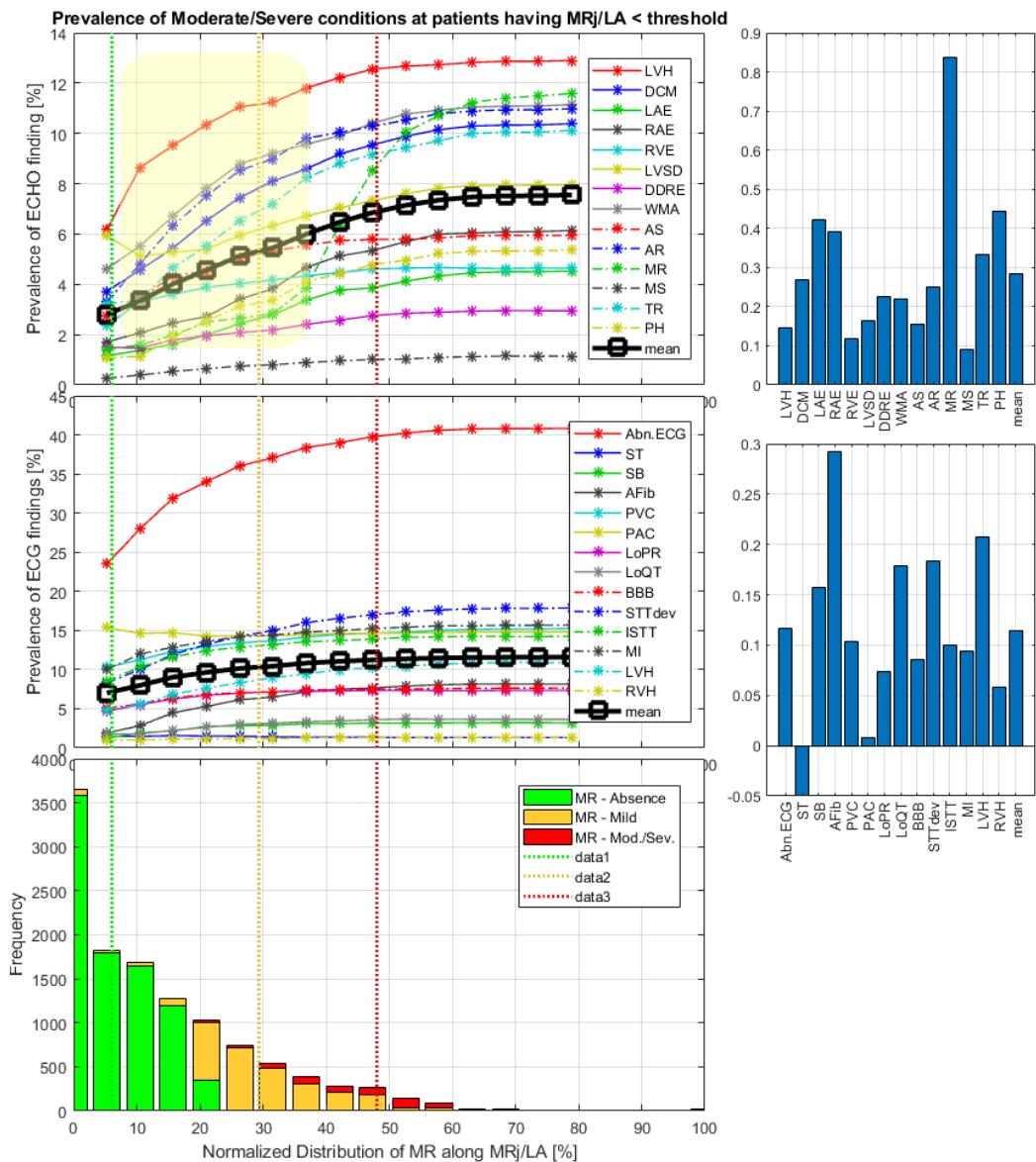


Figure 4-14 Co-morbidity analysis of MR along continual MRj/LA , using CPA database



4.3.13 Tricuspid Regurgitation without Pulmonary Hypertension

Abbreviation	TR
Description	Tricuspid Regurgitation without Pulmonary Hypertension
ICD10 code	I36.1, I07.1
Echo Criteria	TRgr (TR grade) ≥ II
Cardiovascular Risk	<p>in isolated TR, in the absence of pulmonary hypertension, the RV tends to dilate predominantly in the basal segments (conical deformation) with more annular dilation and right atrial remodelling.</p> <p>results from an enlarged lower heart chamber (right ventricle)</p> <p>associated with the use of the diet drug "Fen-Phen" (fenfluramine and phentermine).^{99 100}</p> <p>TR is often diagnosed by chance during echocardiography. The holosystolic murmur typical of TR, when present, should prompt echocardiographic assessment^{101 102}</p> <p>moderate or severe TR can lead to irreversible myocardial damage and adverse outcomes.¹⁰³</p> <p>recent evidence shows that prolonged right ventricular (RV) volume overload due to chronic TR may result in irreversible RV myocardial damage¹⁰⁴</p>
Morbidity	The importance of early referral for isolated TV surgery was demonstrated by Topilsky <i>et al.</i> ²⁷ who showed improved

⁹⁹ <https://www.heart.org/en/health-topics/heart-valve-problems-and-disease/heart-valve-problems-and-causes/problem-tricuspid-valve-regurgitation>

¹⁰⁰ Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg 2005;79:127–132.

¹⁰¹ Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JPIII, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TMIII, Thomas JD, Members AATF. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521–e643.

¹⁰² Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Guidelines ESCCP, Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

¹⁰³ Mani Arsalan, Thomas Walther, Robert L. Smith, II, Paul A. Grayburn, Tricuspid regurgitation diagnosis and treatment, *European Heart Journal*, Volume 38, Issue 9, 1 March 2017, Pages 634–638, <https://doi.org/10.1093/eurheartj/ehv487>

¹⁰⁴ Mani Arsalan, Thomas Walther, Robert L. Smith, II, Paul A. Grayburn, Tricuspid regurgitation diagnosis and treatment, *European Heart Journal*, Volume 38, Issue 9, 1 March 2017, Pages 634–638, <https://doi.org/10.1093/eurheartj/ehv487>



	outcomes in patients with New York Heart Association (NYHA) class II symptoms compared to NYHA III and IV. ¹⁰⁵ Approximately 20–30% of patients undergoing cardiac surgery for left-sided valvular disease (most often MR) present with significant TR. ^{106 107} 21:22
Co-Morbidity	The Co-Morbidity analysis on CPA database (Figure 4-15Figure 4-16) shows significant co-morbidities for LAE, RAE, PH and AFib.
Mortality	When patients with severe TR are operated before they develop severe symptoms (NYHA IV), early mortality decreases to ~6%. ¹⁰⁸ 27

¹⁰⁵ Topilsky Y, Khanna AD, Oh JK, Nishimura RA, Enriquez-Sarano M, Jeon YB, Sundt TM, Schaff HV, Park SJ. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation 2011;123:1929–1939.

¹⁰⁶ King RM, Schaff HV, Danielson GK, Gersh BJ, Orszulak TA, Piehler JM, Puga FJ, Pluth JR. Surgery for tricuspid regurgitation late after mitral valve replacement. Circulation 1984;70:I193–I197.

¹⁰⁷ Simon R, Oelert H, Borst HG, Lichtlen PR. Influence of mitral valve surgery on tricuspid incompetence concomitant with mitral valve disease. Circulation 1980;62:I152–I157.

¹⁰⁸ Topilsky Y, Khanna AD, Oh JK, Nishimura RA, Enriquez-Sarano M, Jeon YB, Sundt TM, Schaff HV, Park SJ. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation 2011;123:1929–1939.

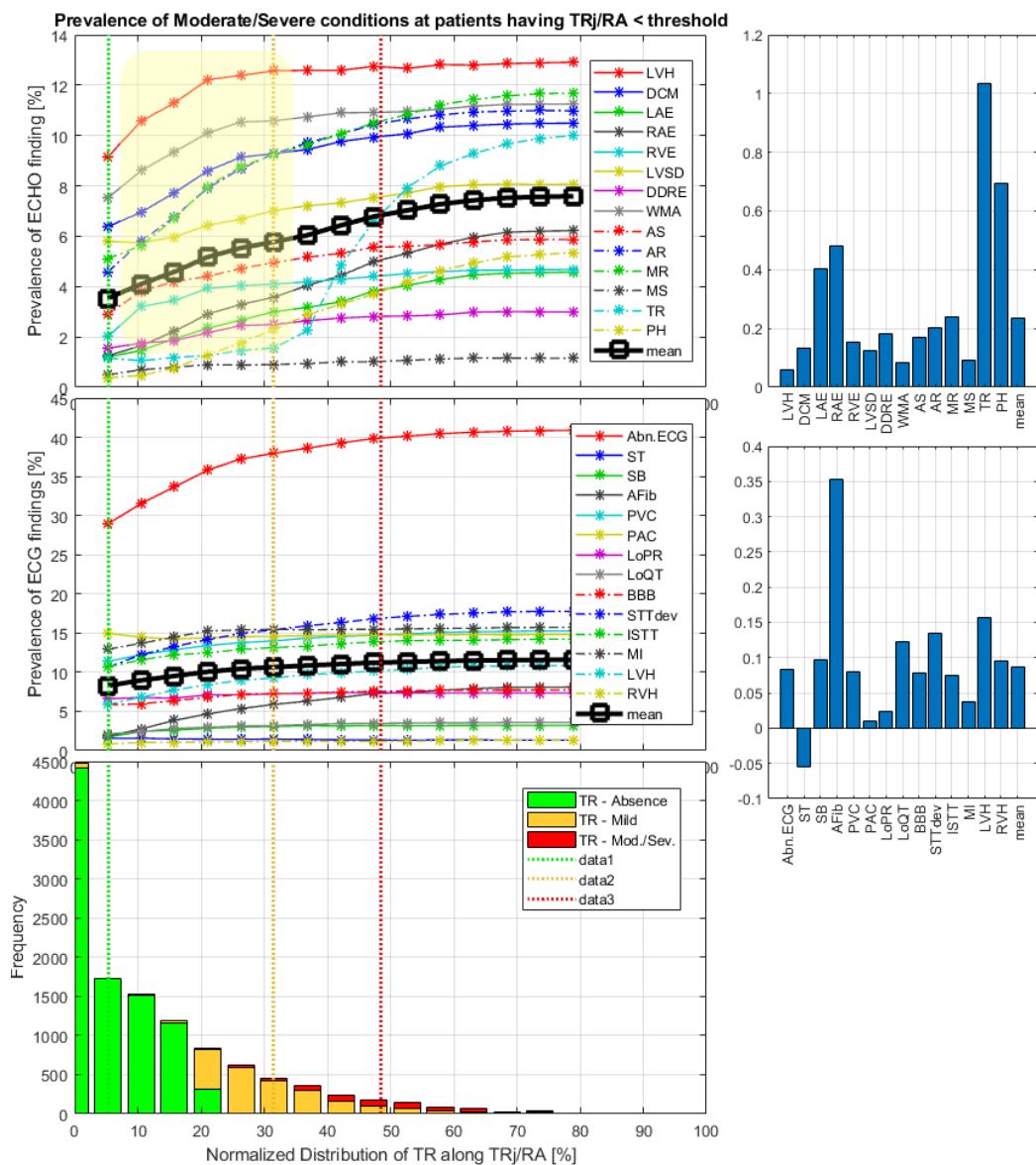


Figure 4-15 Co-morbidity analysis of TR along continual TRj/RA, using CPA database



4.3.14 Pulmonary Hypertension

Abbreviation	PH
Description	Tricuspid Regurgitation with Pulmonary Hypertension
ICD10 code	I27.0
Echo Criteria	RVSP (Right Ventricular Systolic Pressure) > 30 mmHg
Cardiovascular Risk	In the presence of pulmonary hypertension, the RV remodels in the longitudinal direction (elliptical/spherical deformation), leading to increased valvular tethering with only mild tricuspid annular dilation.
Morbidity	PH contributes to markedly poorer outcomes in people with moderate-to-severe TR. Secondary TR is far more common and occurs due to annular dilation, pulmonary hypertension, and/or leaflet tethering in the setting of right- or left-sided heart disease.
Co-Morbidity	The Co-Morbidity analysis on CPA database (Figure 4-16) shows significant co-morbidities for LAE, RAE, TR and AFib.
Mortality	Doubles the risk of Mortality. PH was also identified as a “powerful and independent predictor of all-cause mortality” “The presence of significant TR was associated with a 6-year event-free survival [of] only 57% for both moderate and severe TR. However, PH rather than the grade of TR was the most powerful predictor of outcome,” the study reports.n people with TR, more than doubling a risk of death (2.22 fold higher). During a median follow-up of 6.6 years (80 months), 59% of the patients died, with the mortality rate being similar between groups (61% in the moderate group and 56% in severe). Mortality was higher among people with tricuspid regurgitation and PH (67.4%), than it was in PH patients whose SPAP values were within a normal range (42.3%). ¹⁰⁹

¹⁰⁹ Saeed S, Smith J, Grigoryan K, et al Impact of pulmonary hypertension on outcome in patients with moderate or severe tricuspid regurgitation Open Heart 2019;6:e001104. doi: 10.1136/openhrt-2019-001104

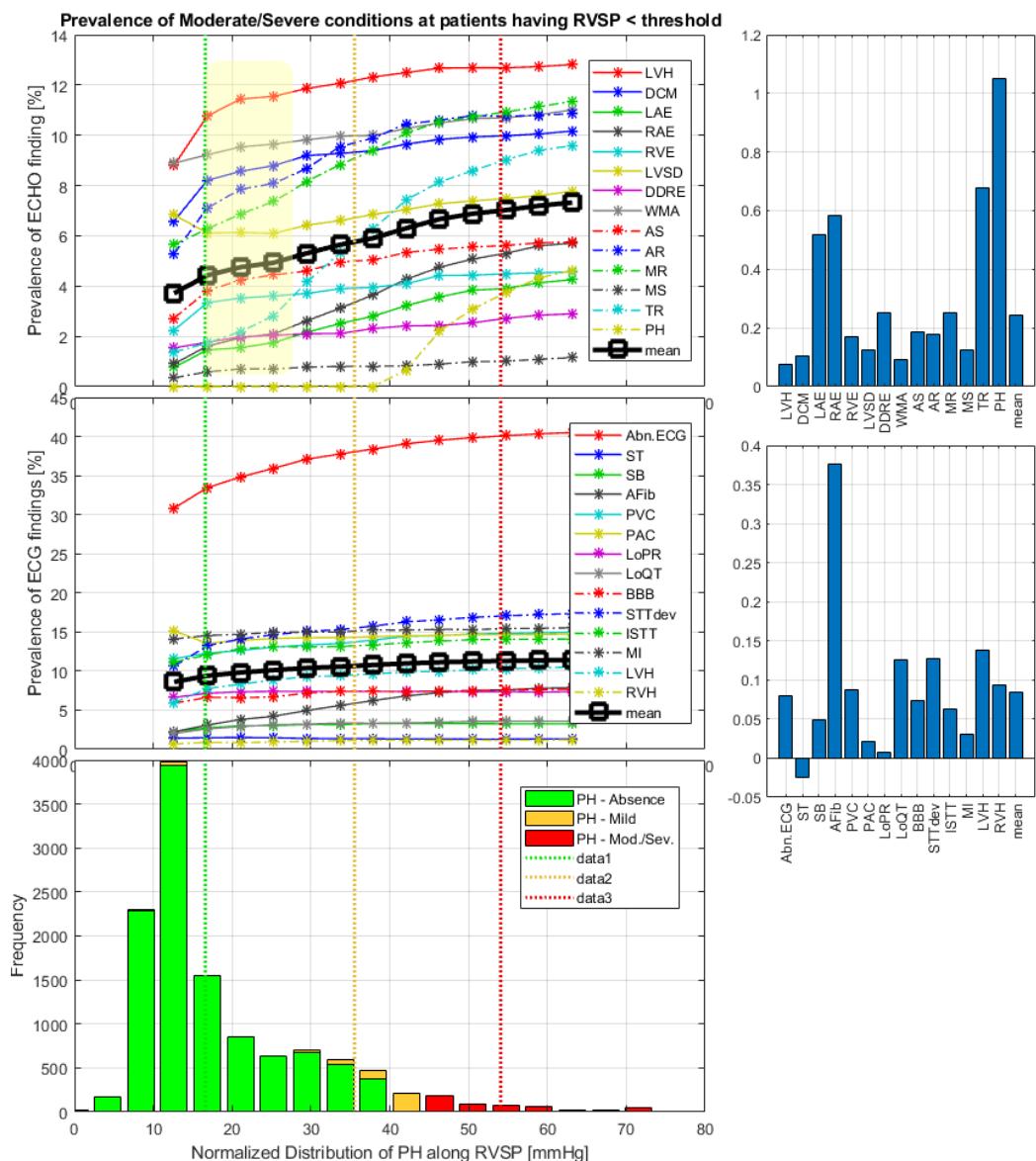


Figure 4-16 Co-morbidity analysis of PH along continual RVSP, using CPA database



5 ECG, PCG, and MCG Finding Performance

This section reflects the performance values of its ECG, PCG and MCG findings predicted by CPA.

Table below provides greater detail on how to interpret different findings CPA detects, including the ranges, results, and clinical meaning.

Table 15 – Bio-signal findings: ECG, PCG and MCG-findings

Group	Finding	Range of possible results
ECG findings	Rhythm	Sinus Rhythm / Sinus Bradycardia / Sinus Tachycardia / Atrial Fibrillation / Atrial Flutter / Other Rhythm
	Premature Ventricular Complex	Absence / Presence
	Premature Atrial Complex	Absence / Presence
	Heart Axis	Normal Axis Left Axis Deviation/ Right Axis Deviation
	Long PR interval	Absence / Presence
	Long QT interval	Absence / Presence
	Bundle Branch Block	Absence / Left Bundle Branch Block / Right Bundle Branch Block / IV Conduction Delay
	Fascicular block	Absence / Left anterior fascicular block / Other block
	Myocardial Infarction	Absence / Presence
	Ischemic ST-T change	Absence / Consider
	ST-T deviation	Absence / ST-T deviation / T wave deviation
	Left Ventricular Hypertrophy	Absence / Possible
	Right Ventricular Hypertrophy	Absence / Possible
	ECG quality	Good /



		Poor / Error (Uninterpretable)
	ECG summary	Normal / Borderline / Abnormal
PCG findings	Systolic Murmur	Absence / Presence
	Diastolic Murmur	Absence / Presence
	Third Sound	Absence / Presence
	Fourth Sound	Absence / Presence
	Ejection Sound	Absence / Presence
	Opening Snap	Absence / Presence
	Wheeze	Absence / Presence
	Artifacts	Absence / Presence
	PCG singal quality	Good / Poor / Error (Uninterpretable)
	PCG summary	Normal / Abnormal
MCG Findings including PCG/MCG STI findings	S1 Wide	Normal / Abnormal
	S2 Wide	Normal / Abnormal
	Eletromechanical Act. Time	Normal / Abnormal
	Myocardial Perf. Index	Normal / Abnormal
	Systolic Performance Index	Normal / Abnormal
	Pre Ejection Period	Normal / Abnormal
	Left Ventricular Ejection Time	Normal / Abnormal
	MCG singal quality	Good / Poor / Error (Uninterpretable)
	MCG summary	Normal / Abnormal



5.1 Bio-signal Finding Validation

CPA uses the EC57 and IEC60601-2-25 standard ECG databases for validating ECG measurements. For the diagnostic ECG findings CPA uses BAPA ECG Validation database including 4513 patient records and contains sufficient number of records for each obesity category. This database contains racial diversity representing the US population: 82% Caucasian, 15.6% African American, 2% Asian, 53% Male and 47% Female, Age = 51.5 +-19.6 year, BMI = 29 +-6.2 kg/m².

For PCG and MCG measurements and findings, CPA uses Cardio Phoenix databases containing synchronized ECG, PCG and MCG bio-signals, and Cardiologist manual references for heart sound and STI findings, and echocardiographic ground truth for confirmation of patient cardiac status:

- Senta2 database with 6000 patient records, and
- Buda6 database with 1860 records.

Additionally PCG and MCG measurements and findings are validated on the public PhysioNet/CinC Challenge 2016¹¹⁰ heart sound classification database, where 405 records has synchronized ECG and PCG bio-signals.

¹¹⁰ <https://physionet.org/content/challenge-2016/1.0.0/>



5.2 Performance Results

Table 16 – ECG, PCG, MCG Finding Performance

5.2.1 ECG Measurement	
Measurement or Finding	Performance
P-duration [ms]	MD= 4.26 ms, <±10 STD= 14.8 ms ≤15
PQ-interval [ms]	MD= 1.29 ms <±10 STD= 7.64 ms ≤10
QRS-duration [ms]	MD = -2.3ms <±10 STD = 8.97 ms ≤10 (QTdb) MAE= 9.25ms
QT-interval [ms]	MD= 3.79 ms <±25 STD= 14.7 ms ≤30
ST-T deviation	MD= -4.36uV <20 STD= 91.8uV <100
Heart Rate [bpm]	HRE= 0.58%



5.2.2 ECG Findings

Requirement	Value Domain	Positive Samples	Performance [95% CI] (mean ± std)
Rhythm	Sinus Rhythm [SR]	84%	SE = 98.2% (95% CI: 97.7-98.6) SP = 96.1% (95% CI: 94.5-97.4) PPV = 99.3% (95% CI: 98.9-99.5) NPV = 91.1% (95% CI: 88.8-93)
	Sinus Tachycardia [ST]	1.1%	SE = 93.9% (95% CI: 83.1-98.7) SP = 99.8% (95% CI: 99.6-99.9) PPV = 83.6% (95% CI: 71.2-92.2) NPV = 99.9% (95% CI: 99.8-100)
	Sinus Bradycardia [SB]	3.2%	SE = 95.2% (95% CI: 90.3-98) SP = 99.8% (95% CI: 99.6-99.9) PPV = 93.9% (95% CI: 88.7-97.2) NPV = 99.8% (95% CI: 99.7-99.9)
	Atrial Fibrillation [AFib]	6.6%	SE = 94% (95% CI: 90.7-96.4) SP = 99.5% (95% CI: 99.2-99.7) PPV = 93.1% (95% CI: 89.6-95.7) NPV = 99.6% (95% CI: 99.3-99.7)
	Atrial Flutter [AFlut]	0.4%	SE = 83.3% (95% CI: 58.6-96.4) SP = 99.8% (95% CI: 99.6-99.9) PPV = 62.5% (95% CI: 40.6-81.2) NPV = 99.9% (95% CI: 99.8-100)
	Other (Aber VC, Ectopic, SVR) [OR]	4.7%	SE = 91.9% (95% CI: 87.4-95.2) SP = 99% (95% CI: 98.7-99.3) PPV = 81.9% (95% CI: 76.3-86.5) NPV = 99.6% (95% CI: 99.4-99.8)
Premature Ventricular Complex [PVC]	Yes/No	7.0%	SE = 90.9% (95% CI: 87.1-93.8) SP = 97.2% (95% CI: 96.7-97.7) PPV = 71.1% (95% CI: 66.4-75.5) NPV = 99.3% (95% CI: 99-99.5)
Premature Atrial Complex [PAC]	Yes/No	6.2%	SE = 83.2% (95% CI: 78.2-87.4) SP = 97% (95% CI: 96.4-97.5) PPV = 64.6% (95% CI: 59.4-69.6) NPV = 98.9% (95% CI: 98.5-99.2)
Heart Axis Deviation [AXD]	Normal, Leftward [LAX], Rightward [RAX], Indetermin. [IAX]	Calibration: 19 Biological: 102	QRSaxis Error = 0.05±0.23 [deg]
PR interval [PR]	Normal, Long PR, Short PR	Calibration: 19 Biological: 102	Calibration PRint Error = -0.9±2.63 [ms] Biological PRint Error = 1.3±7.64 [ms]



B. Branch Block [BBB]	Left Bundle Branch Block [LBBB]	2.1%	SE = 82.1% (95% CI: 72.9-89.2) SP = 99.5% (95% CI: 99.2-99.7) PPV = 78% (95% CI: 68.6-85.7) NPV = 99.6% (95% CI: 99.4-99.8)
	Right Bundle Branch Block [RBBB]	3.4%	SE = 84.4% (95% CI: 77.7-89.8) SP = 99% (95% CI: 98.6-99.3) PPV = 74.7% (95% CI: 67.6-81) NPV = 99.4% (95% CI: 99.2-99.6)
	IV conduction delay [IVCD]	2.4%	SE = 82.6% (95% CI: 74.1-89.2) SP = 99.3% (95% CI: 99-99.5) PPV = 74.4% (95% CI: 65.6-81.9) NPV = 99.6% (95% CI: 99.3-99.7)
Fascicular Block [FB]	L. Anterior Fasc. Block [LAFB]	3.3%	SE = 81.3% (95% CI: 74.2-87.2) SP = 99% (95% CI: 98.6-99.3) PPV = 73.5% (95% CI: 66.1-80) NPV = 99.4% (95% CI: 99.1-99.6)
	Other (AVB 2 nd)	0.7%	SE = 70% (95% CI: 50.6-85.3) SP = 99.8% (95% CI: 99.6-99.9) PPV = 70% (95% CI: 50.6-85.3) NPV = 99.8% (95% CI: 99.6-99.9)
Myocardial Infarction (ECG only crit.) [MI]	Yes/No	18.1%	SE = 69.8% (95% CI: 66.1-73.4) SP = 97% (95% CI: 96.3-97.6) PPV = 83.8% (95% CI: 80.4-86.9) NPV = 93.6% (95% CI: 92.6-94.4)
Ischemia (ECG only crit.) [ISTT]	Yes/No	26.1%	SE = 53.3% (95% CI: 47-59.4) SP = 86.1% (95% CI: 83.4-88.5) PPV = 57.4% (95% CI: 50.9-63.7) NPV = 83.9% (95% CI: 81.1-86.5)
ST-T deviation [STT]	No, STdev, STTdev, TWA	ESC DB, 363 ST episode	STamp Error = -4.36±92 [uV] Tamp Error = -40±193 [uV]
QT interval [QT]	Normal, Long	Calibration: 19 Biological: 102	Calibration: QTint Error = 6.5±5.2 [ms] Biological: QTint Error = 3.8±14.7 [ms]
Ventricular Hypertrophy (ECG only crit.) [VH]	LVH	10.7%	SE = 60.7% (95% CI: 56.2-65.1) SP = 98% (95% CI: 97.5-98.4) PPV = 78.4% (95% CI: 73.9-82.5) NPV = 95.4% (95% CI: 94.7-96)
	RVH	2.4%	SE = 50.9% (95% CI: 41.2-60.6) SP = 99.6% (95% CI: 99.4-99.8) PPV = 75.7% (95% CI: 64.3-84.9) NPV = 98.8% (95% CI: 98.4-99.1)



	BVH	0.7%	SE = 50% (95% CI: 31.3-68.7) SP = 99.7% (95% CI: 99.5-99.8) PPV = 53.6% (95% CI: 33.9-72.5) NPV = 99.7% (95% CI: 99.4-99.8)
ECG Quality [ECGq]	Poor,	2.8%	SE = 71.2% (95% CI: 62.4-78.9) SP = 99.3% (95% CI: 99-99.5) PPV = 74.2% (95% CI: 65.4-81.7) NPV = 99.2% (95% CI: 98.9-99.4)
	Error / Uninterpretable	0.2%	SE = 80% (95% CI: 44.4-97.5) SP = 99.8% (95% CI: 99.6-99.9) PPV = 42.1% (95% CI: 20.3-66.5) NPV = 100% (95% CI: 99.8-100)
ECG Summary	Normal ECG	37.7%	SE = 84% (95% CI: 82.2-85.7) SP = 97.1% (95% CI: 96.4-97.7) PPV = 94.6% (95% CI: 93.3-95.7) NPV = 90.9% (95% CI: 89.9-91.9)
	Borderline ECG	27.7%	SE = 83.1% (95% CI: 80.9-85.2) SP = 93.1% (95% CI: 92.2-93.9) PPV = 82.2% (95% CI: 80-84.3) NPV = 93.5% (95% CI: 92.6-94.3)
	Abnormal ECG	34.6%	SE = 95% (95% CI: 93.8-96) SP = 94.1% (95% CI: 93.2-94.9) PPV = 89.5% (95% CI: 87.9-90.9) NPV = 97.3% (95% CI: 96.6-97.8)



5.2.3 PCG Findings

Requirement	Value Domain	Positive Samples	Performance [95% CI] (mean ± std)
3. Ejection Sound	Absence/ Presence	4.4%	SE = 71.8% (95% CI: 60.5-81.4) SP = 98% (95% CI: 97.2-98.6) PPV = 62.2% (95% CI: 51.4-72.2) NPV = 98.7% (95% CI: 98-99.2)
5. Opening Snap	Absence/ Presence	2.8%	SE = 59.2% (95% CI: 44.2-73) SP = 98% (95% CI: 97.2-98.6) PPV = 46% (95% CI: 33.4-59.1) NPV = 98.8% (95% CI: 98.2-99.3)
6. Third Sound	Absence/ Presence	5.1%	SE = 76.7% (95% CI: 66.6-84.9) SP = 98% (95% CI: 97.2-98.6) PPV = 67.6% (95% CI: 57.7-76.6) NPV = 98.7% (95% CI: 98.1-99.2)
7. Forth Sound	Absence/ Presence	9.2%	SE = 62.1% (95% CI: 54.1-69.6) SP = 96.1% (95% CI: 95-97) PPV = 61.7% (95% CI: 53.8-69.2) NPV = 96.2% (95% CI: 95.1-97.1)
8. Diastolic Murmur	Absence/ Presence	3%	SE = 76.9% (95% CI: 63.2-87.5) SP = 98.1% (95% CI: 97.4-98.7) PPV = 55.6% (95% CI: 43.4-67.3) NPV = 99.3% (95% CI: 98.8-99.6)
9. Wheeze	Absence/ Presence	2.1%	SE = 37.8% (95% CI: 22.5-55.2) SP = 99% (95% CI: 98.4-99.4) PPV = 45.2% (95% CI: 27.3-64) NPV = 98.7% (95% CI: 98-99.2)
10. Artifacts	Absence/ Presence	3.9%	SE = 44.1% (95% CI: 32.1-56.7) SP = 98.5% (95% CI: 97.8-99) PPV = 54.5% (95% CI: 40.6-68) NPV = 97.8% (95% CI: 96.9-98.4)
11. Systolic Murmur	Normal/ Abnormal	22.3%	SE = 80.9% (95% CI: 76.6-84.6) SP = 94.4% (95% CI: 93.1-95.6) PPV = 80.7% (95% CI: 76.4-84.4) NPV = 94.5% (95% CI: 93.1-95.6)
12. S1 Split	Normal/ Abnormal	3.5%	SE = 59.7% (95% CI: 47.5-71.1) SP = 98.1% (95% CI: 97.4-98.6) PPV = 53.1% (95% CI: 41.7-64.3) NPV = 98.5% (95% CI: 97.9-99)
13. S2 Split	Normal/ Abnormal	2.5%	SE = 54.9% (95% CI: 40.3-68.9) SP = 99% (95% CI: 98.5-99.4) PPV = 58.3% (95% CI: 43.2-72.4) NPV = 98.9% (95% CI: 98.3-99.3)



19. PCG Signal Quality	Good/Poor	23.2%	SE = 78.3% (95% CI: 73.6-82.4) SP = 89.6% (95% CI: 87.7-91.3) PPV = 69.4% (95% CI: 64.6-73.8) NPV = 93.2% (95% CI: 91.6-94.6)
	Good or Poor / Error (Uninterpretable)	2.2%	SE = 52.9% (95% CI: 35.1-70.2) SP = 97.6% (95% CI: 96.7-98.3) PPV = 33.3% (95% CI: 21.1-47.5) NPV = 98.9% (95% CI: 98.3-99.4)
20. PCG Summary	Normal/ Abnormal	25%	SE = 87% (95% CI: 83.5-90) SP = 89.4% (95% CI: 87.6-91) PPV = 73.1% (95% CI: 69.1-76.9) NPV = 95.4% (95% CI: 94.1-96.5)



5.2.4 MCG Findings			
Requirement	Value Domain	Positive Samples	Performance [95% CI] (mean ± std)
1. EMAT	Normal/Abnormal	14%	SE = 72.2% (95% CI: 66.7-77.3) SP = 92% (95% CI: 90.7-93.2) PPV = 59.6% (95% CI: 54.2-64.8) NPV = 95.3% (95% CI: 94.2-96.3)
2. MPI	Normal/Abnormal	6.1%	SE = 59.2% (95% CI: 50.1-67.9) SP = 97% (95% CI: 96.1-97.7) PPV = 56.1% (95% CI: 47.2-64.7) NPV = 97.3% (95% CI: 96.5-98)
3. SPI	Normal/Abnormal	7.2%	SE = 69.6% (95% CI: 61.5-76.9) SP = 95.1% (95% CI: 94.1-96) PPV = 52.6% (95% CI: 45.3-59.7) NPV = 97.6% (95% CI: 96.8-98.2)
4. PEP	Normal/Abnormal	11.1%	SE = 65.8% (95% CI: 59.2-71.9) SP = 95% (95% CI: 93.9-96) PPV = 62.2% (95% CI: 55.8-68.4) NPV = 95.7% (95% CI: 94.7-96.6)
5. LVET	Normal/Abnormal	12.5%	SE = 68.1% (95% CI: 62-73.7) SP = 91% (95% CI: 89.6-92.3) PPV = 51.9% (95% CI: 46.4-57.4) NPV = 95.2% (95% CI: 94.1-96.2)
10. MCG Signal Quality	Good/ Poor	3.6%	SE = 45.7% (95% CI: 30.9-61) SP = 99.8% (95% CI: 99.4-100) PPV = 91.3% (95% CI: 72-98.9) NPV = 98% (95% CI: 97.1-98.7)
	Good or Poor/ Error	2%	SE = 52% (95% CI: 31.3-72.2) SP = 99.9% (95% CI: 99.6-100) PPV = 92.9% (95% CI: 66.1-99.8) NPV = 99% (95% CI: 98.3-99.5)
11. MCG Summary	Normal/ Abnormal	19%	SE = 72.3% (95% CI: 67.6-76.7) SP = 89% (95% CI: 87.4-90.5) PPV = 60.6% (95% CI: 56-65.1) NPV = 93.2% (95% CI: 91.9-94.4)



6 P-ECG, CPA-ECG and HART performance comparison

In this comparison only those significant heart diseases are selected, where the standard ECG interpretation has diagnostic finding. These abnormalities are:

- Ventricular size abnormalities
 - LVH (Dilated LV) – ECG has “LVH” criteria, but ECG cannot differentiate dilation from hypertrophy
 - RVH (Dilated RV) – ECG has “RVH” criteria, but ECG cannot differentiate dilation from hypertrophy
- Atrial Size Abnormalities
 - LAE – ECG has “P-mitrale” criteria
 - RAE – ECG has “P-pulmonale” criteria
- Ischemic wall motion abnormality
 - WMA – ECG has associated findings: MI, ST-T deviation, Ischemic T wave

The joined HART validation database is used, that are not used in any training purpose. Some records were excluded due to unacceptable signal quality or doubtful ground truth.

The ground truth of these findings is binary and established by Cardiologist consensus using echocardiographic evidence.

In the comparison a State of the Art ECG algorithm also used as predicate ECG (P-ECG) which used in many ECG devices.



6.1 LVH/ Dilated LV

There are some well-known ECG criteria for LVH, which are performed and compared to LVH ECG findings and LVH HART finding:

- a) SLI – Sokolow-Lyon index criteria
- b) CV - Cornell voltage criteria
- c) LI - Lewis Index criteria
- d) P-ECG-LVH – The LVH findings by the predicate ECG algorithm (a State of the Art ECG algorithm used in many ECG devices). This algorithm uses a modified Romhilt-Estes Score based rules¹¹¹.
- e) CPAECG-LVH – The LVH findings by the CPA knowledge-based algorithm. CPA uses probability-based score system, similarly to predicate ECG.
- f) HART-LVH – The HART model for LVH by the CPA algorithm. It differs from the ECG algorithms in that it also uses PCG and MCG features beside ECG features, and the model is trained using machine learning technics. The model includes NN, which has body size normalization layers.

The performance evaluation is shown on following figure, where:

- Left-top graph plot the individual performance: sensitivity (SE%), specificity (SP%), positive predictive value (PPV), negative predictive value (NPV%), PPV of two sequential positive tests (ni2:PPV%), positive likelihood ratio (LR+), negative likelihood ratio (LR-)¹¹², diagnostic odd ratio (DOR), kappa (K%), positive rate (PR%).
- Right-top graph ROC analysis, where the methods can be compared on a Sensitivity/False positive rate plane. A parametric ROC curve is fitted and plotted on the HART finding (HART-LVH in this case), able to easily compare the methods to each other independently from the sensitivity/specificity balance.
- Left-bottom graph shows the coverage of methods through sensitivity matrix. The numbers are shown as percentages.
- The Right-bottom graph is the precision/recall analysis, which is similar to ROC analysis, but it compares methods on the positive

¹¹¹ Morrison, Iain, Elaine Clark, and Peter W. Macfarlane. "Evaluation of the electrocardiographic criteria for left ventricular hypertrophy." Anatolian Journal of Cardiology/Anadolu Kardiyoloji Dergisi 7 (2007).

¹¹² LR-* plotted on figures for visibility reason. Then times higher value is plotted (LR-* = 10 x LR-)



predictive value (precision) and sensitivity (recall) plane. In this analysis the right-top corner is the perfect classification, while in ROC analysis the left-top corner represents the perfect classification.

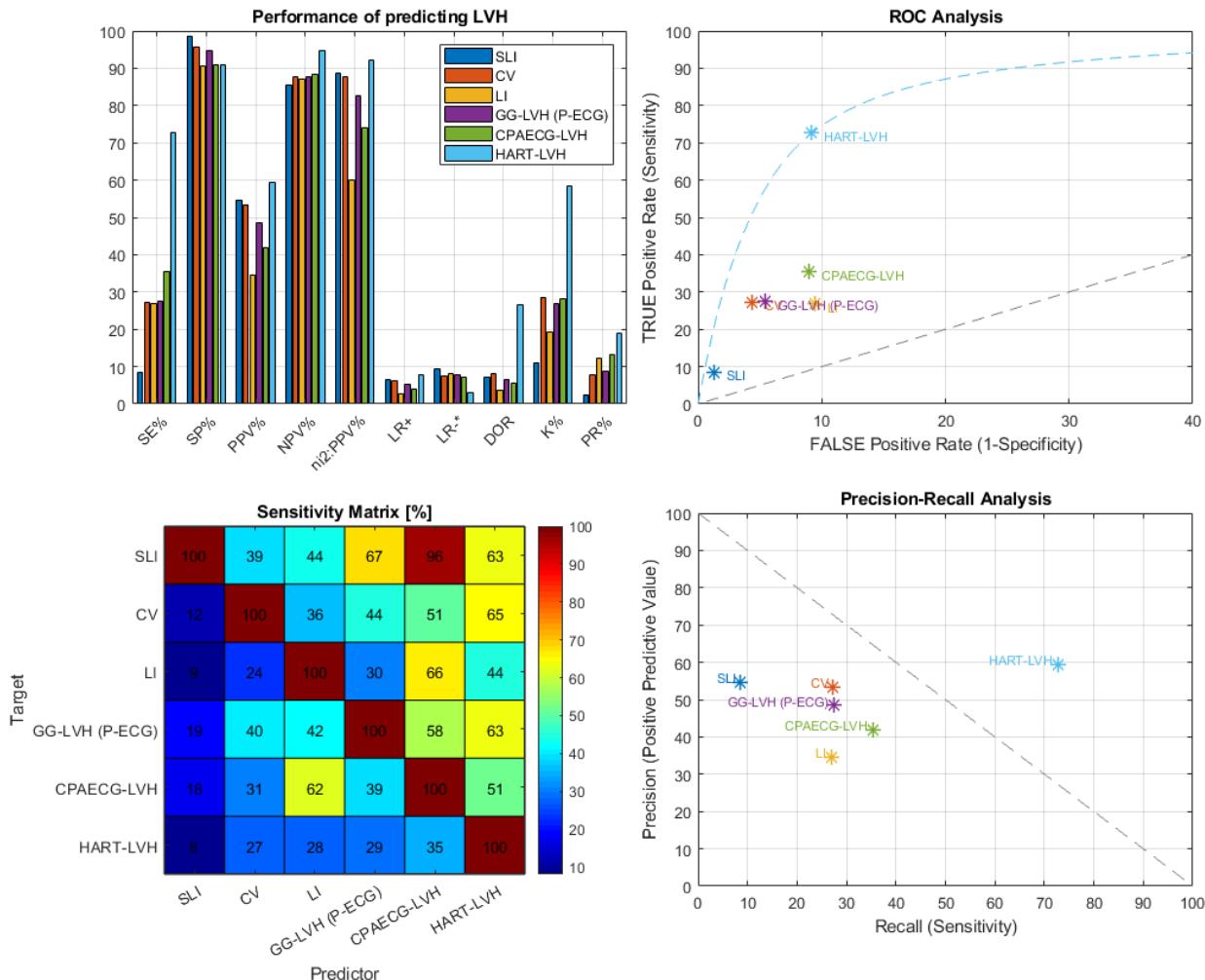


Figure 6-1 - Performance comparison of P-ECG, CPA-ECG and HART findings for Left Ventricular Hypertrophy (or enlargement)

Conclusion:

- The current performance analysis result confirms the CARLA study¹¹³ “sensitivity of the SLI was 5 %, specificity 97 %”, i.e. SLI shows very low sensitivity ($SE < 10\%$).
- The current performance analysis result confirms the Asian study¹¹⁴ “The Cornell ECG criteria for the echocardiographic LVH had better

¹¹³ Schröder, Jochen, et al. "Performance of Sokolow-Lyon index in detection of echocardiographically diagnosed left ventricular hypertrophy in a normal Eastern German population-results of the CARLA study." BMC Cardiovascular Disorders 15.1 (2015): 69.

¹¹⁴ Su, Fang-Ying, et al. "A comparison of Cornell and Sokolow-Lyon electrocardiographic criteria for left ventricular hypertrophy in a military male population in Taiwan: the Cardiorespiratory fitness and Hospitalization Events in armed Forces study." Cardiovascular diagnosis and therapy 7.3 (2017): 244.



performance than the Sokolow-Lyon criteria". However, the Cornell Voltage still shows low sensitivity (SE~30%)

- c) The current performance analysis result shows that the Lewis Index reach similar sensitivity as Cornell Voltage, but lower specificity, i.e. produce more false positives.
- d) The predicate ECG algorithm is closest to the Cornell Voltage criteria.
- e) The CPAECG is similar to predicate ECG; however, it shows higher sensitivity and lower specificity, i.e. has more sensitive criteria.
- f) The HART model reaches the best performance; has significantly higher sensitivity (+40%) with similar specificity level as CPA-ECG. The HART solution for predicting LVH substantially outperforms the ECG based approaches.
- g) The sensitivity matrix analysis confirms the significant variability between these criteria, since the cross-sensitivity numbers are variable (between 20-70%).

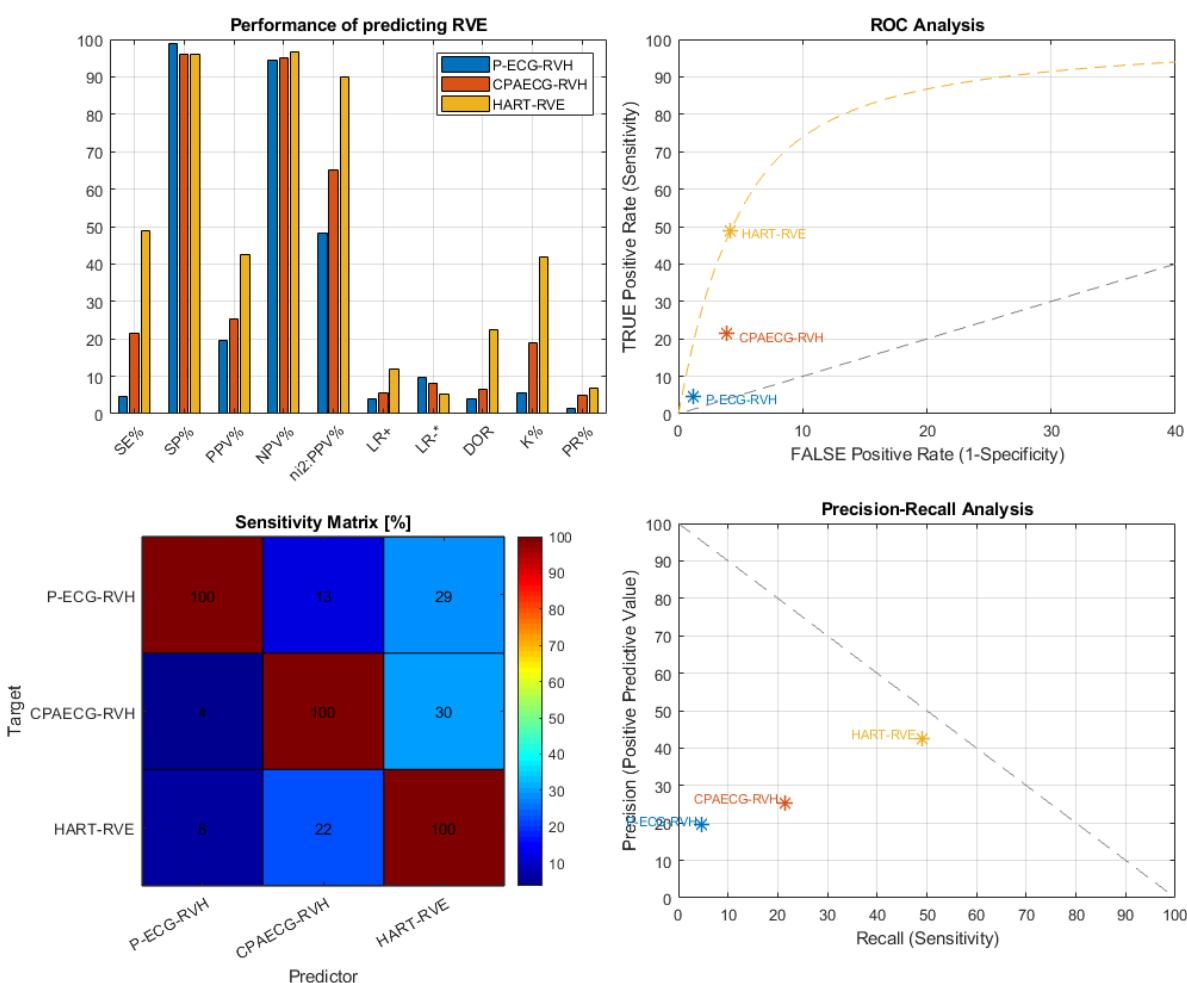


6.2 RVH / Dilated RV

There are ECG criteria for RVH, which implemented by predicate ECG and CPA ECG too. These are compared to RVE HART finding:

- P-ECG-RVH – The RVH findings by the predicate ECG algorithm. This algorithm is based on the known ECG rules¹¹⁵
- CPAECG-RVH – The RVH findings by the CPA knowledge-based algorithm. CPA uses probability-based score system, similarly to predicate ECG and LVH solution.
- HART-RVE – The HART model for RV enlargement by the CPA algorithm. It differs from the previous ones in that it also uses PCG and MCG features beside ECG features, and the model is trained using machine learning techniques. The model includes NN, which has body size normalization layers.

The performance evaluation is shown on following figure, where:



¹¹⁵ <https://litfl.com/right-ventricular-hypertrophy-rvh-ecg-library/>



Figure 6-2 - Performance comparison of P-ECG, CPA-ECG and HART findings for Right Ventricular Hypertrophy (or enlargement)

Conclusion:

- a) The ECG RVH criteria implemented by predicate ECG algorithm show very low positive rate and sensitivity ($SE < 5\%$), but the PPV is very low ($PPV \sim 15\%$).
- b) The CPA-ECG has better performance, the positive rate and sensitivity is higher ($SE \sim 25\%$), but specificity is lower and PPV is higher than ECG RVH but is still low ($PPV \sim 28\%$). The overall diagnostic performance is still low for detecting RVE.
- c) The HART model reaches the best performance; has significantly higher sensitivity ($SE \sim 50\%$) with higher specificity and positive predictive value level ($SP \sim 98\%$, $PPV \sim 70\%$) compared to ECG criteria. The HART solution for predicting LVH substantially outperform the ECG based approaches.



6.3 LA Enlargement

There are ECG criteria for LAE, which implemented by predicate ECG, but not by CPA ECG. The literature proves the ECG criteria for atrial enlargements are not reliable¹¹⁶.

Instead our study revealed that Premature Ventricular Contraction (PVC) is a reasonable indicator of LAE. That is why PVC by predicate ECG and CPA ECG are compared to HART finding:

- a) P-ECG-LAE – The well-known “P-mitrale”-based LAE ECG criteria implemented by the predicate ECG algorithm.
- b) P-ECG-PVC – The PVC findings implemented by predicate ECG algorithm. PVC is a good indicator for LAE based on CHART research.
- c) CPAECG-PVC – The PVC finding by the CPA algorithm. CPA detect PVCs, but does not implement LAE rule-based, because of its weak performance.
- d) HART-LAE – The HART model for LA enlargement by the CPA algorithm. It differs from the ECG algorithms in that it also uses PCG and MCG features beside ECG features, and the model is trained using machine learning technics.

The performance evaluation is shown on following figure, where:

¹¹⁶ Tsao, Connie W., et al. "Accuracy of electrocardiographic criteria for atrial enlargement: validation with cardiovascular magnetic resonance." Journal of Cardiovascular Magnetic Resonance 10.1 (2008): 7.

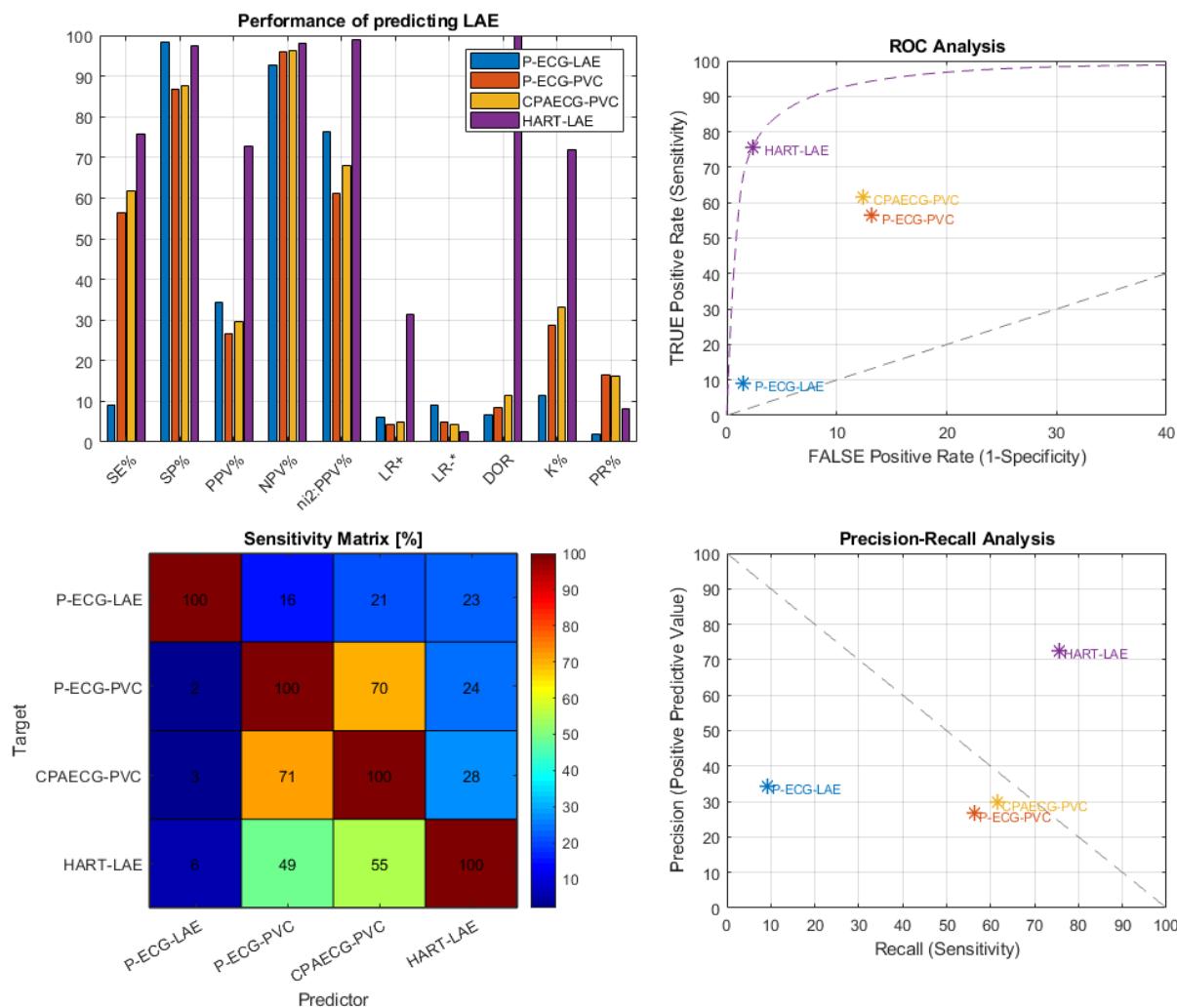


Figure 6-3 - Performance comparison of P-ECG, CPA-ECG and HART findings for Left Atrial Enlargement

Conclusion:

- The ECG LAE criteria implemented by predicate ECG algorithm show very low positive rate and sensitivity ($SE < 10\%$), and its PPV is borderline for diagnosis ($PPV \sim 35\%$).
- The PVC as ECG criteria for LAE has higher sensitivity ($SE \sim 60\%$) compared to official LAE criteria, but the PPV is still borderline ($PPV \sim 30\%$).
- The CPAECG-PVC solution is slightly better than the predicate ECG in both sensitivity and specificity point of views.
- The HART model reaches the best performance; has significantly higher sensitivity ($SE \sim 75\%$) with higher specificity and positive predictive value level ($SP \sim 97\%$, $PPV \sim 75\%$) compared to ECG criteria. The HART solution for predicting LAE substantially outperform the ECG based approaches.



6.4 RA Enlargement

There are ECG criteria for RAE, similarly to LAE, which implemented by predicate ECG, but not by CPA ECG. The literature proves the ECG criteria for atrial enlargements are not reliable¹¹⁷.

Instead our study revealed that Atrial Fibrillation (AFib) is a reasonable indicator of RAE. That is why PVC by predicate ECG and CPA ECG are compared to HART finding:

- a) P-ECG-RAE – The well-known “P-pulmonale”-based RAE ECG criteria implemented by the predicate ECG algorithm.
- b) P-ECG-AFib – The AFib findings implemented by predicate ECG algorithm. Atrial Fibrillation is a good indicator for RAE based in CHART research.
- c) CPAECG-AFib – The AFib finding by the CPA algorithm. CPA detect AFib, but does not implement RAE rule-based, because of its weak performance.
- d) HART-RAE – The HART model for RA enlargement by the CPA algorithm. It differs from the ECG algorithms in that it also uses PCG and MCG features beside ECG features, and the model is trained using machine learning technics.

The performance evaluation is shown on following figure, where:

¹¹⁷ Tsao, Connie W., et al. "Accuracy of electrocardiographic criteria for atrial enlargement: validation with cardiovascular magnetic resonance." Journal of Cardiovascular Magnetic Resonance 10.1 (2008): 7.

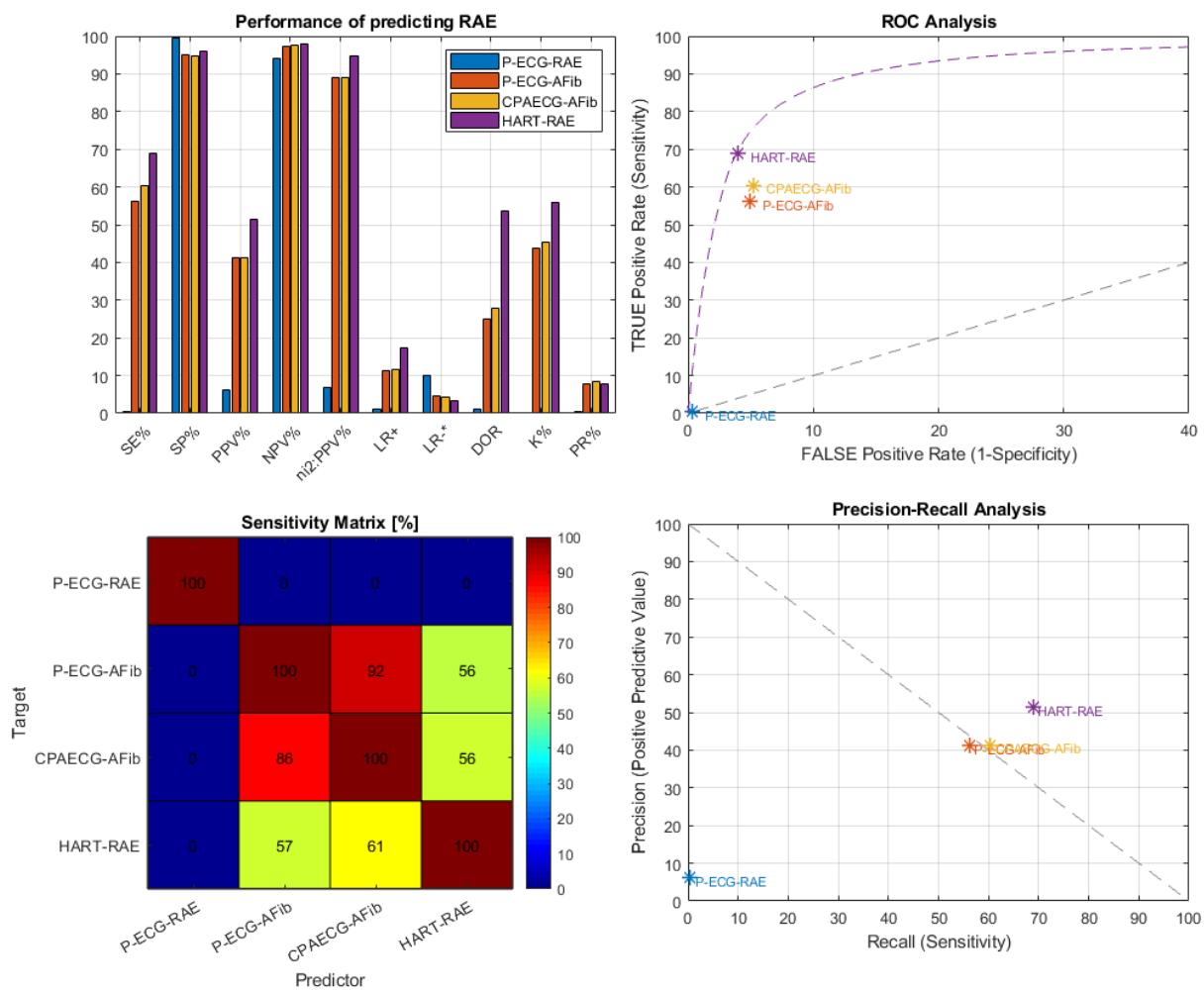


Figure 6-4 - Performance comparison of P-ECG, CPA-ECG and HART findings for Right Atrial Enlargement

Conclusion:

- The situation is similar to LAE discussed in previous section.
- The ECG RAE criteria implemented by predicate ECG algorithm show very low positive rate and sensitivity (SE<2%), and its PPV is very low (PPV<10%).
- The AFib as ECG criteria for RAE has higher sensitivity (SE~60%) compared to official RAE criteria, and the PPV is higher (PPV~45%).
- The CPA-AFib solution is slightly better than the predicate ECG in sensitivity point of view.
- The HART model reaches the best performance; it has significantly higher sensitivity (SE~70%) with higher specificity and positive predictive value level (SP~97%, PPV~50%) compared to ECG criteria. The HART solution for predicting RAE substantially outperforms the ECG based approaches.



6.5 Wall Motion Abnormality

There are ECG criteria for Myocardial Infarction (MI), ST-T deviation (including T wave abnormalities) and Ischemic T wave changes, but there are no direct criteria for wall motion abnormalities, which are typically assessed by echocardiography. However, the ischemic behavior is the background of the most of wall motion problems and the ST-T changes too, which lead to Myocardial Infarction.

In this analysis these ECG findings are compared (from both predicate and CPA side) to the HART finding approach:

- a) P-ECG-MI – The Myocardial Infarction (MI) criteria implemented by the predicate ECG algorithm.
- b) P-ECG-Isch – The Ischemic T wave criteria implemented by predicate ECG algorithm.
- c) P-ECG-STTdev – The ST-T wave deviation group finding implemented by predicate ECG algorithm. This group includes specific and non-specific ST changes, T wave changes (ischemic and non-ischemic)
- d) CPAECG-MI – The Myocardial Infarction (MI) criteria implemented by CPA
- e) CPAECG-ISTT – The Ischemic T wave criteria implemented by predicate CPA algorithm.
- f) CPAECG-STTdev - The ST-T wave deviation group finding implemented by predicate CPA algorithm.
- g) HART-WMA – The HART model for WMA by the CPA algorithm. It differs from the ECG ones in that it also uses PCG and MCG features beside ECG features, and the model is trained using machine learning technics.

The performance evaluation is shown on following figure, where:

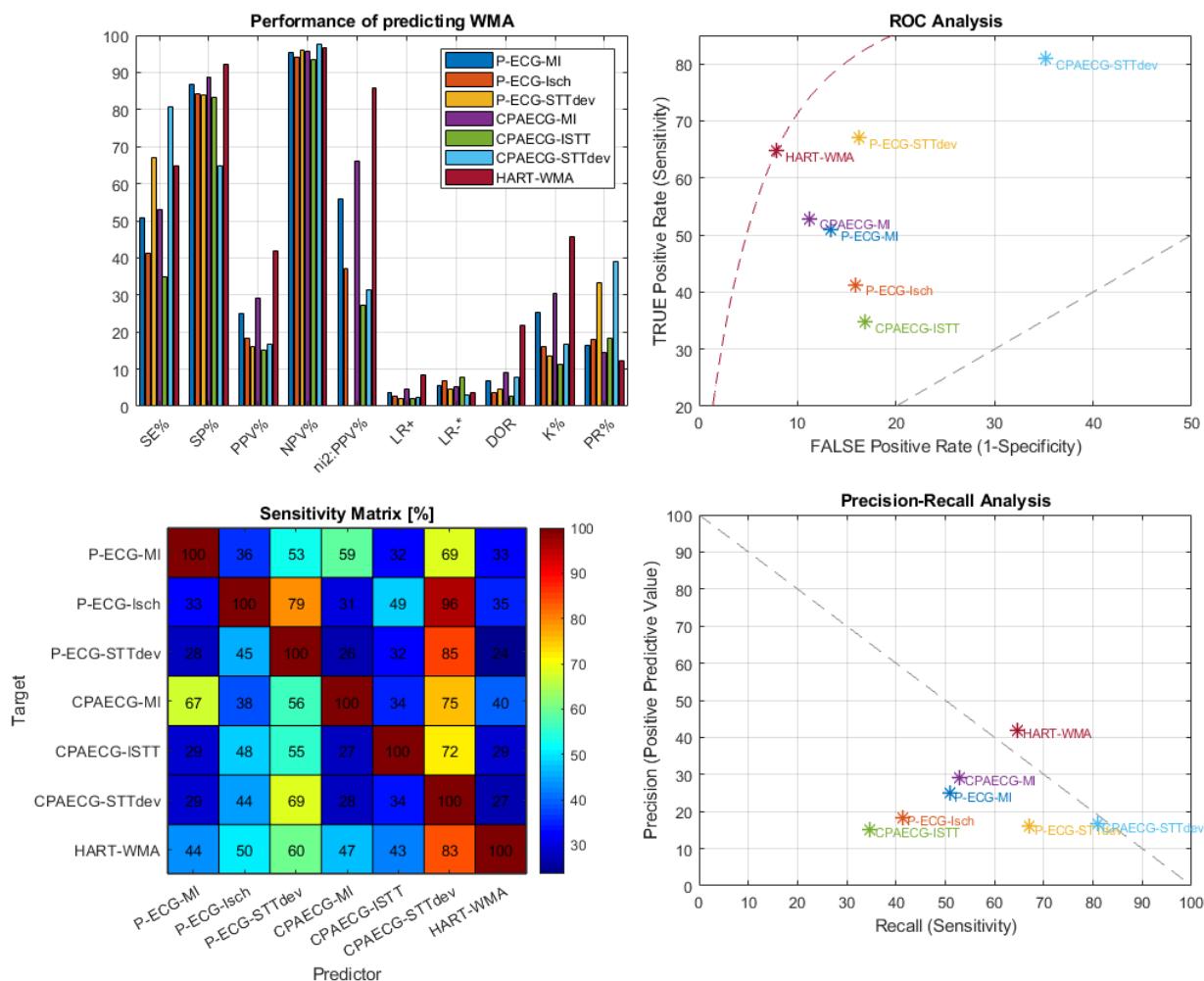


Figure 6-5 – Performance comparison of P-ECG, CPA-ECG and HART findings for Wall Motion Abnormalities

Conclusion:

- The best ECG criteria for the WMA is the myocardial infarction (MI) from the three examined ECG criteria (MI, Ischemia, ST-T deviation), however it has moderate sensitivity (SE~50%) with low positive predictive value (PPV~35%). It can be concluded based on both ECG algorithm implementation. MI by CPA shows slightly better performance compared to P-ECG.
- The Ischemic T wave ECG finding has low sensitivity and specificity for WMA.
- The ST-T deviation ECG group finding reaches the highest sensitivity (SE~70%), but specificity (SP~70-80%) and positive predictive value (PPV~20%) are low. The CPA implementation is more sensitive compared to predicate ECG.



- d) The HART model reaches the best performance for WMA; it has higher sensitivity ($SE \sim 56\%$) with higher specificity ($SP \sim 92\%$) and positive predictive value level ($PPV \sim 50\%$) compared to the best ECG criteria, the MI. The HART solution for predicting WMA substantially outperforms the ECG based approaches.
- e) The sensitivity matrix analysis confirms the significant variability between these criteria, since the cross-sensitivity numbers are variable (between 30-80%).



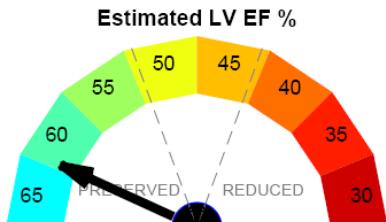
7 Appendix

7.1 Appendix A – CHART Report Sample

7.1.1 CHART Findings and HF indication

Patient General Data	
Patient ID	"10005291132"
DOB	1946-05-20
Age [year]	69
Gender	MALE
Race	Caucasian
BMI [kg/m^2]	26.78
BSA [m^2]	1.7
Height [cm]	157
Weight [kg]	66
CHART-BSI [$\text{m}+1/\text{kg}^{0.27}$]	2.19
Hip Size [cm]	95
Waist Size [cm]	100
Waist/hip ratio	1.05263
Sys. BP [mmHg]	130
Dia. BP [mmHg]	85

HART Findings	
LV Hypertrophy	Absent
Dilated Cardiomyopathy	Absent
RV Enlargement	Absent
LA Enlargement	Absent
RA Enlargement	Absent
LV Wall Motion	Mild
LV Systolic Function	Absent
Impaired Relaxation	Mild
AV Stenosis	Absent
MV Stenosis	Absent
AV Insufficiency	Absent
MV Insufficiency	Absent
TV Insufficiency	Absent
Pulm. Hypertension	Absent



Heart Failure	EF%	Systolic	Diastolic
Absent	EF>52%	Absent	Absent
HFpEF	EF>52%	Absent	Mild
HFmrEF	EF>40%	Mild	Mild/Abnormal
HFrEF	EF<40%	Abnormal	Abnormal

ECG Findings	
Rhythm	Sinus
Prem. Vent. C. (PVC)	Prem. Vent. C. (PVC)
Prem. Atrial C. (PAC)	Absence
PR interval	Normal
QT interval	Normal
Axis Deviation	Normal
B. Branch Block	IVCD
L. A. Fasc. Block	Absence
V. Hypertrophy Criteria	Absence
STT deviation	Twave abnormality
Ischemic ST-T	Consider Bord. Ischemia
Myocardial Infarction	Myocardial Infarction
ECG Signal Quality	Good
ECG Summary	ABNORMAL

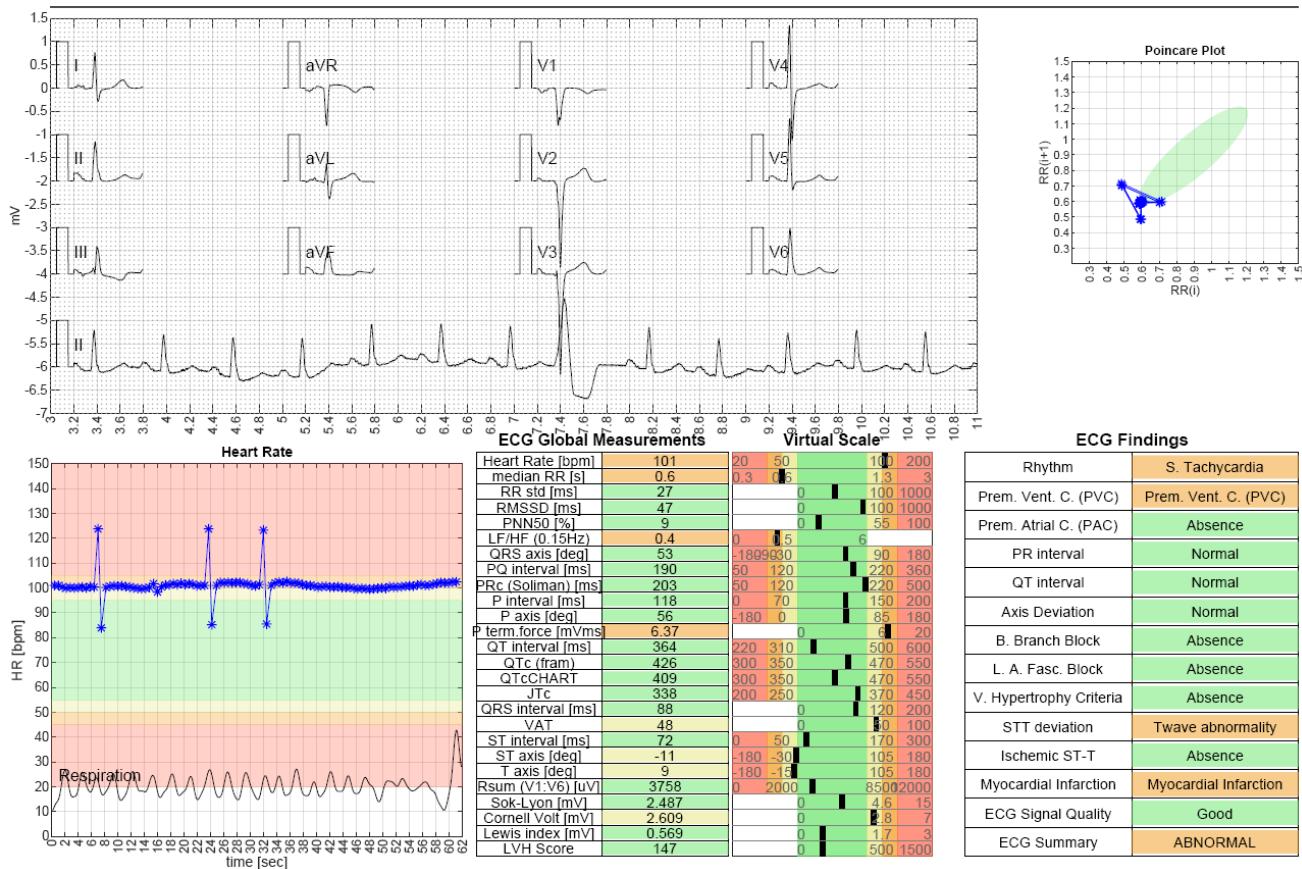
PCG Findings	
Systolic Murmur	Absence
Diastolic Murmur	Diastolic Murmur
Ejection Click	Absence
Opening Snap	Absence
3rd Sound	Absence
4th Sound	4th Sound
S1 Wide	Normal
S2 Wide	S2 Wide
Wheeze	Absence
Artifact	Artifact
PCG Signal Quality	POOR
PCG Summary	ABNORMAL

CPA Warnings			
No warnings!			
CPA version: 2021_210127-210204			

MCG Findings	
EMAT (Q-MitralClosure)	Normal
PEP - Pre Ejection	Normal
LVET - Vent. Ejection	Normal
SPI - Systolic Perf.	Normal
MPI - Myocardial Perf.	Normal
MCG Signal Quality	Good
MCG Summary	Normal

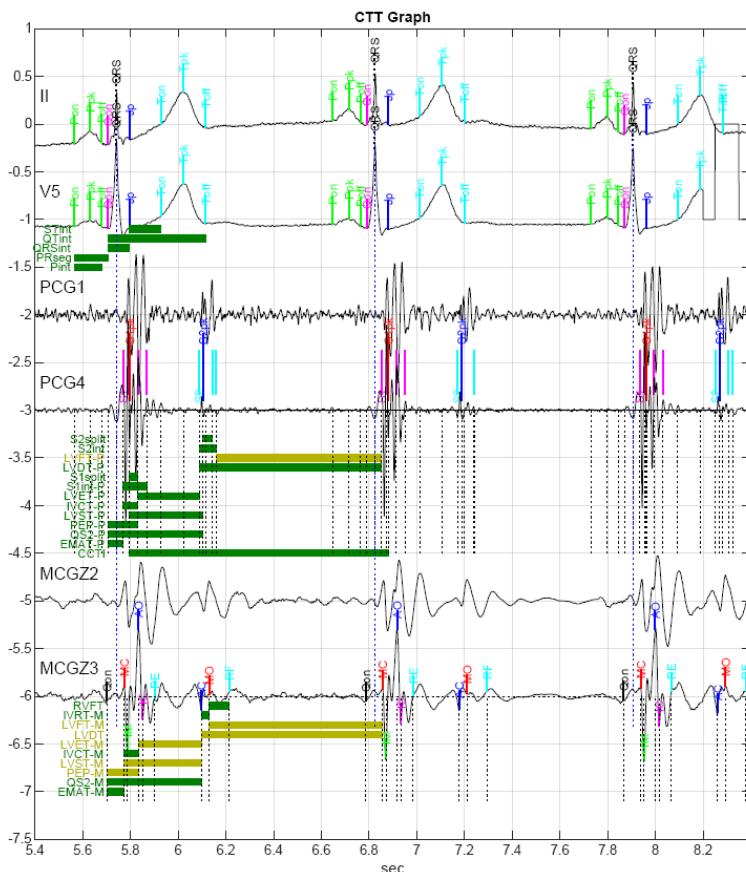


7.1.2 CPAECG Report





7.1.3 CTT Graph



PCG STI Measurement		Virtual Scale
PCG CCTI [ms]	1084	300 600 1200 8000
PCG EMAT [ms]	63	0 79 170
PCG QS2 [ms]	398	200 492 600
PCG PEP [ms]	121	0 146 250
PCG LVST [ms]	307	150 292 387 500
PCG IVCT [ms]	58	20 84 140
PCG LVET [ms]	260	100 237 337 450
S1 interval [ms]	98	60 128 150
S1 split [ms]	34	0 15 44 70
PCG LVDT [ms]	767	150 328 315 1100
PCG LVFT [ms]	695	130 300 706 1000
S2 interval [ms]	72	30 80 120
S2 split [ms]	38	0 60 70
PCG MPI (ivct+ivrt)/lvet	500	50 704 1200
PCG SPI (pep/lvet)	465	100 595 1300
PCG QS2I (qs2+2.1HR)	514	400 614 700
PCG PEPI	143	60 175 300
PCG LVETI	353	200 360 444 550
PCG EMATc (emat/rr)	58	0 94 200
Heart Rate [bpm]	55	20 50 100 200

MCG STI Measurement		Virtual Scale
MCG EMAT [ms]	71	0 85 170
MCG QS2 [ms]	392	200 500 600
MCG PEP [ms]	131	0 40 250
MCG LVST [ms]	321	150 310 460 500
MCG IVCT [ms]	60	20 100 140
MCG LVET [ms]	261	100 250 390 450
MCG LVDT [ms]	763	150 300 600 1100
MCG LVFT [ms]	731	130 300 706 1000
MCG IVRT [ms]	33	10 90 150
MCG RVFT [ms]	84	0 110 200
MCG MPI (ivct+ivrt)/lvet	356	50 500 1200
MCG SPI (pep/lvet)	502	100 595 1300
MCG EMATc (emat/rr)	66	0 100 200
MCG QS2I	508	400 625 700
MCG PEPI	153	60 165 300
MCG LVETI	355	200 375 490 550
MCG LVFTc (lvft/rr)	674	300 390 640 800
MCG S1int [ms]	94	30 128 220



7.1.4 Other plots

7.1.4.1 12 lead ECG plot

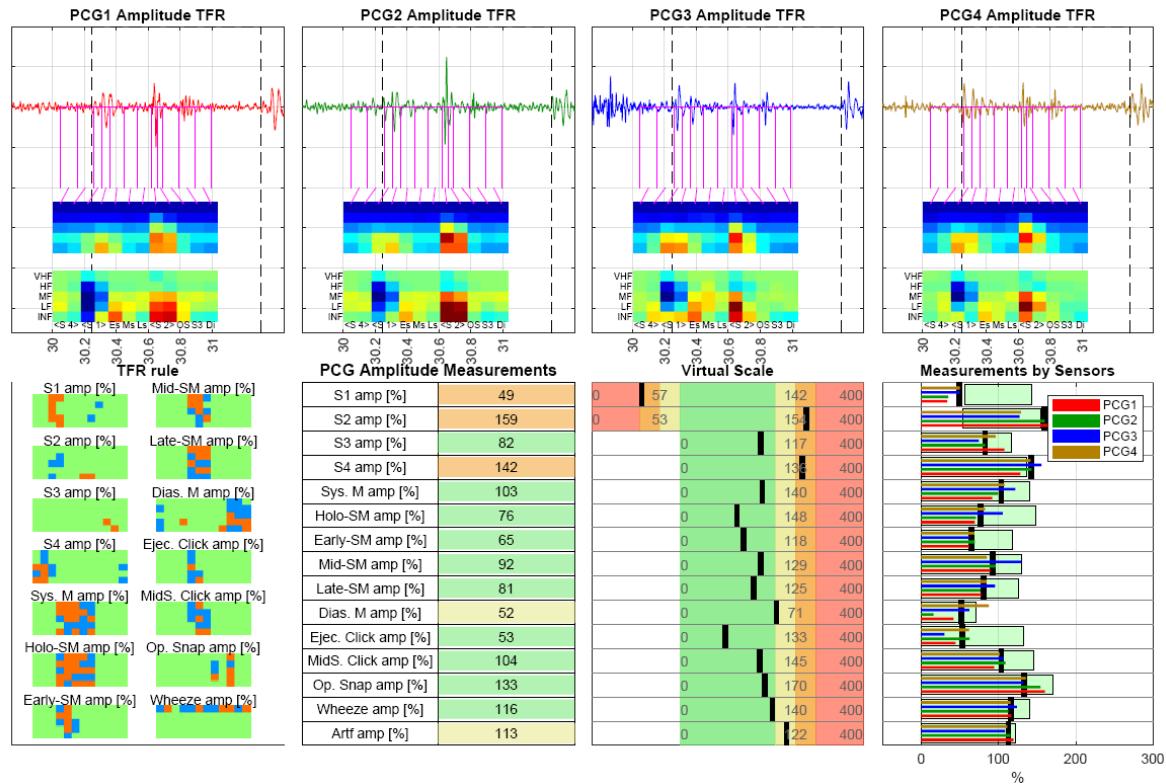


7.1.4.2 1 lead ECG rhythm plot

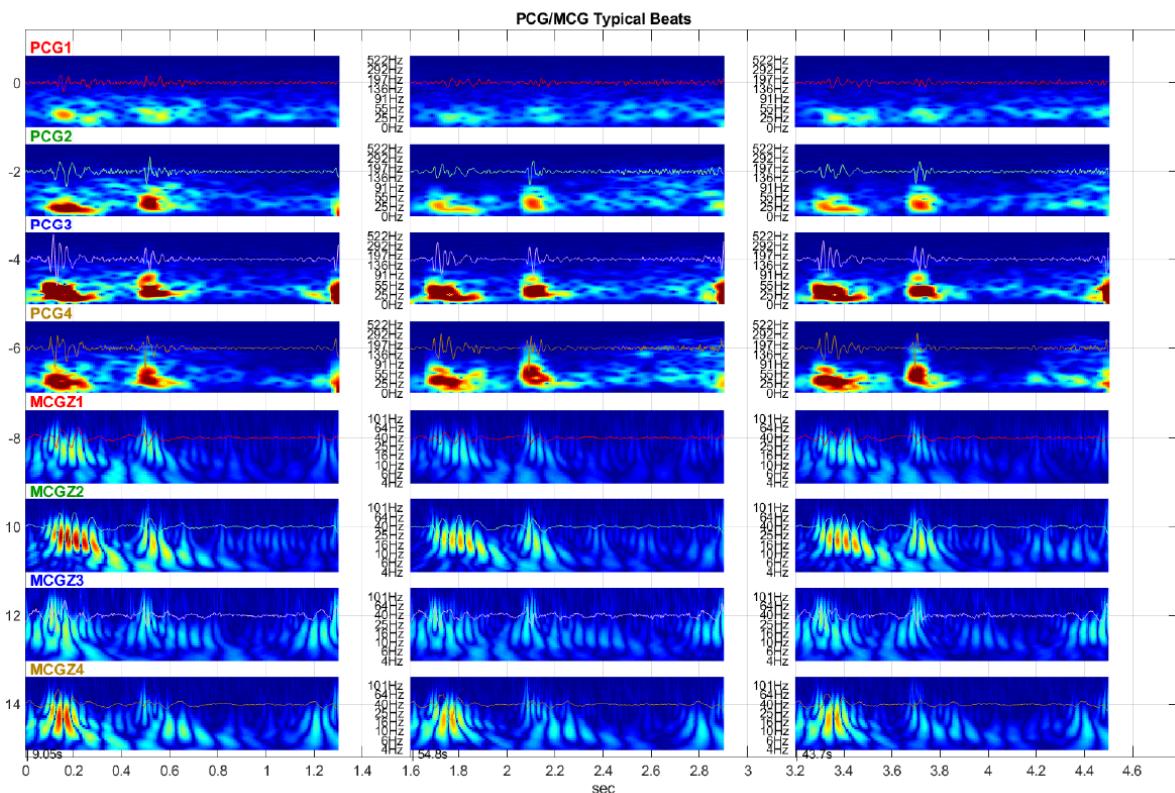




7.1.4.3 PCG amplitude plot - Requirement CH0806

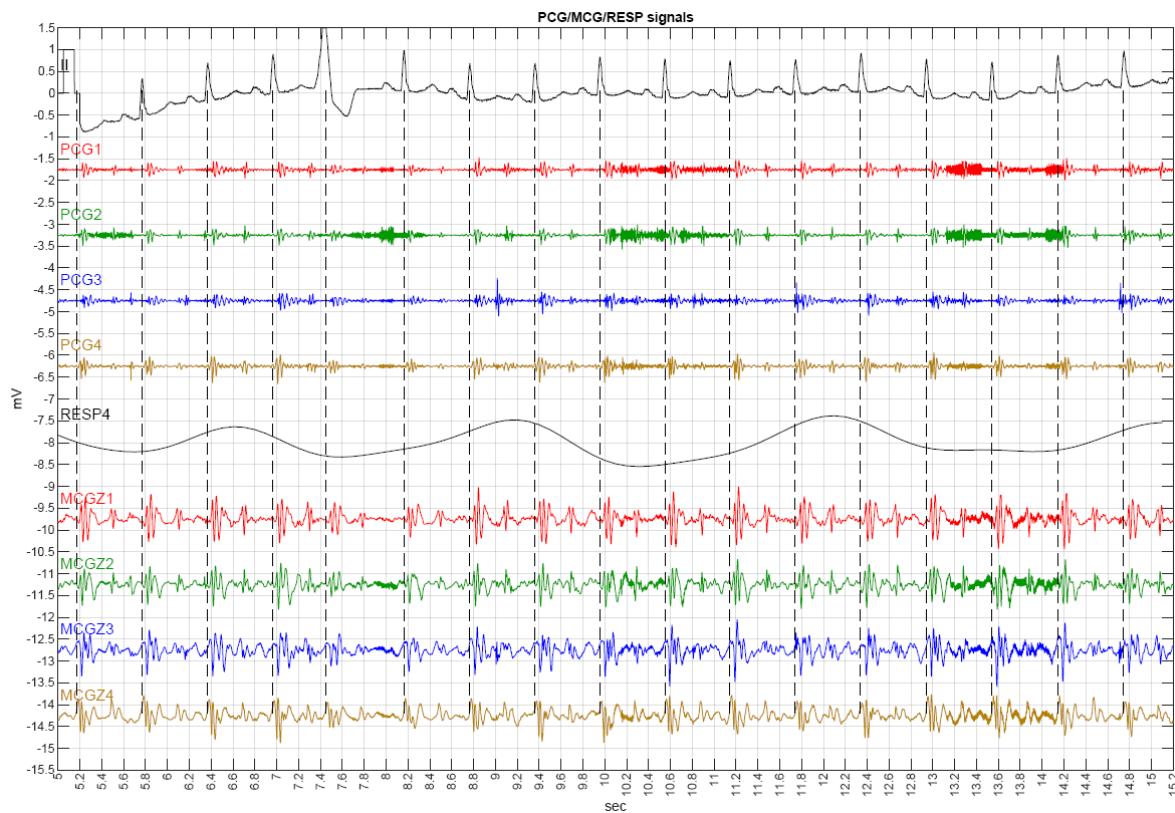


7.1.4.4 PCG/MCG typical beat plot





7.1.4.5 PCG/MCG/RESP plot





7.2 Appendix B – CE certifications



**EC Certificate –
Full Quality Assurance System**
Directive 93/42/EEC on Medical Devices, Annex II excluding (4)
Certificate No. MDD-168

Issued to: Cardio-Phoenix Inc.
44, Rosemead Close, Markham, L3R 3Z3, Ontario
Canada

Place of production: Cardio-Phoenix Inc.
Henrika Sjenkjevića br. 14, 24000 Subotica, Serbia

Place of production: L-Tek d.o.o.
Obртна cesta 18, 8310 Šentjernej
Slovenia

Product category: Electrical, Acoustical and Physiological Heart diagnostic system
GMDN: /

Product category: Medical software for heart diagnosis - CHART Processing Algorithm
GMDN: /

SIQ has audited the quality system in accordance with MDD Annex II excluding (4) and found that the above-mentioned manufacturer's quality system meets the requirements of the Directive 93/42/EEC concerning medical devices Annex II. This certificate is based on

Audit report No.:
OSV 00094/2020, 2020-04-29
OSV 00445/2020, 2020-05-28
OSV 00068/2020, 2020-06-30
OSV 00376/2020, 2020-06-30

See also decision of NB's commission for medical devices.

This certificate remains valid as long as the Manufacturer's quality system is subject to periodical surveillance as referred to in Directive 93/42/EEC concerning medical devices Annex II (5) and continues to meet the above requirements.

Certification date: 2020-07-13

Issue : 1/2020-07-13

Valid until: 2024-05-27



Director of SIQ

Igor Likar

SIQ Ljubljana, Mašera-Spasičeva ulica 10, SI-1000 Ljubljana, Slovenia, Notified Body No. 1304
tel.: +386 1 4778 100 • fax: +386 1 4778 444 • e-mail: info@siq.si • <http://www.siq.si>



7.3 Appendix D – CHART examination

7.3.1 Conducting a CHART examination.

A CHART examination is expected to be conducted by an ECG trained nurse or medical assistant. Once the test is administered, they do not see or receive the results as the CHART report is sent directly to the physician.

An ECG trained nurse, can typically learn how to administer a CHART test in less than 20 minutes. It was designed to slip directly into the current workflows as a direct substitute to ECG.

The CHART device is connected to a computer where the Cardio-Client is used to operate the device, capture the bio-signals and upload them for AI processing. The UI is very intuitive and easy to understand, with extensive human interface testing to reduce the potential of human error.

The device is a full 12-Lead Standard ECG device. As such there are 10 leads. Standard ECG electrodes are used for the ECG component of the device.

There are 4 mechano/phono leads (Combi-sensors), that are placed on the thoracic wall, in the 4 standard auscultation points. A harness is used to apply light pressure on these sensors during a test. Each sensor has its own cable connecting it to the device, the sensors and cables are colour coded to reduce potential for errors.

A typical examination lasts between 5-8 minutes longer than a typical ECG. This is because each examination includes:

- a. Recording 2 x 1-minute long tests, with a 15 second rest between tests. (optionally 3x 1 minute tests, clinic preference)
- b. Prior to the test, taking a patient's "vital signs", Blood Pressure, weight, height, waist and girth (can be done beforehand).

Once the leads are on, recording of the tests is very quick. There is a countdown clock that shows the test duration. There is a warning at the 45 second interval to indicate when a patient should hold their breath for the last 10 seconds of the test. There is a quick break of 15 seconds to allow any patient to catch their breath, and two tests recorded. After each test, a quality algorithm is invoked to ensure the test was good.

Once two good tests are captured, they are automatically packaged, encrypted and uploaded for AI processing. During this time, the Nurse removes the sensors and cables from the patient and the test is done.



The 4 PMCG sensors, cables and harness are then cleaned and disinfected using medical grade disinfectants.

7.3.2 Patient information

The screenshot shows the 'Patient's basic information' screen of the Cardio Tri-Test v3.2 software. At the top, it displays 'RISQ™' and 'Patient's basic information'. On the right, there is a user icon labeled 'admin_o4_c1'. The patient information section includes fields for Height (123 cm), Weight (123 kg), Measurements (Waist: 231 cm at belly button, Hip: 123 cm at gluteus), Menopause status (Pre selected), Using a pacemaker (No selected), Systolic Pressure (123 mmHg), Diastolic Pressure (111 mmHg), and BP medication status (No selected). Below these, there are options to select Questionnaire Type (Complete, Quick, Skip) and a progress bar with five green dots. At the bottom, there are 'Back' and 'Next' buttons.

7.3.3 Risk Factor Survey. [optional].

Optionally, a risk factor survey can be conducted prior to the test. The purpose of this survey is to ensure the HCP has basic info about the patient's risk factors, which is most useful in a Telehealth situation where the patient might be remote to the HCP.

The survey can be completed just prior to the test, in the examination room, or beforehand, in the Clinic waiting room, prior to the patient entering the examination room.

There are two surveys, that can optionally be used, the Quick or the Complete. For list of questions, send request to documents@cardiophoenix.com, and ask for Questionnaire document.

7.3.4 Pandemic Questionnaire [Option].

During the Pandemic Emergency, a special "infection" survey as recommended by the World Health Organization (WHO) will be completed by examiner. Part 1, is 10 questions that the Nurse answers from observations of the patient. Part 2, is 10 questions the patient must answer.

The purpose of the pandemic Survey is to provide the HCP with information that might not otherwise be available during a Telehealth visit.