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Imaging Guided Cardio-Protective Treatment in a Community Elderly Population of Stage B Heart Failure- a Randomized Controlled Trial

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Running title: Imaging guided Treatment for Stage B Heart Failure

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Abstract

Background. The detection of non-ischemic stage B heart failure (SBHF) has been facilitated by advanced echocardiographic imaging modalities. However, improved outcomes have not been proven as they are predicated on benefit of treatment.

Objectives. The purpose of the study was to evaluate the benefit of care guided by the detection of SBHF using advanced echocardiography for the reduction of new HF in the community.

Method. Between 9/2013 and 11/2015, 618 asymptomatic community-based patients with HF risks (age 71 ± 5 years) were randomized to care guided by advanced echocardiography (AE; myocardial deformation and detailed diastolic function) versus usual care (UC). Evidence of SBHF led to advice to the patient and their primary physician to initiate treatment with angiotensin converting enzyme inhibition and beta adrenoceptor blockade. The trial followed Prospective Randomized Open Blinded Endpoint design. Participants were followed for 1 year for the primary composite endpoint of death from cardiovascular causes and new HF.

Results. AE identified 219 as having SBHF and treatment was advised. Over a mean follow-up of 13 ± 6 months, 67 reached the primary end-point. The incidence rate of HF was no different between the two arms ($p=0.47$), likely because only 43% initiated therapy, and only 9% achieved target dose. Among subjects needing therapy on the basis of imaging and adherent to therapy, imaging guided care showed a 77% lower hazard for the primary outcome ($p=0.04$).

Conclusion. The detection of SBHF from strain and diastolic function evaluation was associated with a higher incidence of incidence HF and death. The efficacy of pharmacological intervention with angiotensin converting enzyme inhibition and beta-adrenoceptor blockade is limited by its uptake, and alternative strategies should be considered.

Keywords: stage B heart failure, randomized controlled trial, community detection, pharmacological intervention, medication non-adherence

Abbreviations and Acronyms

ACEi: angiotensin converting enzyme inhibitor

AE: advanced echocardiography arm

ARB: angiotensin receptor blocker

BB: beta-blocker

GLS: global longitudinal strain

HTN: hypertension

HF: heart failure

LV: left ventricular

SBHF: stage B heart failure

SBP: systolic blood pressure

T2DM: type 2 diabetes

UC: usual care arm

Stage B heart failure (SBHF), has been defined in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines to include asymptomatic patients with abnormal left ventricular (LV) structure or function (1). Patients with SBHF are at higher risk for developing overt heart failure (HF)(2). In contrast to Stage A HF (SAHF, i.e. HF risk factors) (3), where therapy is directed towards the control of cardiovascular (CV) risk factors, cardio-protective therapies are recommended in SBHF (1), on the basis of trials showing pharmacological interventions to delay and reduce the burden of HF in the SBHF population (4,5). The difference between SAHF and SBHF is a problem, because although highly prevalent, non-ischemic SBHF requires an effective screening strategy for its recognition. While modern imaging techniques may be able to provide this strategy, their incorporation into routine care needs evidence that management will be altered.

Accordingly, we developed a community-based screening program in elderly patients for detection of SBHF using echocardiography and subsequent cardio-protection. Our primary aims were: 1) to assess whether imaging guided cardio-protective therapy, when added to usual care, would reduce the rate of incident heart failure, 2) to assess the feasibility of coupling an effective community screening program with interventional treatment in high risk asymptomatic elderly individuals with SBHF.

Methods

Study design. The Tasmanian Study of Echocardiographic Detection of LV Dysfunction (TasELF) is a community based screening and interventional program. The study followed a Prospective Randomized Open Blinded Endpoint (PROBE) design (6). Individuals were randomized to either undergo an imaging guided screening strategy for early detection and treatment of SBHF or to continue with usual care (7). The data were collected at various clinical sites within the State of Tasmania, Australia.

Patient selection. Asymptomatic community-based patients (≥ 65 years old) with HF risks volunteered for enrolment through local community presentations and media advertising. Patients with stage A HF risk factors were eligible for inclusion(1), including hypertension (HTN, based on

blood pressure $\geq 140/90$ mmHg and self-report of HTN including anti-hypertensive medication); type 2 diabetes mellitus (T2DM, based on self-report of diagnosis including medical management); obesity (body mass index [BMI] ≥ 30); previous chemotherapy; family history of heart failure; previous history of heart disease (but not existing heart failure). We excluded subjects with: symptoms or a known history of HF; known coronary artery disease; more than moderate valvular heart disease; reduced left ventricular ejection fraction (LVEF) ($<40\%$) on baseline echo; already taking both trial medication, beta-blocker (BB) and angiotensin converting enzyme inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB), at baseline and contraindication of BB and/or ACEi and ARB. We also excluded those in whom we were unable to acquire interpretable images from baseline echocardiography (inclusion and exclusion in **Appendix T1**).

End-point. The primary composite endpoints were incident HF and death from CV causes. Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. New onset HF was adjudicated by a blinded end-point committee using Framingham criteria at 1 year. Loss to follow-up was defined as not having replied for evaluation in ≥ 2 months.

Sample size. Sample size was calculated based on the following: 1) an expected prevalence of abnormal cardiac function in $\sim 50\%$ using advanced echocardiographic imaging, 2) an expected 7.5% annual rate of loss to follow-up, 3) a previously reported 12% annualized rate of incident heart failure among patients with evidence of SBHF under usual care (8), 4) assumption of a 50% reduction of events with intervention compared with usual care. A sample size of 400 in each randomized group would provide 80% power to document benefit of therapy at a two sided $\alpha=0.05$. The trial was monitored by a Data and Safety Monitoring Board (DSMB) with termination guidelines for futility (if conditional probability of rejecting the null hypothesis was unlikely to achieve statistical significance) and feasibility (if recruitment or other aspects of its conduct were unable to fulfil requirements due to unforeseen circumstances).

Randomization. Randomization was done using central web-based program with adaptive allocation stratified by diabetes status. The eligible participants were randomized to advance echocardiographic imaging (AE, involving measurement of global longitudinal strain and diastolic

function), versus usual care (UC, continuing with their usual care treatment for primary risk factors such as hypertension and diabetes). The randomization list and intervention list were prepared by assigned persons who were blinded to details of the investigations.

Patient report outcome measures (PROMs) and functional capacity. All participants enrolled in the study underwent a physical examination and standard PROMs questionnaires relating to health status (EuroQol 5 Dimensions Index, EQ5D), activity status (Duke Activity Score Index, DASI), symptom status (Minnesota Living with HF Questionnaire, MLHFQ), depression (Patient Health Questionnaire-9, PHQ9) and anxiety (generalized anxiety disorder questionnaire, GAD7). Functional capacity was assessed using a 6-minute walk test (6MW) distance following a standardized protocol (9).

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines(10). Diastolic function was assessed by measuring mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT)(11-13). Echo left ventricular hypertrophy (LVH), left atrial enlargement (LAE) was assessed according to recommended cutoffs (10). Diastolic dysfunction (DD) grade was defined as previously described(11,12). Grade I: $E/A < 0.8$, $E/e' < 10$, pulmonary venous inflow $S < D$. Grade II: $0.8 < E/A < 1.5$, $E/e' > 13$ or LAE, or presence of mid diastolic forward flow (L wave), or positive Valsalva ($> 50\%$ increased of E/A ratio). Grade III: $E/A > 1.5$, $DecT < 140$ ms. LV peak longitudinal strain measurements were obtained from gray scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analyzed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). GLS was measured on-line by averaging strain from the region of interest in three apical views. Impaired GLS was defined using cut-off of $< 18\%$ (14). All echocardiographic measurements were obtained on-line **before** participants left clinic. Echocardiographic definition of SBHF was: 1) Impaired GLS ($< 18\%$) and/or 2) $\geq$ grade I diastolic dysfunction.

Cardio-protective treatment for SBHF. The treatment protocol was a combination of ramipril (starting with 1.25 and up titrate to 10 mg/day) with the addition of Metoprolol (start 12.5 and up to 100 mg/day) (titration plan in Appendix T2). Cardioprotection was initiated by the patient's general physicians (GP), under guidance by the investigators. The titration plan and guidance for monitoring was proposed to subjects with evidence of SBHF who required treatment in AE arm and their physicians. As some patients were already on one of the two agents (at submaximal dose) at recruitment, any pre-existing ACEi/ARB or BB, other than ramipril and Metoprolol, were up-titrated to the maximal tolerable dose (**Appendix T2**).

General guidance regarding risk reduction was shared with all subjects, and a report (including clinical and imaging information, according to randomization arms) was shared with all patients and their physicians.

Medication adherence. The primary analysis involved comparison on an intention to treat basis, in the belief that this would provide direct evidence of the clinical effectiveness of screening for SBHF.

Those who required treatment based on results of AE were notified of this at the screening visit and re-contacted within 4-6 weeks to reinforce the need to follow-up with their GP.

A process evaluation was performed within a period of 3 months, to allow reasonable time for up titration. Adherence to protocol was defined on the basis of treatment initiation and dose maximization.

Statistical analysis. Data are presented as mean ($\pm$ standard deviation [SD]) after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. All analyses were performed on an intention to treat basis. The comparability of baseline characteristics in the two arms was assessed by chi-square tests for categorical variables and the Mann-Whitney U test for continuous variables. Cox proportional hazard regression model with time-dependent covariates was used to assess the relative risk of primary outcome of individuals under usual care versus those under imaging guided care. Survival analysis was performed using the Kaplan-Meier method, and the differences in survival between groups were assessed by the log-rank test. Statistical analyses

were performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Statistical significance was defined by $p < 0.05$.

This report follows the recommendations of the 2010 Consolidated Standards of Reporting Trials Statement (15). This study was performed in accordance with a research protocol approved by the Tasmanian Human Research Ethics Committee (HREC), and registered with the Australian and New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/>; ACTRN12614000080628). Individual written informed consent was obtained from participants after explanation of the nature and purpose, complexity and level of risk of the study.

Results

Patient selection and characteristics. Between September 2013 and November 2015, a total of 1026 self-referred community participants at or over the age of 65 years, and with non-ischemic HF risk factors, volunteered in response to advertising through community organizations and local media. After clinical and echocardiographic screening for eligibility, 618 (age: 71 ± 5 years, 48% men) met inclusion criteria. The most common HF risk factors were hypertension (79%), diabetes mellitus (51%) and obesity (44%), 79% of individuals having ≥ 2 of the listed risk factors. Of the total, 6.5% of participants were already taking BB and 67% were on ACEi or ARB treatment at baseline; none were taking both at baseline and none were at maximal doses.

Of these 618 individuals who underwent randomization, 308 were assigned to the advanced echocardiography-guided care arm (AE). The remaining 310 were assigned to the usual care (UC) arm (**Figure 1**). There were no differences in the demographic, clinical, socio-economic features, nor were the patient reported symptoms and activity status between the two groups (**Table 1**).

There were 23 patients who were in AF at baseline, 12 in AE arm and 11 in UC arm. Of the 12 in AE arm, all had abnormal GLS and treatment was required based on abnormal GLS. None of 11 AF of UC arm required treatment for abnormal EF.

Screening results and pharmacological intervention. Comprehensive echocardiograms were performed in all subjects. Of the 308 individuals in AE arm, evidence of SBHF was found in 219 (71%) defined by abnormal GLS or DD, with abnormal GLS present in 113 (37%) and diastolic

dysfunction in 211 (69%); 83 individuals (27%) had both. Patients with abnormal function were older and had significantly higher Atherosclerosis Risk in Communities (ARIC) HF risk score and Charlson comorbidity score compared with the remaining AE patients ($p<0.002$). Treatment advice with titration plan were proposed to these 219 as well as their GP. **There were 18 patients in the AE group who had a mid-range EF (40-53%), of whom 17 required treatment on the basis of abnormal GLS or DD.** Of the 310 individuals in UC arm, no treatment was advised based on GLS and DD criteria. However, 5 individuals were started on treatment based on mild reduction of left ventricular ejection fraction (LVEF 40-53%); none had LVEF $<40\%$.

Side-effects. Side-effects were self-reported in a total of 31 individuals, but there was no reported syncope or other severe adverse effects. The most common side-effects were dry cough from ramipril and bradycardia and lethargy from beta blocker. Side-effects led to discontinuation of the medication in 4% in the AE arm and none in the UC arm, with most continuing with minor adjustment of medication. Side-effects were also reported in individuals in usual care group. These are summarized in **Table 3**.

Intention-to-treat analysis. At the last follow-up clinic (March 2016), 23 (11 from AE) participants were contactable but unable to attend the follow-up assessment. Contact was lost with 8 participants (1.3%) - 4 from the AE arm. At 13 ± 6 months, a total of 22 (4%) participants (18 from the AE arm and 4 from the UC group) had withdrawn from the study because of reluctance to attend further follow-up, unwillingness to take additional medication, but in only 3 due to side-effects. Therefore, follow-up for this outcome assessment was 91% complete (275/308 vs 290/310) (**Figure 1**).

There were 5 deaths (2 of cardiovascular causes). New HF symptoms developed in 65 patients. The primary composite end-point of new HF and CV death occurred in 67 (11.8%) with an annualized incidence rate of 10.9%. The three deaths from non-CV causes were in both arms while the two CV deaths were both in the AE group. The incidence of the primary end point was 13% (37/275) in the AE arm and 10.3% (30/290) in the UC arm ($p=0.25$). There was no difference in event free survival using Kaplan-Meier analysis between two arms (Log rank Chi-square=0.53, $p=0.47$) (**Figure 2**).

Initiation and up-titration of medication. Medication initiation and up-titration was assessed using self-reporting questionnaires and telephone calls. Almost all patients - 307 of 308 in the AE arm and 309 of 310 from the UC arm - responded to our evaluation. **Figure 3** summarizes medication status in the entire cohort. An increment of medical therapy (determined by initiation or up-titration) was achieved in total of 146 individuals across both arms. In the AE arm, an adjustment of medication was achieved in 94 out of the 219 (43%) SBHF patients with abnormal imaging (**Figure 3**). Of these 219 subjects, 20 (9%) had achieved recommended target dose, and 64 had initiated one or both medications without dose increments because of concern about reduction of BP or other potential sources of intolerance. For other reasons (generally blood pressure control) an **adjustment of medication** was also achieved in 15% of the UC arm, and in 7 subjects in the AE arm without evidence of SBHF. The DSMB stopped the trial in November 2015, on the basis of poor therapeutic adherence (~40%) in both initiation and up-titration of medication.

Protocol analysis. The potential clinical benefit of screening guided care was evaluated in Cox proportional hazard model and with the adjustment of number of subjects who required treatment. Given the fact that a low medication adherence (43%), the model was also adjusted for subjects who were actually adherent to treatment (Treatment up-titration). Echocardiographic imaging guided care was associated with 77% lower risk for primary outcome at one year, hazard ratio 0.23 (95% CI 0.06-0.98, $p=0.047$).

In the absence of treatment protection, individuals with abnormal GLS, diastolic dysfunction and the presence of both was associated with worse outcome (**Figure 4**). No treatment benefit was observed in subgroups with abnormal GLS, DD and the presence of both ($p>0.4$).

Discussion

The results of this study show that among individuals in the community ≥ 65 years old, with mainly multiple HF risk factors, evidence of SBHF was identified in 71% with the use of advanced echocardiography, and these showed an annualized event-rate of 10.9%. Despite the prognostic information from imaging, the trial emphasizes the difficulties in providing cardioprotection in asymptomatic elderly individuals at risk of HF. Pharmacological intervention was unsuccessful in

intention to treat analysis, although there may have been potential benefits from imaging-guided care in adherent patients.

Definition of new HF. Heart failure is a clinical diagnosis, and patients may minimize or deny their symptoms in the early phases, making clinical recognition difficult. Prevalence estimates may vary broadly depending on the diagnostic criteria; a recent meta-analysis reported that incident HF diagnosis in 8 of 15 included studies was based on a non-standardized clinical description (16).

Differences in the diagnostic criteria for HF may also impact the outcome assessment in these studies. Among four commonly used HF diagnostic criteria (Framingham, Boston, Gothenburg, and European Society of Cardiology (ESC) criteria) (17), there were significant differences in predicting clinically relevant outcomes including incident hospital admission. As disturbances of cardiac structural and functional characteristics at baseline were best predicted using the Framingham HF criteria (17), we selected the Framingham HF criteria to adjudicate events in our study. However, although the absolute 3-year risk of hospital admission following a Framingham HF diagnosis was 6.1% (odds ratio 6.9, 95% CI 1.3-36.1, $p=0.022$) (17), the annualized rate of incident HF in our study was 10.3%. This likely reflects the high clinical risk of these subjects, most of whom had multiple HF risk factors. In addition, although we excluded symptomatic HF at entry, Framingham criteria may not capture mild or early HF (stage C1) in individuals with atypical symptoms(2). Moreover, a high rate of incident HF was observed in a similar community study of a cohort with combined diabetes and hypertension (8), in whom $E/e' > 15$ (detected in 23%) was used to categorized stage B HF. In our cohort, the prevalence of increased E/e' was similar in those with both HTN and T2DM (20%).

Diagnosis and management of SBHF. Imaging screening for SBHF is based on the concept that this stage is a precursor of overt clinical HF, and has been advocated in practice guidelines (18) because SBHF is associated with a 5-fold greater risk of symptomatic HF (19). Imaging by echocardiography is generally believed to be a safe and accurate for the diagnosis SBHF. Although EF as the only functional feature in the conventional criteria for SBHF (20), both strain and diastolic dysfunction are associated with adverse outcome and impaired functional capacity (21).

Of course, the accuracy and prognostic value of diagnostic tests have no direct effect on patient outcomes unless indirectly by influencing the therapeutic pathway. The evidence to date for pharmacological therapy in SBHF is largely based on EF. This supports ACEi as the foundation of management of SBHF (22), with the improvements in all-cause mortality, recurrent cardiovascular events and progression to HF (23,24). In the Heart Outcomes Prevention Evaluation study (HOPE) (25), ACEi also significantly reduced the rate of death, myocardial infarction, and stroke, and reduction of HF admission and death was reported after treatment in a similar population with SAHF (26). Evidence also supports the use of beta blockers in asymptomatic patients (22). In the Survival and Ventricular Enlargement (SAVE) and Studies of Left Ventricular Dysfunction (SOLVD) trials, concomitant use of beta blocker therapy was associated with reductions in cardiovascular death and heart failure (23,24).

In this study, we sought to gather evidence on the benefit of early detection of SBHF using new functional markers to guide management. We assessed this by randomizing subjects to either screening strategy or usual care and comparing their outcomes, using an “intention to treat” approach (7). This design allows assessment of the benefit of early detection, as well as recognition of potential risks associated with diagnostic procedures, including false positives resulting in over treatment. In addition, our intention was also to determine whether an intervention works among a community screening population. Unfortunately, the negative results of the current study were attributable to lack of effectiveness (27) in medication delivery following imaging screening. Side-effects were uncommon, and the main causes were reluctance of patients and physicians to initiate and up-titrate therapy in the presence of a normal EF and the absence of symptoms.

Limitation. This study has several limitations. The follow-up time was only one year. The method adopted for assessment of medication use was self-report rather than pill counts and rate of prescription refills. However, there is no optimal means of achieving this (28), and self-report is simple and feasible in the context of community screening and has been strongly associated with adverse cardiac events (29).

We excluded patients with EF <40% because previous clinical trials showed a benefit from therapy (30)(30). The study did not incorporate the analysis of HF with mid-range EF, a category that has

been recently proposed in the guidelines (31), and only one patient was in this category in the absence of abnormal GLS.

AF was not excluded in the initial design, because the optimal management of this important subgroup in non-ischemic stage B HF is unclear. However, the numbers of patients with AF was small, and they were equally distributed among the groups. Of the 12 in AE arm, all had abnormal GLS and treatment was required based on abnormal GLS. None of the 11 AF patients in the UC arm required treatment for abnormal EF.

Conclusions. The application of advanced echocardiographic markers is feasible in the community diagnosis of SBHF, and predicts incident HF. Despite their risk levels, the adherence to intervention in this asymptomatic group with a normal EF was poor. Subsequent attempts with this study design might include a disease management program to ensure adherence with therapy.

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Clinical Perspectives:

Competency in Medical Knowledge. Patients of >65 years old with heart failure risk factors have a high prevalence of stage B heart failure, evidenced by LV hypertrophy, LV diastolic or systolic dysfunction. These patients are at risk of early development of clinical heart failure.

Competency in Patient Care. The appropriate therapeutic response to the detection of stage B heart failure is undefined. This study showed no benefit from screening for stage B heart failure, but uptake of cardioprotective therapy and dose titration were both inadequate.

Translational Outlook. A strategy to identify stage B heart failure seems unlikely to alter the progression to heart failure in the absence of an integrated disease management program.

References

Figure legends

Figure 1. CONSORT chart describing patient allocation.

Patients were randomized to imaging guided care, advanced echocardiography (AE) or usual care (UC), guidance was given based on the findings of echocardiography.

Figure 2. Kaplan-Meier analysis for primary outcome between AE and UC arms

There is no difference of primary outcome between imaging guided care (AE arm, label in red) and usual care (UC arm, label in blue).

Figure 3. Medication initiation and up-titration in the advanced echo-guided (AE) and usual care (UC) arms.

In the AE arm, an increment of medication was achieved in 84 out of the 219 (43%). Of the 84, 20 had reached targeted maximum dose of both ACEi and BB agents.

SBHF patients with abnormal imaging (shown in red). In addition, 7 subjects in the AE arm (labeled in yellow) had cardioprotective medications started for control of hypertension, without evidence of SBHF. An increment of medication was also achieved in 14% of the UC arm.

Figure 4. Kaplan-Meier analysis of outcome between abnormal GLS, DD and abnormal GLS+DD. There is no difference of primary outcome between imaging guided care and usual care.

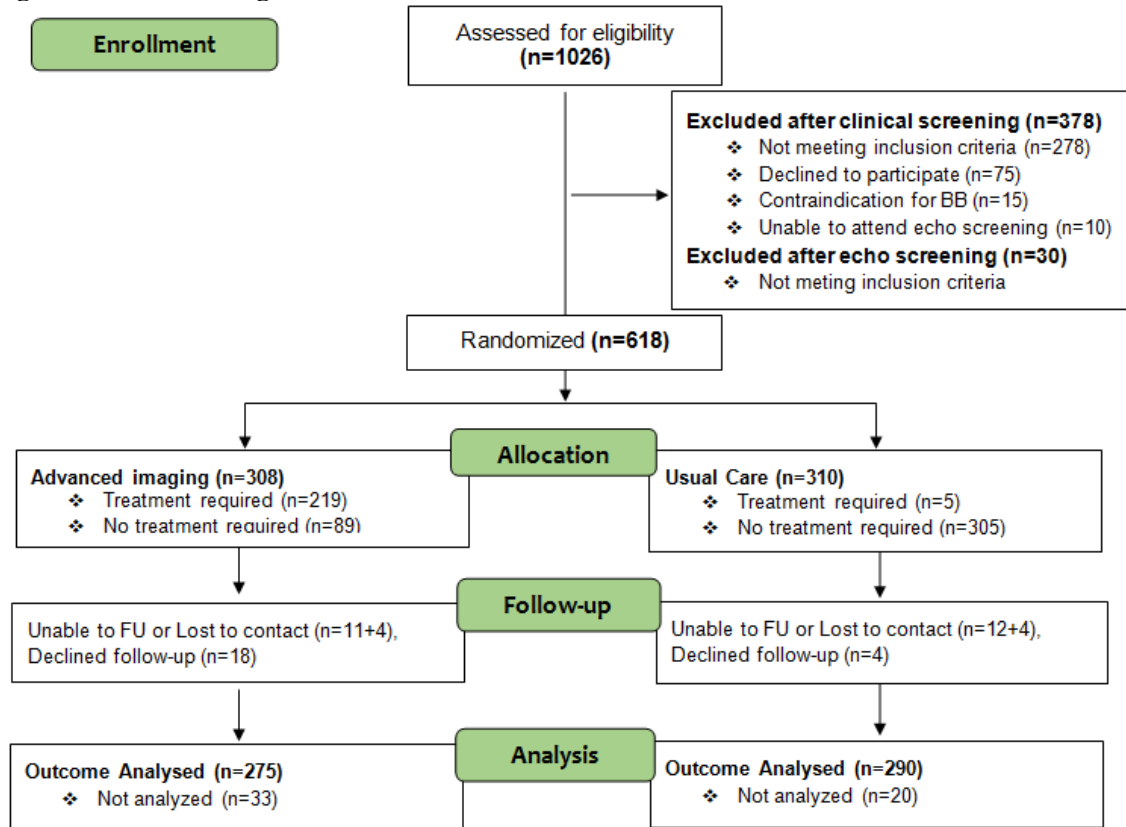
Figure 1. Contort diagram

Figure 2. Kaplan-Meier analysis of event free survival between two arms

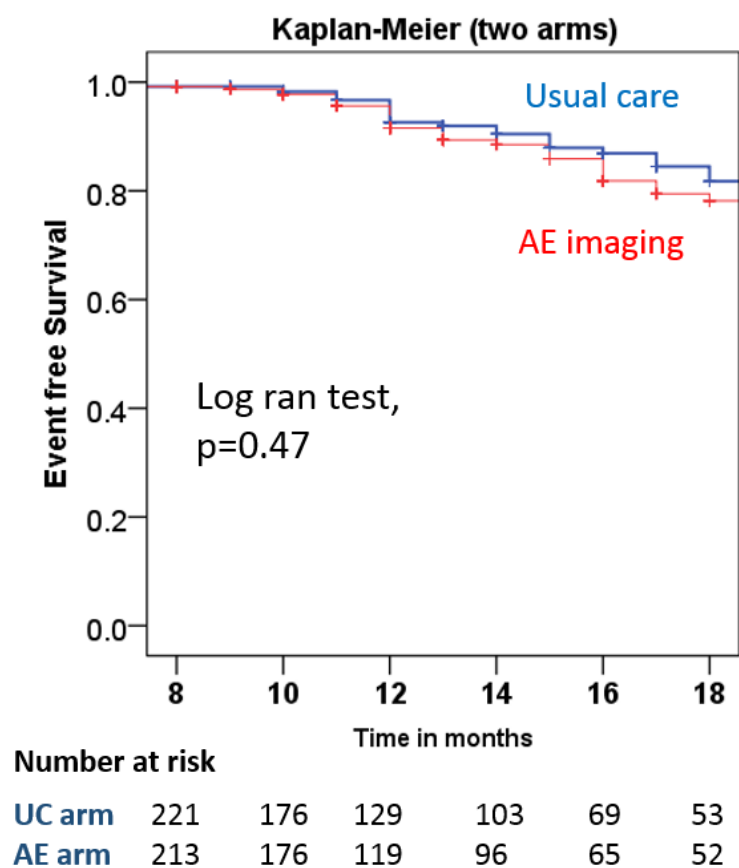


Figure 3. Medication initiation and up-titration in two arms

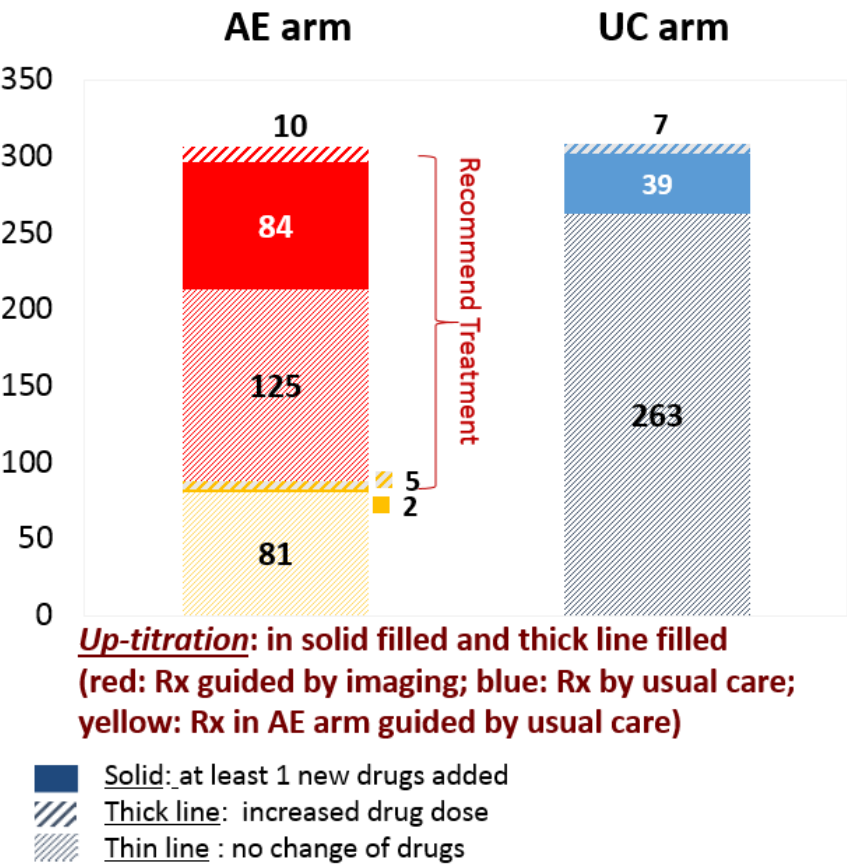


Figure 4. Kaplan-Meier analysis of outcome between abnormal GLS, DD and abnormal GLS+DD

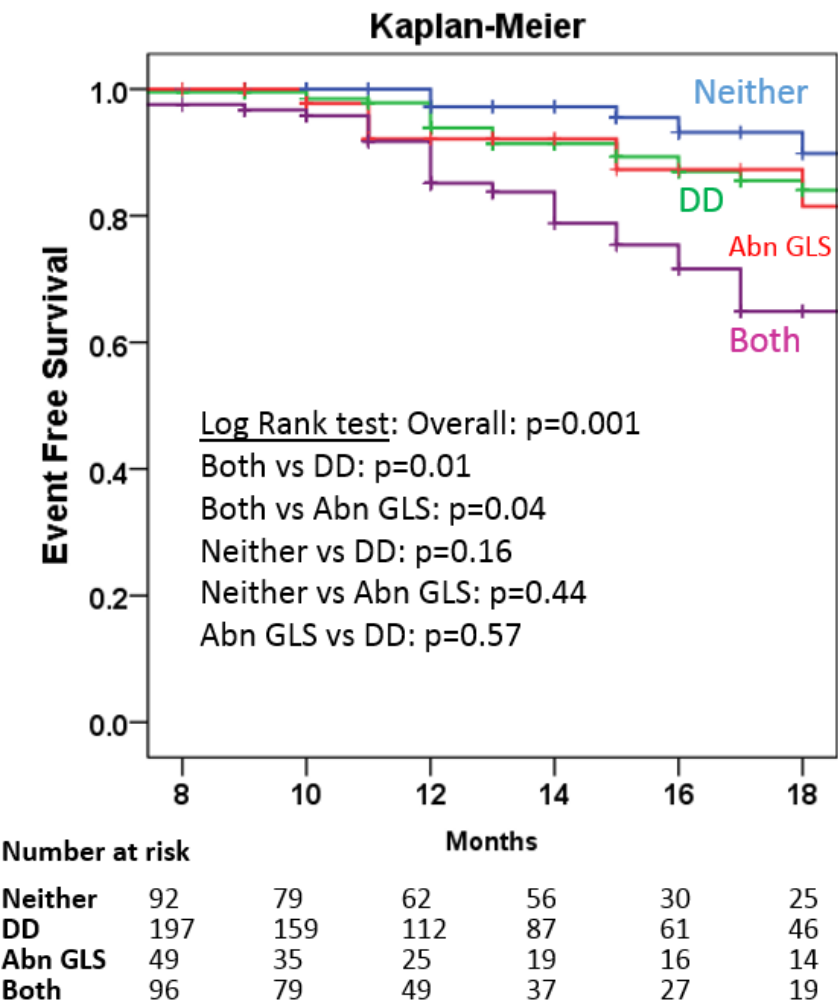


Table 1. Baseline clinical, social economical and echocardiographic characteristics of two randomized groups - “usual care, UC” versus “advanced echocardiography, AE”

	UC (n=310)	AE (n=308)	p value
Demographic and clinical characteristics			
Age (year)	70 (67-74)	70 (67-74)	0.22
Age>75 year, n (%)	54 (17)	54 (18)	0.97
Gender male, n (%)	140 (45)	152 (49)	0.29
Body Mass Index (g/m ²)	29 (26-32)	29 (26-33)	0.89
Systolic blood pressure (mmHg)	140 (128-150)	140 (129-149)	0.88
Diastolic blood pressure (mmHg)	82 (75-89)	81 (75-88)	0.58
Ever Smoking, n (%)	152 (49)	150 (49)	0.93
ARIC score (%)	5.8 (3.7-10.7)	6.3 (3.4-11.9)	0.67
T2DM, n (%)	158 (51)	155 (50)	0.87
Obese, n (%)	139 (45)	135 (44)	0.8
Hypertension, n (%)	243 (78)	243 (79)	0.88
Previous Chemotherapy, n (%)	32 (10)	43 (14)	0.17
Family history, n (%)	107 (35)	117 (38)	0.37
Previous heart condition, n (%)	25 (8)	26 (8)	0.87
Charlson score	1.0 (0-2)	1.0 (0-2)	0.52
ACEi, n (%)	208 (67)	208 (68)	0.91
Beta-blocker, n (%)	19 (6.1)	14 (4.5)	0.38
Calcium Antagonists, n (%)	60 (21)	70 (25)	0.32
Diuretics, n (%)	44 (15)	35 (12)	0.31
Lipid lowering medication, n (%)	166 (58)	149 (52)	0.19
Anti-platelets, n (%)	107 (37)	105 (37)	0.94
6 minute walk distance (meters)	485 (432-546)	480 (410-530)	0.19
Patient report outcome measures (PROMs)			
Duke activity score index (MET)	8.3 (7.3-8.9)	8.3 (7.0-8.9)	0.94
General Health utility (EQ5D)	0.84 (0.74-1.0)	0.84 (0.77-1.0)	0.62
General Health utility (EQVAS)	80 (70-90)	80 (70-90)	0.82
Minnesota Living with HF score	1 (0-8.3)	1 (0-8.0)	0.62
Depression status (PHQ9)	2 (0-4)	1 (0-3)	0.24
Anxiety status (GAD7)	1 (0-3)	0 (0-2.8)	0.26
Socio-economic determinants			
Social economical index for areas (ranking 1-10)	4 (2-6)	4 (2-6)	0.48
Education level ≥ high school, n (%)	245 (83)	247 (82)	0.76
Living alone, n (%)	90 (30)	107 (36)	0.12
Private Health insured n (%)	216 (72)	211 (71)	0.79
Total Number of medication pills /day	5 (3-8)	5 (3-8)	0.46
Baseline echocardiographic characteristics			
Valve disease*, n (%)	11 (3.5)	13 (4.2)	0.67
Left ventricular ejection fraction (%)	64 (60-68)	64 (60-68)	0.75
GLS (%)	18.5 (16.7-20.3)	18.4 (16.8-20.1)	0.67
E/e' (average)	8.4 (7.1-10.3)	8.4 (7.1-10.3)	0.66
Abnormal GLS (18 cutoff), n (%)	103 (33)	113 (37)	0.37
Diastolic dysfunction (≥ grade I), n (%)	206 (67)	211 (69)	0.58
Diastolic dysfunction (≥ grade II), n (%)	43 (14)	41 (13)	0.92
Left ventricular hypertrophy, n (%)	42 (14)	39 (13)	0.74
Left atrial enlargement, n (%)	117 (38)	104 (34)	0.29
Abnormal E/e', n (%)	39 (13)	34 (11)	0.55

Abbreviations: AE=advanced echocardiography arm; ACEi=angiotensin converting enzyme inhibitors;

ARIC=atherosclerosis risk in communities; UC=usual care arm; GLS (global longitudinal Strain); T2DM=type 2 diabetes mellitus.

Valve disease includes mitral regurgitation, aortic regurgitation, tricuspid regurgitation and aortic stenosis.

Table 2. Clinical effect of screening for primary outcome

	Crude			Adjusted**	
	No. of endpoints/ total assessed* (%)	HR (95% CI)	p value	HR (95% CI)	p value
New HF and CV death					
Advanced Imaging (AE) versus Usual care (UC)	37/275 (13%) 30/290 (10%)	1.22 (0.75, 1.97)	0.43	0.23 (0.05, 0.95)	0.04
SBHF identified by imaging versus SBHF not identified or unknown	35/219 (16%) 32/346 (9%)	1.99 (1.23, 3.23)	0.01	7.01 (1.65, 29.9)	0.01
Treatment up-titration (+) versus Up-titration (-)	24/143 (17%) 43/422 (10%)	1.51 (0.91, 2.49)	0.11	1.09 (0.64, 1.86)	0.75

* A total of 565 out of 618 were assessed for primary outcome at 1 year follow up

**Adjusted for (in the model as binary variables): randomization status + SBHF by imaging + Treatment up-titration

Table 3. Medication side effects and alterations

	AE arm	UC arm	total
ACEi/ARB			
no change in dose	7	2	9
reduce dose	0	0	0
ceased but stay on trial	2	0	2
ceased and wish to withdraw	1	0	1
Beta blocker			
no change in dose	8	1	9
reduce dose	2	2	4
ceased but stay on trial	2	1	3
ceased and wish to withdraw	3	0	3
total	25	6	31

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