DETECTION OF STAGE B HEART FAILURE IN TYPE 2 DIABETES MELLITUS

BY

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Declaration of originality

This thesis contains no material, which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis. To the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of Ethical Conduct

All research associated with this thesis abides by the International and Australian codes on human and animal experimentation, and all procedure were approved by the Tasmanian Human Research Ethics Committee for the study outlined in this thesis. All individual participants provided written informed consent for involvement in the research study.

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Scientific Presentations arising from this thesis

International

European Society of Cardiology 2017

- Oral presentation – *"Global Longitudinal Strain: the Incremental Prognostic Value in Asymptomatic T2DM with Preserved Ejection Fraction in the Community"*
- *"Subclinical LV Dysfunction, Functional Capacity and Clinical Outcomes in Stage A Heart Failure: Are All Etiologies the Same?"*

Cardiac Society of Australia and New Zealand 2017

- *"Incremental Value of Global Longitudinal Strain in Predicting Heart Failure in Patients with Type 2 Diabetes Mellitus"*
- *"Changes in Longitudinal Myocardial Deformation in T2DM with Preserved Ejection Fraction During a 2-year Observation"*

American College of Cardiology 2016

- *"Cost-Effectiveness of Myocardial Imaging to Identify Subclinical Left Ventricular Dysfunction in Elderly Patients with Asymptomatic Type 2 Diabetes"*
- *"Subclinical LV dysfunction, exercise capacity and quality of life in T2DM vs other Stage A heart failure – An Observational substudy of the TasELF study"*
- *"Association of Left Ventricular Mass with Systolic Deformation and LV Diastolic Dysfunction: Effect of Differences in Stage A Heart Failure Etiology"*

European Society of Cardiology 2015

- *"Exercise Intolerance in Older Asymptomatic Type 2 Diabetes: Left Ventricular Dysfunction, Diabetes Control, Therapy or Insulin Resistance?"*

American Heart Association 2014

- *"Clinical Prediction of Incident Heart Failure in Type 2 Diabetes Mellitus in 507,637 Patients: A Systematic Review and Meta-Analysis"*

National

Annual Graduate Research Conference, University of Tasmania 2015

- *"Clinical Prediction of Incident Heart Failure in Type 2 Diabetes Mellitus in 507,637 Patients: A Systematic Review and Meta-Analysis"*

Australia Chinese Association for Biomedical Sciences Satellite Conference, Menzies Institute for Medical Research 2014

- *"Prediction of Incident Heart Failure in Type 2 Diabetes Mellitus"*

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Abbreviations

6MW – Six-minute walk

6MWT- Six-minute walk test

6MWD- Six-minute walk distance

AA - aldosterone antagonist

AF – atrial fibrillation

ACEi – angiotensin-converting-enzyme inhibitor

BB – beta-blocker

BMI - body mass index

BP - blood pressure

SBP - systolic blood pressure

DBP - diastolic blood pressure

BSA – body surface area

CAD – coronary artery disease

CHD- Congenital heart disease

DASI - Duke Activity Status Index Questionnaire

EQ-5D - EuroQol-5 Dimensions questionnaire

EF – Ejection fraction

E - mitral valve early peak velocity

A - mitral valve atrial contraction velocity

E/A - Transmitral diastolic flow velocity ratio

E/e’ – ratio of transmitral flow to annular tissue velocity

e’ - early diastolic medial and lateral mitral annular velocity

DT - deceleration time

eGFR - estimated glomerular filtration rate

ESRD - end-stage renal disease

GLS – global longitudinal strain

HbA1c – hemoglobin A1c

HR – heart rate

HT - hypertension

HFpEF - HF patients with preserved ejection fraction

IR - insulin resistance

MI - myocardial infarction

LAV - left atrial volume

LAE - left atrial enlargement

LVEF – ejection fraction

LV - left ventricle

LVD - left ventricle dysfunction

LVSD - left ventricle systolic dysfunction

LVDD - left ventricle diastolic dysfunction

LVH - left ventricle hypertrophy

LVM - left ventricle mass

LVMi - left ventricle mass index

METs - metabolic equivalents

PHQ-9- Patient Health Questionnaire 9

QoL – quality of life

QALY - quality-adjusted life years

STE - speckle tracking echocardiogram

SAHF – stage A heart failure

SBHF – stage B heart failure

T2DM - type 2 diabetes mellitus

UAC - urinary albumin concentration

WC - waist circumference

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Abstract

Heart failure (HF) is a complex clinical syndrome associated with significant mortality and morbidity, which leads to a significant burden for patients and healthcare systems[1,2].There is a well-established association between diabetes and HF that is partly but not entirely linked to coronary heart disease and hypertension. The Framingham Study firmly established the epidemiologic link between diabetes and HF[3, 4]. This study showed the risk of HF was increased 2.4-fold in men and 5-fold in women[5, 6], and 12% diabetes already have established HF[7]. The frequency of HF in diabetic patients is even higher among elderly adults with a 3.3% annual incidence rate[7].

HF is usually a progressive condition. In recognition of the importance of this concept, American College of Cardiology (ACC) and the American Heart Association (AHA) have identified four stages of HF[8]. Stage A HF (SAHF) comprises patients with any of the HF risk factors (diabetes, hypertension, coronary artery disease, metabolic syndrome and obesity) without evidence of left ventricular (LV) remodelling or low ejection fraction (EF). LV hypertrophy and reduced LVEF is associated with even greater risk of incident HF, hence, asymptomatic patients with these structural changes are categorized as having stage B HF (SBHF). Stage C and Stage D HF is clinical symptomatic HF while stage D is the end stage of HF. Patients may only move forward through the stages and not regress. The AHA and ACC recommend that an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) and a beta-blocker (BB) should be prescribed in the presence of Stage B HF (SBHF), to reduce the risk of developing symptomatic HF[9]. Two considerations are important. First, the recommendation is based on the assumption that patients with non-ischaemic HF respond in the same way as the evidence involving patients with ischemic heart disease. Second, a large number of patients are classifiable as Stage B HF, but currently unrecognised.

If there is a benefit in HF prevention, screening programs may need to be implemented to detect these individuals, but the optimal tools for doing so are unclear. The most commonly used measure of systolic function in clinical practice, LVEF, is not a robust index of myocardial or chamber contractility for this purpose because of its load dependence and sensitivity to chamber size. A more robust echo marker is desired. Global longitudinal strain (GLS) by speckle tracking imaging is potentially a useful marker as it measures longitudinal function being an early marker of disease and conveys more detailed information about LV systolic function than EF can provide. However, the usefulness of GLS in clinical decision-making still needs to be tested.

T2DM is an important HF risk factor, and provides a readily-recognised group for screening for SBHF. This thesis investigates the clinical role and implication of early detection of HF by echocardiography in elderly asymptomatic patients with T2DM.The work in this thesis is divided into four parts:

The first part (chapter 2) sought to improve the assessment of HF risk in patients with T2DM – a step that would be critical for effective HF screening. A systematic literature search and meta-analysis was performed to determine the effect size of each risk factor for incident HF in T2DM. Among elderly patients with T2DM, five common clinical variables are associated with significantly increased risk of incident HF and T2DM patients with these risks represent a target group for HF screening.

The next part (chapter 4-8), pertains to the Tasmanian Study of Echocardiographic detection of Left ventricular dysfunction (Tas-ELF study), which sought to determine the role of early detection of HF by GLS in patients with T2DM in the Tasmanian community. Several studies were carried out to understand this. First, we assessed the association between insulin resistance (IR) and impaired exercise capacity to better understand the cause of exercise intolerance in

T2DM, which is associated with LV dysfunction and adverse cardiac outcome including HF. In addition, this study supports the contribution of diabetic myocardial disease that contributes to the development of HF in diabetes[10]. Second, longitudinal community studies were carried out to clarify the rate of progression through asymptomatic stage A to stage B HF in both diabetes and non-diabetes, in order to addresses the incidence and predictors of HF and all-cause mortality in this cohort, and define strategies for prevention of HF progression in T2DM. The result suggested the predictors of prognosis in SAHF patients due to T2DM and other causes of SAHF were different. SAHF due to T2DM had worse subclinical LV function, functional capacity and adverse outcome than other causes of SAHF. Impaired GLS was independently associated with prognosis in T2DM-SAHF, whereas not for other-SAHF patients. This study emphasised that not all types of SAHF are the same, and better targeting of interventions at the most vulnerable SAHF group – those with T2DM – seems appropriate. Third, we evaluated different echocardiographic markers including increased LV mass index, left atrial enlargement, LV diastolic dysfunction and impaired GLS as potential echocardiographic features of stage B HF in T2DM. The result suggested that GLS would be the optimal echocardiographic feature of stage B HF in T2DM for community screening. Fourth, the features associated with incident HF risk in T2DM are incompletely understood. In addition to myocardial disease, a number of other factors including mental factors are likely to influence the process. Therefore, we explored the association of depression and incident HF in elderly T2DM without any baseline cardiovascular symptoms. The result suggested that depression is prevalent in asymptomatic elderly patients with T2DM, and its role as an independent and incremental association with incident HF is an important confounder to the effect of myocardial disease. Finally, we observed the evolution of longitudinal changes of GLS among elderly T2DM patients, as little is known about the natural history of GLS over time. During our 2-year observation, the change of GLS in asymptomatic T2DM with

preserved EF was only mild, but mental status had an independent association with worsening GLS.

The last part (chapter 9) was a study that used a Markov model to assess the cost-effectiveness among different strategies for HF prevention from a healthcare payer perspective. The three strategies were elderly asymptomatic patients with T2DM receiving; 1) usual care; 2) primary prevention without screening; 3) screening of LVD and GLS guided prevention. The results showed that based on this Markov model, screening for asymptomatic LV dysfunction (evidenced by abnormal GLS) in elderly patients with T2DM appears cost-saving. These results could be used to inform clinical trials aimed at the early detection and treatment of LV dysfunction, with the intent of preventing the development of HF in T2DM.

Conclusions. The results of the studies contained within this thesis suggest that subgroups of patients with diabetes are at the highest risk, and suitable for screening. Detection of LV dysfunction by strain imaging can predict the development of HF and all-cause of mortality in elderly asymptomatic patients with T2DM. Preventive treatment guided by GLS for HF prevention in elderly patients T2DM appears to be cost-saving.

Chapter 1. Introduction

Published in part in[11]:

- Wang Y, Marwick TH. Update on Echocardiographic Assessment in Diabetes Mellitus. *Curr Cardiol Rep*. 2016; 18: 85.

1.1 Epidemiology of Heart Failure in Type 2 Diabetes Mellitus

1.1.1 Epidemiology of Heart Failure

Heart failure (HF) is a common clinical syndrome associated with high morbidity and mortality. It has become a major public health problem, affecting at least 26 million worldwide[12]. This epidemic is one of increased prevalence, largely due to increased survival, and may be attributable to increased incidence – although we have not yet witnessed this. In Australia, a recent systematic review reported that the overall prevalence of HF ranges between 1-2 %, and is similar to western countries [1]. (**Figure 1.1**) HF incidence varies from studies and countries. Currently in US, there are 915,000 incident HF presentations annually, giving an event rate approaching 10/1,000 person-years among individuals ≥65 years[2]. HF incidence is higher in the aging population, particularly in patients aged ≥65 years. The majority of prevalent HF is due to heart failure with preserved ejection fraction (HFpEF) [2].

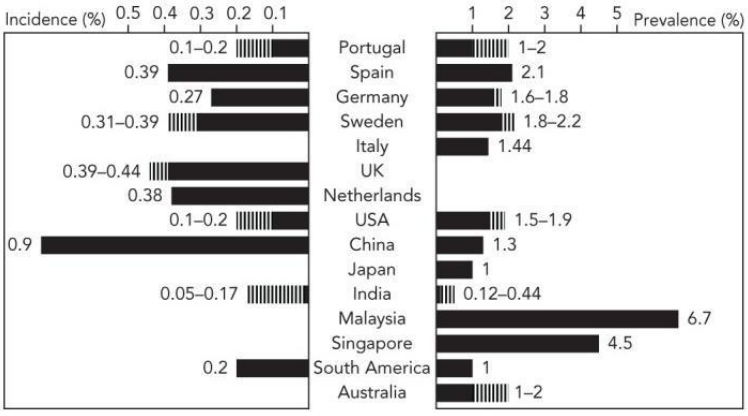


Figure 1.1 Prevalence and Incidence of Heart Failure Worldwide

Savarese G and Lund LH. Cardiac Failure Review. 2017; 3 (7-11)

The cost of HF continues to increase and has become a heavy burden to the economy and healthcare system. In United States (US), more than 10% of the total health expenditure was attributed to cardiovascular diseases in 2012 (approximately $31 billion), and between 2012 to 2030, the total costs are expected to increase by 127% [13].

1.1.2 Definition and Classification of Heart Failure

According to American Heart Association/American College of Cardiology (AHA/ACC) guidelines, the definition of HF is "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood" [14, 15]. Chronic heart failure (CHF) is a chronic progressive condition that is often referred to simply as "Heart Failure". As HF is a complex clinical syndrome but not a disease, the aetiology of the problem should always be considered. The diagnosis of HF is mainly based on clinical examination including history and physical examination, chest radiography, electrocardiogram, laboratory assessment and echocardiogram. There are several instruments have been proposed to diagnose HF in particular including the Framingham criteria[16], the Gothenburg criteria[17], the Boston criteria[18] and the European Society of Cardiology criteria[19]. These criteria all rely on similar indicators from the clinical examination, and the most widely used are the Framingham criteria (**Table 1.1)**. Compared with other criteria, the Framingham criteria can capture more possible HF providing 100% sensitivity and is less influenced by time and diagnostic tests [12]. The Framingham criteria is well suited for research and long-term trends.

Table 1.1 Framingham CHF clinical diagnosis criteria (requiring the simultaneous presence of at least 2 major or 1 major with 2 minor criteria).

MAJOR CRITERIA	MINOR CRITERIA
▪ Paroxysmal nocturnal dyspnea or orthopnea ▪ Neck vein distension ▪ Rales ▪ Cardiomegaly ▪ Acute pulmonary edema ▪ S3 gallop ▪ Increased venous pressure≥16cm water ▪ Circ.time≥25 sec ▪ Hepatojugular reflux ▪ Weight loss≥4.5 kg in 5 days in response to treatment	▪ Ankle edema ▪ Night cough ▪ Dyspnea on exertion ▪ Hepatomegaly ▪ Pleural effusion ▪ Vital capacity decreased 1/3 from maximum ▪ Tachycardia rate of ≥120 beat/min

The current ACC/AHA heart failure guidelines defines the evolution of HF in four stages. Stage A heart failure (SAHF) exists in subjects with risk factors for heart failure (HF), in the absence of structural heart disease or symptoms [14]. These risk factors include obesity, hypertension, atherosclerosis, diabetes mellitus (DM), exposure to cardiotoxins and family history of HF, and they may be present in up to a third of subjects aged ≥45 years. The natural history of SAHF is that patients may progress to functional or structural abnormalities (i.e. reduced ejection fraction, left ventricular hypertrophy and chamber enlargement) without symptoms (stage B, SBHF), clinical manifestations of HF (stage C) and eventually, refractory or end-stage HF (stage D)[8] (**Table 1.2**.)In this system classifies the evolution of HF, rather than the level of symptoms captured in the New York Heart Association (NYHA) functional classification system. Thus, patients only move forward from prior stages to an advanced stage and do not regress. Note that, few certain causes of HF are reversible – including those due to tachycardia-mediated cardiomyopathy, toxins and mitochondrial abnormalities[20]. The current ACC/AHA HF classification system describes the progression of HF from HF risks through subclinical LV dysfunction, to symptomatic clinic HF and end-stage HF. In contrast, the NYHA class system is focused on the level of HF symptoms and functional limitations. The identification of HF risk should stimulate efforts to identify SBHF, as therapeutic interventions in this setting may prevent the development of clinical HF and improve prognosis[8].

Table 1.2 American College of Cardiology/American Heart Association Classification of Heart Failure

Stage A High risk for HF but without structural heart disease or symptoms
Stage B Structural abnormalities but without signs of symptoms of HF
Stage C Structural heart disease with prior or current symptoms of HF
Stage D Refractory or end-stage HF requiring specialized interventions

1.1.3 Incidence and Prevalence of Heart Failure in Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes; by 2025, it is expected to affect 380 million people throughout the world[21]. Diabetes is a strong and independent risk factor for cardiovascular disease (CVD), and the management of cardiovascular health will be a cornerstone of managing the T2DM epidemic. Results from a health maintenance organization show that about 12% of 10,000 patients with diabetes had HF at baseline, and 3.3% of the rest developed heart failure during each year of follow-up [5, 22]. The Framingham Heart Study reported a 2 to 5 fold increased HF risk in T2DM, and the frequency of HF is even higher among elderly subjects [6]. Several subsequent studies have confirmed the significant increase in incident HF in patients with T2DM compared with non-diabetic patients[5, 7, 22-26]. Nichols et al. published a retrospective study demonstrating that the odds ratio (OR) for incidence of HF in patients with T2DM is approximately 2.5 compared with those without diabetes[5, 22]. A study from the Reduction of Atherothrombosis for Continued Health (REACH) registry, an international registry of 45,227 individuals and 4-year follow-up published in 2015, reported that T2DM was associated with a 33% higher risk of hospitalization for HF (9.4% vs 5.9%; adjusted OR 1.33, 95% CI 1.18-1.50) compared with non-diabetic subjects[23].

1.1.4 Prognosis of Heart Failure with Type 2 Diabetes Mellitus

The presence of T2DM can adversely affect long-term survival as well as risk of hospitalization in patients with CHF. The 5-year survival rate of HF is analogous to that of malignancy and the morbidity and mortality rates of diabetic heart failure are 4-8 fold higher than in the non-diabetic population [27]. The mortality ratio is approximately 9-fold higher in elderly patients [7]. A recently published systematic review including 31 registries and 12 clinical trials with 381,725 patients with acute and chronic HF over a median follow-up of 2 years showed that the presence of diabetes was associated with a greater risk of all causes of death (random-effect HR 1.28, 95% CI 1.20-1.50) as well as cardiovascular death (HR 1.34, 95% CI 1.20-1.49)[28].

However, the trend for in-hospital mortality in HF patients with diabetes reported from a large US national inpatient sample survey from 2000 to 2010 has significantly decreased during past decade, despite increased diabetes prevalence and comorbid conditions [29].

In addition, among patients with T2DM, those who develop their first episode of HF have markedly worse survival than those who are free of HF. A study of 115,803 elderly US patients with diabetes showed that incident significantly increased with age and diabetes-related comorbidities, and in patients with diabetes, incident HF was significantly associated with high mortality when compared with those who remained HF free over 60-months of follow-up (HR 10.6, 95% CI 10.4–10.9)[7] (**Figure 1.2**).

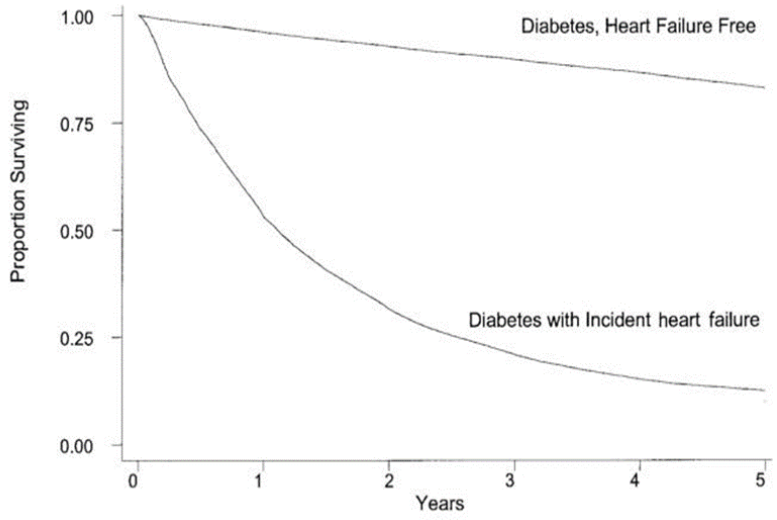


Figure 1.2 Five-year Kaplan-Meier survival estimates for 115,803 adults age ≥65 years in fee-for-service Medicare with diabetes by incident heart failure status.

Bertoni AG, et al. Diabetes Care. 2004; 27(3): 699-703

1.2 Cardiovascular Risks Associated with Type 2 Diabetes Mellitus

1.2.1 Ischemic Heart Disease in Type 2 Diabetes Mellitus

Ischemic heart disease (IHD) is recognized as the leading cause of morbidity and mortality in T2DM – to the extent that DM contributes to 75% of deaths among all forms of CVD [30].

Compared with subjects without diabetes, patients with T2DM have a higher prevalence of coronary heart disease (CHD) and are more likely to have myocardial infarction (MI). Stress echocardiography is an effective modality for diagnosis and prognostic evaluation of IHD in T2DM [31]. However, screening for IHD has not proven effective [32] – first, because the observed event-rates are less than anticipated in the era of considering DM as an IHD-equivalent [33, 34], and second, because of the limited benefits of interventional responses to previously unrecognized IHD [35].

1.2.2 Increased Heart Failure Risk and Mortality in Type 2 Diabetes Mellitus

The independent association of HF with T2DM is not entirely related to atherosclerosis and hypertension. Diabetic cardiomyopathy (DCM), which is manifest by cardiac functional abnormalities [36, 37], is defined as diabetes-associated ventricular dysfunction that is not attributable to other causes [38]. Subclinical left ventricular systolic and/or diastolic dysfunction (LVSD/LVDD) may be a precursor of subsequent overt HF in T2DM [39], and the risk of progression from asymptomatic LVSD or LVDD to symptomatic HF is increased in DM [40]. However, ~50% of subjects with LVSD remain unidentified [36].

Pathophysiologic manifestations of DM include coronary microvascular or macrovascular injury, myocardial fibrosis and autonomic dysfunction, and echocardiography permits demonstration of the contributions of functional disturbance and left ventricular hypertrophy (LVH) [41]. Disturbed myocyte contraction and relaxation are related to the underlying metabolic disturbances of both pre-diabetes and diabetes - hyperinsulinemia, inflammation and oxidative stress. In addition, structural changes arise from changes in extracellular matrix proteins, such as excess deposition of collagens, abnormal glycosylation/crosslinking, and alterations in diastolic compliance [42]. Impaired myocardial relaxation and cardiomyocyte resting tension could give rise to increased LV stiffness and diabetic autonomic neuropathy leads to

sympathetic imbalance, which in turn drives enhanced fatty acid metabolism and fetal gene expression. Activation of the angiotensin-renin system is linked to increased deposition of myocardial collagen, advanced glycation and products (AGEs), and cardiac remodelling/hypertrophy [36]. Diabetic microangiopathy, vascular endothelial dysfunction and coronary flow reserve impairment may arise from small vessel disease[43].

1.2.3 Atrial fibrillation in Type 2 Diabetes Mellitus

Apart from contributing to CHD and HF, DM also favours the occurrence of arrhythmias - especially among women, although the underlying mechanism is still unclear. In the Framingham Heart Study, DM was associated with an increased risk of new-onset atrial fibrillation (AF) among both sexes (odds ratio, OR 1.4 for men and 1.6 for women) at 38 year-follow-up [44]. Subsequently, a large observational cohort showed that DM was an independent determinant of AF prevalence compared with the non-DM population (3.6% vs 2.5%, P<0.0001) and also significantly predicted incident AF in women (HR 1.26, 95% CI 1.08-1.46]) but not in men (HR 1.09, 95%CI 0.96-1.24) at a mean follow-up of 7.2 years [45]. AF and diabetes share common antecedents such as obesity, atherosclerosis and hypertension, which can be compiled into a clinical risk score [46]. The role of DM in embolic risk is reflected in its contribution to the CHA_2DS_2-VASc score [47].

1.3 Screening for Diabetic Cardiomyopathy: An Expression of Stage B Heart Failure

In undiagnosed patients with preclinical DCM, treatment is not initiated until the development of symptoms (stage C or D HF) [48]. At this stage, changes may be irreversible and the ability to change the trajectory of the illness may be limited. Consequently, the AHA/ACC heart failure guidelines have drawn attention to the earlier stages of HF. DM is a key HF risk factor, meaning

that all patients are considered to be in stage A HF. These patients may develop abnormal LV structure (LVH) or function, which are features of stage B HF. These patients are at even greater risk of transitioning to symptomatic stage C HF – usually HFpEF.

1.3.1 Role of Diabetes in Pathophysiology of HFpEF

Pathophysiologic manifestations of DM include coronary microvascular or macrovascular injury, myocardial fibrosis and autonomic dysfunction, and echocardiography permits demonstration of the contributions of functional disturbance and LVH [41]. Disturbed myocyte contraction and relaxation are related to the underlying metabolic disturbances of both pre-diabetes and diabetes - hyperinsulinemia, inflammation and oxidative stress. In addition, structural changes arise from changes in extracellular matrix proteins, such as excess deposition of collagens, abnormal glycosylation/crosslinking, and alterations in diastolic compliance [42]. Impaired myocardial relaxation and cardiomyocyte resting tension could give rise to increased LV stiffness and diabetic autonomic neuropathy leads to sympathetic imbalance, which in turn drives enhanced fatty acid metabolism and foetal gene expression. Activation of the angiotensin-renin system is linked to increased deposition of myocardial collagen, advanced glycation and products (AGEs), and cardiac remodelling/hypertrophy [36]. Diabetic microangiopathy, vascular endothelial dysfunction and coronary flow reserve impairment may arise from small vessel disease[43].

Advanced echocardiographic techniques including tissue Doppler imaging and deformation imaging can not only detect subclinical DCM, but also define the contribution of each aspect of pathophysiology. The ratio (E/e′) of pulsed Doppler early diastolic transmitral peak inflow velocity (E) to pulsed tissue Doppler mitral early diastolic annular velocity (e′) may be clinically valuable to obtain information about LV filling pressure (LVFP) and to unmask the pseudonormal Doppler inflow pattern, potentially a turning point in the progression towards

advanced heart failure. The E/e′ ratio can also be assessed following exercise, which offers a valuable perspective in patients who are dyspnoeic on exertion. In the absence of epicardial coronary artery stenosis, the ultrasound assessment of coronary flow reserve (CFR) may identify dysfunction of the coronary microcirculation [49]. Deformation imaging allows alterations of functional markers (peak strain and strain-rate) to be detected before the development of myocardial systolic dysfunction in patients with DM but without overt heart disease [50].

1.3.2 Detection of Diabetic Cardiomyopathy

Numerous epidemiological and clinical studies have supported the existence of DCM, which is defined as left ventricular dysfunction (LVD) and/or left ventricular hypertrophy (LVH) independent of hypertension and coronary disease or other potential etiologies, that appears to result in cardiovascular complications and congestive HF.[51] Echocardiography has been the most widely used technique to determine the prevalence of these LV structural or functional changes. The structural evidence of preclinical DCM is common in older subjects with diabetes, ranging from 36-48% [52, 53].

1.3.2.1 Left Ventricular Hypertrophy.

LVH is highly prevalent in asymptomatic DM; Kiencke et al [53] reported that 24% older diabetic subjects without evidence of heart disease had LVH while Dawson et al [54] reported 43% in an unselected older cohort using the same criteria of LVH. However, as hypertension, atherosclerosis, obesity, abnormal lipid profile and LVH frequently coexist, it has been controversial as to whether T2DM has an independent association with increased LV mass (LVM). Apart from hypertension, the two main risk factors for LVH in diabetes are insulin resistance (IR) and visceral adiposity [55]. Metformin, as an insulin sensitizer, is associated with an attenuation of LVH in hypertensive diabetes and longer duration of metformin use is

associated with greater effect [56]. Recently, several studies have shown an association between T2DM and LVH and LV remodelling, in the absence of hypertension or atherosclerosis. In the multi-ethnic Northern Manhattan Study (NOMAS) cohort study, T2DM increased the risk of LVH by about 1.5-fold, independent of various covariates [57]. Al-Daydamony et al. reported that normotensive patients with the metabolic syndrome had significantly higher LV wall thickness, LVM and incident LVH compared with healthy controls [56]. However, in the Framingham study, DM was associated with increased LV mass only in women, in contrast to the Cardiovascular Health Study, where this association was reported in both sexes [58, 59].

EKG is a traditional and relatively inexpensive approach in the diagnosis of LVH. In daily clinical practice, LVH is usually first noticed on the basis of 12-lead ECG abnormalities. However, EKG is considered as an approach with lower sensitivity or specificity to diagnose anatomic LVH compared with imaging with either echocardiography or cardiac magnetic resonance imaging. Using echocardiography as standard, the sensitivity for different electrocardiographic criteria is <30%[60, 61]. Because of this problem with low sensitivity, particularly in the elderly[60], echo was used to determine LVH in our study.

The prevalence of LVH by echocardiography in subjects with T2DM is highly dependent on indexation methodology. LVM is most widely indexed to either body surface area (BSA), height$^{1.7}$or height$^{2.7}$. Chowdhury et al have recently proposed that LVH indexed to BSA to the power of 115/95shows the best predictive power for both short- and long-term cardiovascular events [62]. Cardiac magnetic resonance imaging (CMR) is the established non-invasive gold standard measurement for LV volume and LVM due to its high accuracy, better spatial resolution, less restricted viewing window and reproducibility [63, 64]. While 2D echocardiography is unlikely to miss substantial LVH, a low concordance was found between the diagnosis of LVH by 2D echo and CMRi; the presence of LVH by CMRi was found nearly twice as commonly as by echocardiography in the same population [65]. 3D echocardiography

has closed this gap between echocardiography and CMR, but while it provides the optimal echocardiographic means for quantifying LV volume and mass, it still presents challenges.

1.3.2.2 LV Diastolic Dysfunction.

Both diabetes and glucose intolerance have a negative influence on LV diastolic filling, and abnormal diastolic function often manifests in the presence of normal systolic function. Diastolic dysfunction in T2DM has been reported in between 27-75% in different populations and with different definitions.[53,66, 67]LV diastolic dysfunction is significantly associated with diabetes duration, glycaemic control, level of serum-free fatty acids and the type of hypoglycaemic medication [68]. Unfortunately, the diagnosis of diastolic dysfunction may be complicated, and recent guidelines have re-emphasized the importance of transmitral flow and tissue Doppler measurements[69]. Increased left atrial volume is a marker of prolonged elevation of filling pressures.

1.3.2.3 Left Ventricular Strain.

Not only diastolic, but also systolic function is impaired in T2DM. Despite widespread use, LV ejection fraction (EF) may be insensitive to minor changes in LV function. The early detection of both systolic and diastolic myocardial dysfunction may be more readily accomplished using strain and strain-rate imaging. From the technical standpoint, strain measurement is a measure of cardiac tissue deformation, used for quantification of regional left ventricular (LV) function. During ventricle contraction and relaxation, the myocardium shortens, thickens and lengthens. The relative change in length of myocardium during contraction and relaxation (expressed as percentage of resting length) defines strain as a dimensionless measure (shortening is negative and lengthening is positive). Strain imaging can be measured by tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE) -

currently, STE is the most widely used method to measure strain as it is independent of imaging angle.

As the ventricle contracts in systole, there is longitudinal shortening (negative), circumferential shortening (negative) and transmural (wall) thickening (positive). Global longitudinal strain (GLS) has been well validated against sonomicrometry and MRI[70-72], with a normal range of >18%[73, 74]. GLS is a more robust marker than standard parameters such as ejection fraction (EF) for several reasons; a) it is automated, b) averaging of individual segments over the entire length of the myocardial wall is a means of controlling random noise, c) it is informed by the entire myocardium within the region of interest rather than designation of the myocardial border[75]. However, like any ejection-phase index, GLS is load (especially afterload-) dependent, to a similar degree to EF. Nonetheless, GLS is superior to EF because it measures longitudinal function, which is an early marker of disease. In contrast, EF is relatively insensitive to subclinical abnormalities of LV function and mainly determined by circumferential strain[76], so GLS is not strongly reflected in EF. This suggests that GLS conveys more detailed information about LV systolic function than EF can provide.

STE is feasible with both 2DE and 3DE, although 2D is the most reproducible approach for assessing LV systolic function. The assessment of GLS using 2D is feasible as a routine echo assessment in most patients[77-79], but it is affected by image quality, BMI, age and atrial fibrillation. For 3DSTE, demographic, cardiac factors and technical requirements may all influence the values[80-82]. Currently, the feasibility of 2D STE is higher than it in 3D in daily practice as 3D[82]. The low intra- and inter-observer reproducibility of GLS values has been confirmed in many studies[74, 83-85]. In addition, the variability of GLS measurement among different vendors is small, and was superior to conventional echocardiographic measurements in many cases[86].

Previous studies have shown that in asymptomatic T2DM, the reported prevalence of abnormal global longitudinal strain (GLS) (≥-18%) ranges from 37-54% (**Figure 1.3**) [87, 88]. Radial and circumferential strains have been shown to be sensitive for detection of early LV contractile dysfunction in diabetic mice. However, epidemiological studies in patients with uncomplicated T2DM have found impairment of LV longitudinal systolic and diastolic function, with preserved circumferential and radial function [89, 90]. 3D strain offers a means of overcoming artefacts due to through-plane motion [91], but this technique has significant challenges for measuring strain/strain rate.

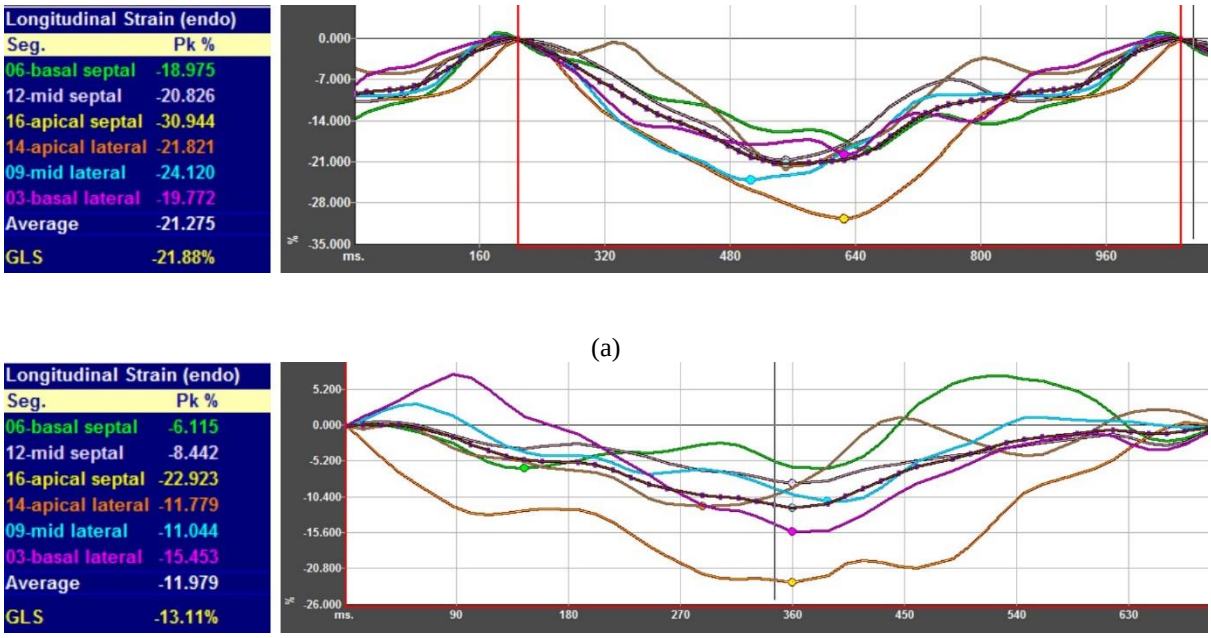


Figure 1.3. LV longitudinal strain curves in the apical 4-chamber view of asymptomatic individuals with DM and normal EF. The normal subject (a) has a normal global strain (GLS) of -22% and the curves are reasonably homogeneous. Currently, GLS is more robust than are segmental strains. The patient with subclinical LV systolic dysfunction (b) has a reduced GLS (-13%) and heterogeneity of magnitude and timing of segmental strain.

1.3.2.4 Atrial Size and Function in Diabetes.

In the absence of atrial fibrillation, left atrial (LA) enlargement (measured as LA volume) is recognised as a marker of LV diastolic dysfunction and elevated filling pressures. However, the LA does not readily reverse-remodel [92] and functional indices provide incremental prognostic value, not only for outcome, but also regarding the risk of atrial fibrillation [93]. The

conventional indices of LA function are obtained from Doppler imaging of pulmonary venous and transmitral flow, and myocardial tissue Doppler [94, 95]. Speckle tracking can measure LA strain, most simply as the total deformation attributable to LA filling and contraction, by triggering the strain curve to the R wave. An alternative is to trigger the strain calculation on the P wave, which permits a more direct focus on atrial contraction. Patients with DM develop an atriopathy, as evidenced by detection of abnormal LA mechanics in the presence of normal LA volume or standard indexes of LA function, independent of other potential clinical and echo confounders [95]. The effects of DM are incremental to co-existent hypertension [95].

1.4 Current Evidence and Literature Gaps

HF is a well-known burden to the health care system and the outcomes of treatment in late stage are poor. However, many patients with significant abnormalities of cardiac function are apparently asymptomatic. Intervention in these patients may be beneficial. It implies that early screening followed by prevention programs will need to be implemented to detect and protect these individuals. For the SBHF screening strategy, LVEF is the most commonly used measure of systolic function in clinical practice, but it is not a robust index of myocardial or chamber contractility because of its variability, load dependence and sensitivity to chamber size. GLS is a more robust marker, but before it is designated as the optimal marker, its usefulness in clinical decision-making still needs to be tested. For prevention of SBHF, angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor blocker (ARB) may be prescribed if individuals have diabetes. Once diabetic patients develop Stage B HF, a beta-blocker (BB) could be added to prevent or delay symptomatic HF. BB and ACEI could reduce the risk of incident HF but no evidence is available on the value of a prevention strategy guided by GLS. The most effective screening and intervention approach for SBHF among patients with T2DM remains unknown.

1.5 Hypothesis and Aims of This Thesis

The overall **hypothesis** of this thesis is:

Early detection by strain imaging (GLS) followed by preventive treatment for LV dysfunction can prevent the development of HF in elderly asymptomatic patients with T2DM.

Objectives:

- **Prediction on HF in T2DM.** What is the effect size of each risk factor for incident HF in T2DM? Is it feasible to develop a clinical risk score to predict HF in T2DM? Among T2DM, who should undergo screening?
- **Prevalence and functional implications.** Is the prevalence of subclinical LV dysfunction, exercise capacity, quality of life and clinical outcome different between T2DM-SAHF versus other-SAHF? What is the prevalence of stage B HF in patients with T2DM in the community?
- **Outcomes.** Do asymptomatic diabetic patients with DCM really develop into symptomatic HF? If yes, over what period? From a natural history standpoint, how does diabetic cardiomyopathy change over time? Is there any predictive factor for evolution of diabetic cardiomyopathy?
- **Development of a community screening program.** Could a community-based screening program combined with cardio-protective therapy improve the prognosis in T2DM?
- **Cost-effectiveness.** Is the preventive treatment guided by the GLS screening strategy for HF in patients T2DM cost-effective?

1.6 Structure of thesis

Chapter 1. Introduction

Chapter 2. Prediction of heart failure in patients with T2DM

Chapter 3. Methodology

Chapter 4. Association of insulin resistance with impaired function capacity in T2DM

Chapter 5. Subclinical LV Dysfunction, function capacity, quality of life and outcomes in Stage A Heart Failure

Chapter 6. Use of Echocardiographic Markers to Predict Heart Failure in T2DM

Chapter 7. Association of Depression with Heart Failure in T2DM

Chapter 8. Evolution of Subclinical Left Ventricular Function during a 2-year Observation in T2DM

Chapter 9. Cost-effectiveness implications of a HF screening program

Chapter 10. Summary and conclusions

1.6 Concluding remarks

This chapter provides an overview of the background of T2DM in stage B heart failure. Summary of the findings suggests the following;

1) Stage B heart failure is highly prevalent in patients with T2DM.

2) The mechanism behind the independent association between incident HF and T2DM is through diabetic cardiomyopathy, as defined by subclinical LV systolic dysfunction, diastolic dysfunction or LV hypertrophy.

3) A more aggressive stance towards screening for and better targeting of interventions of SBHF in diabetes seems necessary, and GLS is a potential optimal biomarker of SBHF in the community.

4) Evidence-based studies show an intervention benefit in ischemic Stage B heart failure; however, no evidence is available on the basis of a cardio-protective strategy guided by strain imaging in asymptomatic patients with T2DM.

This thesis aims to identify the highest risk diabetic patients for most effective screening and follow this with a cardio-protective intervention approach to prevent incident HF.

1.7 Postscript

The next chapter is a systematic review and meta-analysis aiming to identify predictors of incident HF among clinical, laboratory and echocardiographic parameters in patients with T2DM. This study sought to improve the assessment of HF risk in patients with T2DM – a step that would be critical for effective HF screening.

Chapter 2. Prediction of Heart Failure in Patients with T2DM

Published in part in[96]:

- Wang Y, Negishi T, Negishi K and Marwick TH. Prediction of heart failure in patients with type 2 diabetes mellitus-A systematic review and meta-analysis. *Diabetes research and clinical practice.* 2015.

2.1 Preface

T2DM is a major predictor of HF, independent of atherosclerosis and hypertension, and HF is a leading cause for hospital admissions and death in T2DM. While the outcomes of treatment in late stage HF are poor, therapy has been shown to be beneficial in the early stage of ischaemic HF with reduced ejection fraction (EF).If (as seems likely) treatment were also beneficial in early non-ischaemic HF, the recognition of early stage HF in the community would be an important step. Numerous methods including cardiac imaging tests can be used to help identify subclinical HF in T2DM. Of these, echocardiography is inexpensive and widely available, and recent developments in myocardial strain, 3-dimensional transthoracic echocardiography and echo contrast allow detection of subclinical abnormalities of heart. However, the best way of identifying the highest risk T2DM patients for screening and therapy approach remains undefined.

2.2 Abstract

Background: Heart failure (HF) is a major cause of mortality and disability in type 2 diabetes mellitus (T2DM). This study sought to improve the assessment of HF risk in patients with T2DM – a step that would be critical for effective HF screening.

Methods: A systematic literature search was performed on electronic databases including MEDLINE and EMBASE, using MeSH terms 'heart failure', 'risk factor', 'T2DM', 'cardiac dysfunction', 'stage B heart failure', 'incident heart failure', 'risk assessment', 'risk impact', 'risk score', 'predictor', 'prediction' and related free text terms. The search was limited to human studies in full-length publications in English language journal from 1946 to 2014. Univariable and multivariable relative risk (RR) and hazard ratio (HR) were obtained from each study.

Results: Twenty-one studies (n=1,111,569, including 507,637 subjects with T2DM) were included in this analysis with a follow-up ranging from 1 to 12 years. Associations between incident HF and risk variables described in ≥3 studies were reported. This association was greatest for insulin use (HR 2.48; 1.24-4.99), HbA1c 7.0-8.0% (2.41; 1.62-3.59), 5 years increase in age (1.47; 1.25-1.73), fasting glucose (1.28; 1.10-1.51 per standard deviation) and HbA1c (1.18; 1.14-1.23 each 1% increase). After adjustment for confounders, there were strong associations with coronary artery disease (1.77; 1.31, 2.39), HbA1c≥10% (1.66; 1.45-1.89), insulin use (1.43; 1.14-1.79), HbA1c 9.0-10.0% (1.31; 1.14-1.50), fasting glucose (1.27; 1.10-1.47 per standard deviation) and 5 years increase in age (1.26; 1.13-1.40).

Conclusion: Among patients with T2DM, five common clinical variables are associated with significantly increased risk of incident HF.

2.3 Background

In addition to its association with ischaemic heart disease, diabetes confers a demonstrably higher risk of developing cardiomyopathy [48]. Subclinical dysfunction may be a precursor to the development of subsequent symptomatic heart failure in patients with diabetes mellitus. However, at least 50% of those patients with asymptomatic left ventricular (LV) dysfunction are still unidentified [48]. The underlying metabolic disturbance of both pre-diabetes and diabetes leads to hyperinsulinemia, inflammation and oxidative stress. Multiple pathophysiological changes at the microscopic level culminate in abnormal cardiac function. Examples include impaired myocardial relaxation and cardiomyocyte resting tension giving rise to increased LV stiffness and diabetic autonomic neuropathy leading to sympathetic imbalance, which in turn drives increased fatty acid metabolism and foetal gene expression. Activation of the renin-angiotensin system is linked to increased deposition of myocardial collagen, advanced glycation and products (AGEs), and cardiac remodelling [48]. Diabetic microangiopathy, vascular endothelial dysfunction and coronary flow reserve impairment may arise from small vessel disease [43].

Although the epidemiology and mechanisms of the association of diabetes mellitus with heart failure are understood, an effective strategy for early diagnosis and effective intervention has not yet been demonstrated. Fundamental to this is the fact that not all patients are at equal risk, and a screening and intervention approach would be most effective if it involved the highest risk patients. The purpose of this study was to better quantify heart failure risk in subjects with diabetes mellitus.

2.4 Methods

2.4.1 Search Strategy.

This approach followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [97]. A systematic literature search was performed on MEDLINE and EMBASE using the medical subject heading (MeSH) terms 'heart failure', 'risk factor', 'type 2 diabetes mellitus' 'LV dysfunction', 'cardiac dysfunction', 'stage B heart failure' 'incident heart failure', 'risk assessment', 'risk impact', 'risk score', 'predictor', 'prediction' and related free text terms. The search was limited to human epidemiological and clinical studies in English language (updated on February 2014). The search strategy, study selection, and analysis followed the recommendations in the Cochrane Handbook.[98] No previous reports of this nature have been identified. The review was registered with the Prospective Registration Of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014008821), as PROSPERO 2014:CRD42014008821.

2.4.2 Study inclusion.

Inclusion criteria for the review were: (1) full-length publication of original data in a peer-reviewed English language journal; (2) human adults >18 years of age with T2DM; (3) reported incident HF in subjects with T2DM; (4) analysis of risk factors relating to incident heart failure in T2DM, reporting effect sizes as Relative Risk (RR), Odds Ratio (OR) or Hazard Ratio (HR) with 95% confidence intervals (CIs). Exclusion criteria were (1) review articles, editorial comments, and letters to the editor, practice guidelines, cost-effectiveness study, adjunctive therapy study, program evaluation. systematic review, case study and articles without full text; (2) studies included T2DM patients had heart failure at baseline or used an inappropriate comparison group (the comparison was not between diabetic incident HF group non-HF groups),(3) publication in other language.

Two independent investigators (YW and TN) assessed the eligibility of the studies. Titles, abstracts and keywords, information of identified studies were assessed for the first screening. The second screening was based on the full texts review. The information of included studies was entered into an inclusion/exclusion form. Full texts were further assessed when the collected information of a primary study indicated that it was eligible to be included in this review. The references in the identified articles were also reviewed for possible inclusion.

2.4.3 Data extraction.

Data were carefully extracted from all eligible studies independently by two reviewers (YW and TN). A third reviewer (TM) was included for unresolved discrepancies, all discrepancies were reviewed and resolved by consensus. The recorded study characteristics included first author's name, publication information, study design, time frame of study, age, sex distribution, follow-up time, number of participants, number of incident HF cases, method of assessment of HF, numbers of T2DM subjects with different risk factors of incident HF, and covariates included in the adjusted models. Outcome measures (RR, OR, HR) and their associated 95% confidence intervals (CIs) were extracted from included studies or calculated from available data. Only the largest dataset was included in the analysis when multiple articles represented data from the same dataset, except when different variables were reported in each article.

The outcome was defined as new onset heart failure and the study was excluded if participants had a heart failure history. The definition of an incident heart failure event varied somewhat from different studies, but in general it was defined as a physician diagnosis of heart failure or a hospital discharge diagnosis coded as heart failure (ICD-9, code 428 or 518.4).

2.4.4 Assessment of Methodological Quality.

Two investigators (YW and TN) independently assessed the quality of included studies. The assessment of methodological quality was based on the Newcastle-Ottawa Quality Assessment

Scale (NOS) for cohort studies with slight modifications to accommodate the topic of this review (**Appendix 2.1**).

2.4.5 Assessment of Heterogeneity.

Heterogeneity across included studies was tested using the Cochran Q and I^2 tests. A chi-square >25% and p<0.10 was defined as evidence of significant heterogeneity across studies. The I^2 test was used to estimate the extent of heterogeneity that is attributable to inter-study variation;[99, 100] a value >30% represents moderate heterogeneity and a value >50% represents substantial heterogeneity. Possible sources of heterogeneity were explored by subsequent meta-regression and sensitivity analyses. Meta-regression models were established to screen the affected factors resulting in heterogeneity using Comprehensive Meta-analysis software (version 2.0, Biostat, Englewood, NJ). For sensitivity analyses, data was extracted from relevant articles individually for pooled RRs to test the results of HRs.

2.4.6 Assessment of Publication Bias.

Publication bias and 'small-study effects' were assessed using funnel plots. Asymmetry identified in the funnel plot implied possible publication bias. A modified Egger's regression test was performed to detect such asymmetry, and p<0.10 was used to identify publication bias.

2.4.7 Data synthesis and analysis.

The RR, OR or HR for each risk variable was pooled and analysed across studies. The RR (or OR) were derived or extracted from each individual study, and HRs with 95% CIs were extracted from each available article directly. Calculated effect sizes were then pooled into a combined analysis for each RR, OR and HR. Meta-analysis was performed using RevMan 5.2 (Cochrane Information Management System, Oxford, UK) with random effect-models weighted by inverse variance. Two-tailed P values < 0.05 was considered significant.

2.5 Results

2.5.1 Study characteristics.

We identified 2309 eligible articles for further examination of the title and abstracts by electronic and hand search. Of these, 338 duplicated articles were excluded and 1818 articles were excluded after title and abstract review. After full text evaluation, 31 articles met the inclusion and good quality criteria and were analysed in this meta-analysis (**Figure 2.1**). These articles were published from 2000 to 2013.

The 21 eligible studies (**Table 2.1**) included a total of 1,111,569 subjects of which 507,637 had T2DM, ranging from 2.2%-100% of total subjects (weighted mean 83%). The reported mean age of T2DM participants was 62±5.7 years old and male subjects of T2DM ranged from 39.6% to 100% (weighted mean 56.6%). During the mean follow-up period of 4.8 years (range 1-12 years), the mean cumulative incident HF rate in T2DM participants was 10.7%, an annualised rate of 2.2% per year.

Figure 2.1 Flow chat of articles selection based on PRISMA guideline

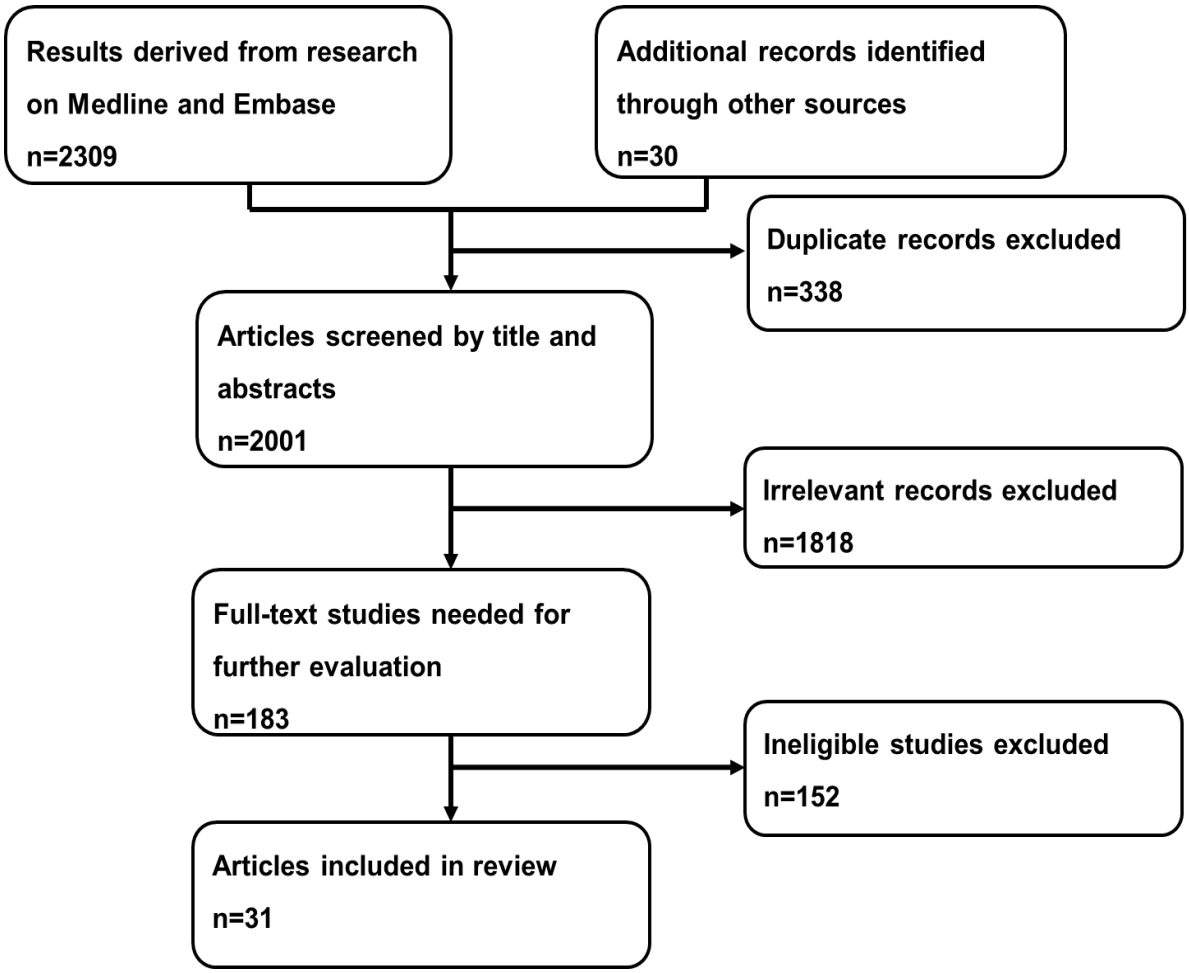


Table 2.1 Baseline characteristics of included studies.

Study	Publication year	Study Name	Data Collection (year)	Total (n)	Total T2DM n	Total T2DM %	Follow-up (years)*	HF develop (n)*	Incident Rate (1000 p-y)*	Cumulative Incidence rate (%)*	Age (years)*	Male(%)*
Stratton, I. M. et al[101]	2000	UKPDS	1977-1997	3642	3642	100%	10.4	NA	NA	NA	53±8	60
Adler, A. I. et al[102]	2000	UKPDS										
Gerstein, H. C.et al[103]	2001	HOPE study	1994-1999	9043	3498	39%	4.5	156	9.9/1000	4.5	65.4±6.5	62.9
Iribarren, C. et al[104]	2001	KPMCP	1995-1997	48858	46675	96%	2.2	935	8.7/1000	1.9	58±13	53.1
Karter, A.J et al[105]	2005	KPMCP	1999-2002			100%	0.85	320	21.5/1000	1.4	58.9±12.3	52.4
Nichols, G. A. et al[106]	2001	KPNW	1997-1999	18747	9591	51%	2.5	650	33.3/10000	7.7	63[t]	52.5
Nichols, G. A. et al[107]	2004	KPNW	1997-2003	17076	8231	48%	6	1167	30.9/1000	30.9	63.9±11.9	52.2
Delea, T. E. et al[108]	2003	U.S.PIOD	1995-2001	33544	33544	100%	3.3	523	4.7/1000	1.6	58.5±12.8	57.1
Vaur, L.et al[109]	2003	DIABHYCAR study	1995-1998	4912	4912	100%	4	187	10/1000	3.8	65.2±8	70.1
Rajagopalan, R. et al[110]	2004	PMPCD	1998-2002	3336	3336	100%	2	100	15/1000	3	51.2±0.2	50.9
Maru, S.et al[111]	2005	U.K. GPRD	1988-1999	25690	25690	100%	2.5	1409	20.8/1000	5.5	61.5[t]	NA
Filion,K.B et al[112]	2011	U.K. GPRD	2000-2006	63462	63462	100%	7	2632	13.7/1000	9.6	72.4±9.1	52.1
Barzilay, J. et al[113]	2005	CHS study	1989-2001	829	829	100%	8	203	31.3/1000	24.5	72.8±5.4	46.3
Banerjee, D. et al[114]	2013	CHS study	1989-2013	4425	4425	100%	12	1216	21.4/1000	27.5	72.7±5.5	39.6
Held, C.et al[115]	2007	ONTARGET/TRANSCEND	2001[t]	31546	12714	40%	4.5	668	11.7/1000	5.3	66±7	65
Erdmann, E.et al[116]	2007	PROactive study	2001-2004	5238	5238	100%	2.9	257	16.9/1000	4.91	61.8±7.7	66.1
Erdmann, E.et al[117]	2010	PROactive study										
Pfister, R. et al[118]	2011	PROactive study						253	16.7/1000	4.84		
Lipscombe, L.L et al[119]	2007	ODBP	2002-2006	159026	159026	100%	3.8	12491	20.7/1000	7.9	74.7[t]	NA
Yang, X. et al[120]	2008	HKDR	1995-2005	7067	7067	100%	5.5	274	7.17/1000	3.32	57[t]	45.4
McAlister, F. A et al.[121]	2008	SHD study	1991-1999	5631	5631	100%	4.7	981	41/1000	17.4	65.8±13.3	43

Leung, A. A. et al[122]	2009	SHD study	1991-1999	565037	12272	2.2%	5.2	718	11.7/1000	6	63±13.5	55
Cheung, N.et al[123]	2008	ARIC study	1993-2003	1021	1021	100%	8.9	106	11.7/1000	10.1	59.7±5.6	46.2
Pazin-Filho, A. et al[124]	2008	ARIC study	1987-2003	1827	1827	100%	9.9	328	18.1/1000	17.9	58.0±5.7	48.4
From, A. M. et al[125]	2010	Olmsted County Study	2001-2007	1760	1760	100%	2.9	NA	NA	NA	60±14	49
Simone, G.et al[126]	2010	Strong Heart Study	1989-2001	2740	1206	44%	12	201	13.9/1000	16.7	56.1±7.9	85.2
Komajda, M. et al[127]	2010	RECORD clinical trial	2001-2009	4447	4447	100%	5.5	90	2.6/1000	2	58.4±8.3	51.6
Toprani, A. et al[128]	2011	VISN 16	1996-2004	3956	3956	100%	5.5	1157	53.2/1000	39	61.5[1]	100
Lind, M.et al[129]	2012	SNDR	1998-2009	83021	83021	100%	7.2	10969	18.4/1000	13.2	65.8±11.7	55.3
Glogner, S. et al[130]	2013	SNDR										
Ebong, I. A. et al[131]	2013	MESA	2000-2012	5688	616	11%	8.5	48	11/1000	7.8	NA	NA
Sum		Studies	1988-2012	1111569	507637		152.25					
Mean(weighted)				42752.65	19525	83%	4.8			10.7	62	56.6
SD (Weighted)						30%				9.8	5.7	13.2
Maximum					159026	100%		12491		39	74.7	100
Minimum					616	11%		48		1.4	51.2	39.6

*Data all came from T2DM group;

[1] not reported

2.5.2 Risk of incident HF for T2DM.

Fifty-five risk factors were associated with incident HF in T2DM in these 21 studies (Appendix 2.1). Twenty-five risk variables reported ≥3 times were selected for the meta-analysis (**Appendix 2.2**). Significant risk factors in this meta-analysis for incident HF in T2DM were age, hypertension, fasting glucose, HbA1c, atherosclerotic vascular disease (coronary, cerebrovascular, peripheral), use of insulin. For risks reported in hazard ratio, the association was greatest for insulin use (2.48; 1.24-4.99), followed by HbA1c 7.0-8.0% (2.41; 1.62-3.59), 5 years increase in age (1.47; 1.25-1.73), fasting glucose (1.28; 1.10-1.51 per standard deviation) and HbA1c (1.18; 1.14-1.23 each 1% increase). After adjustment for confounders, the association was still strong for coronary artery disease (1.77; 1.31, 2.39), followed by HbA1c≥10% (1.66; 1.45-1.89), insulin use (1.43; 1.14-1.79), HbA1c 9.0-10.0% (1.31; 1.14-1.50), fasting glucose (1.27; 1.10-1.47 per standard deviation), 5 years increase in age (1.26; 1.13-1.40), male gender (1.15; 1.00-1.32), and HbA1c (1.13; 1.12-1.15 each 1% increase) (**Table 2.2**). Forest plots of individual meta-analysis are listed in **Appendix 2.3.**

Adjusted HRs could be analysed from 17 relevant studies and the adjustments for each article are listed in **Table 2.3**. The most frequent adjustment was age (16) followed by gender (15), smoking status (12), HbA1c (12), BMI (11), coronary disease history (11), hypertension (10), oral hypoglycaemic agents (10), cardio protective medication (11), insulin use (9), diabetes duration (8), total cholesterol (7) and peripheral or cerebrovascular disease (7).

Table 2.2 Results of meta-analysis - hazard ratio of risk variables of incident HF in T2DM.

Risk Variables	Dichotomous/ Continuous	Unadjusted HR				Fully adjusted HR			
		Total (95%CI)	I^2	P	P(I^2)	Total (95%CI)	I^2	P	P(I^2)
Age	5y increase	1.47[1.25,1.73]	91%	P<0.00001	P=0.0007	1.26[1.13,1.40]	100%	P<0.0001	P<0.00001
Gender(male)	Y/N					1.15[1.00,1.32]	60%	P=0.04	P=0.06
BMI	1 unit increase					1.04[1.01,1.06]	93%	P=0.003	P<0.00001
Hypertension	Y/N					1.06[0.81,1.40]	74%	P=0.67	P=0.02
HbA1c	1% increase	1.18[1.14,1.23]	0%	P<0.00001	P=0.62	1.13[1.12,1.15]	72%	P<0.00001	P=0.0004
	6.0-7.0%	1.25[0.47,3.29]	69%	P=0.65	P=0.07	1.02[0.73,1.43]	54%	P=0.89	P=0.11
	7.0-8.0%	2.41[1.62,3.59]	0%	P<0.00001	P=0.51	1.29[0.97,1.70]	75%	P=0.08	P=0.003
	8.0-9.0%					1.10[1.02,1.19]	0%	P=0.02	P=0.97
	9.0-10.0%					1.31[1.14,1.50]	21%	P=0.0001	P=0.28
	≥10%					1.66[1.45,1.89]	18%	P<0.00001	P=0.29
Fasting glucose	1 SD increase	1.28[1.10,1.51]	48%	P=0.002	P=0.17	1.27[1.10,1.47]	69%	P=0.001	P=0.04
	7.4-8.4mmol/L	1.09[0.40,3.01]	81%	P=0.87	P=0.02				
	8.5-10.6mmol/L	1.32[0.82,2.12]	19%	P=0.26	P=0.27				
	10.6-36.5mmol/L	2.01[0.98,4.15]	70%	P=0.06	P=0.07				
Insulin use	Y/N	2.48[1.24,4.99]	91%	P=0.01	P=0.001	1.43[1.14,1.79]	53%	P=0.002	P=0.09
TZDs	Y/N					1.42[0.79,2.55]	96%	P=0.48	P<0.00001
Metformin	Y/N					0.92[0.69,1.22]	89%	P=0.55	P<0.0001
Sulfonylurea	Y/N	1.20[0.98,1.46]	65%	P=0.07		1.14[0.85,1.53]	89%	P=0.37	P=0.0001
CAD	Y/N					1.77[1.31,2.39]	79%	P=0.0002	P=0.002

Table 2.3 Confounding factors and statistics methods for adjustments

Source	Effect size	Confounding Factors																	
		Age	Gender	BMI	waist-to-hip ratio	Hypertension	Smoking Status	HbA1c	Fasting glucose	Cholesterol	Hypoglycaemic agents	Insulin use	Cardio protective meds	Diabetes duration	BP	peripheral or cerebrovascular disease	coronary disease history	Other diabetes complications*	Other
Stratton, 2000[102]	HR	☆					☆	☆		☆				☆	☆				☆
Iribarren,2001[104]	HR	☆	☆	☆		☆	☆	☆			☆	☆	☆						☆
Vaur, 2003[109]	HR	☆	☆	☆			☆	☆					☆		☆	☆	☆		☆
Delea, 2003[108]	HR	☆	☆			☆		☆			☆		☆			☆	☆	☆	☆
Nichols, 2004[107]	HR	☆	☆	☆				☆				☆		☆			☆	☆	☆
Barzilay, 2005[113]	HR	☆		☆	☆		☆		☆		☆	☆					☆		☆
Maru, 2005[111]	HR	☆	☆	☆		☆	☆				☆	☆		☆		☆	☆		☆
Karter, 2005[105]	HR	☆	☆	☆				☆		☆	☆	☆	☆				☆		☆
Erdmann, 2007[116]	HR	☆	☆	☆			☆	☆		☆	☆	☆	☆	☆		☆	☆		☆
Held, 2007[115]	HR	☆	☆		☆	☆	☆		☆				☆				☆		☆
Yang, 2008[120]	HR	☆	☆	☆		☆	☆	☆		☆			☆	☆		☆	☆	☆	☆
McAlister, 2008[121]	HR	☆	☆										☆						☆
Pazin-Filho, 2008[124]	HR	☆	☆	☆	☆		☆	☆		☆			☆		☆				☆
Komajda, 2010[127]	HR	☆	☆	☆	☆	☆	☆	☆		☆		☆	☆	☆		☆	☆		☆
Toprani, 2010[128]	HR	☆		☆			☆	☆		☆	☆	☆	☆		☆	☆	☆		☆
From, 2010[125]	HR	☆	☆	☆		☆											☆		☆
Lind, 2012[129]	HR	☆	☆	☆		☆	☆	☆			☆	☆	☆	☆			☆		☆

**Other diabetes complications refers to renal, ophthalmic, neurological disease.*

2.5.3 Sensitivity analysis.

The pooled RRs were used to verify the results of crude and adjusted HRs of risk factors. Data was extracted from relevant studies in which comparison in incident HF was made between DM and non-DM group, and then pooled into a combined analysis for crude RRs. For pooled RR, atherosclerotic vascular disease (coronary, cerebrovascular, peripheral) had a strong association with incident HF (RR 1.5-2.5), followed by insulin use (RR 1.95; 95%CI1.52-2.50), rosiglitazone (RR 1.82; 95%CI 1.38-2.40), TZDs (RR 1.67; 95%CI1.43-1.96), hypertension (RR 1.63; 95%CI1.21-2.20) and male gender (RR 1.16; 95%CI 1.08-1.25) (**Table 2.4**)

Table 2.4 Results of meta-analysis – pooled RRs for risk factors of incident HF in T2DM

Risk Variables	RR			
	Total (95%CI)	I^2	P	P(I^2)
Gender(male)	1.16[1.08,1.25]	48%	P<0.00001	P=0.05
Smoking(Current smoker)	1.00[0.93,1.09]	0%	P=0.92	P=0.92
Hypertension	1.63[1.21,2.20]	90%	P=0.001	P<0.00001
Microalbuminuria and proteinuria	2.15[0.84,5.47]	95%	P=0.11	P<0.00001
Microalbuminuria	1.68[0.44,6.39]	99%	P=0.45	P<0.00001
Insulin use	1.95[1.52,2.50]	89%	P<0.00001	P<0.00001
Metformin	1.18[1.06,1.31]	0%	P=0.002	P=0.75
TZDs(Rosiglitazone & Pioglitazone)	1.67[1.43,1.96]	0%	P<0.00001	P=0.84
Rosiglitazone	1.82[1.38,2.40]	57%	P<0.0001	P=0.13
Pioglitazone	1.33[0.76,2.30]	68%	P=0.32	P=0.08
Sulfonylurea	1.02[0.86,1.22]	82%	P=0.80	P=0.0231
Beta-blockers	1.83[1.04,3.24]	92%	P=0.04	P<0.00001
ACEI/ARB	1.55[1.38,1.74]	17%	P<0.00001	P=0.30
Calcium-channel blocker	1.76[1.30,2.40]	78%	P=0.0003	P=0.01
Diuretics	2.41[2.25,2.59]	0%	P<0.0001	P=0.92
Nitrates	2.59[2.39,2.80]	0%	P<0.00001	P=0.36
Ischemic heart disease	2.50[2.28,2.75]	46%	P<0.00001	P=0.13
Peripheral vascular disease	1.91[1.71,2.13]	0%	P<0.00001	P=0.74
Peripheral and cerebrovascular vascular disease	1.82[1.68,1.96]	0%	P<0.00001	P=0.78
Stroke	1.77[1.21,2.60]	51%	P=0.003	P=0.13

2.5.4 Meta-regression.

The summary of meta-regression analyses across different clinical, laboratory and geographic factors is presented in **Table 2.5**. There were positive associations between BMI (p=0.03) and

coronary heart disease history (p=0.01) with log RR of male gender; age (p=0.01), BMI (p=0.01), follow-up years (p=0.02), insulin use (p<0.05) and coronary heart disease history (p<0.05) with log RR of insulin use. However, there were no significant associations of effect measures of current smoker, hypertension and cardiac protective drugs with listed clinical, laboratory and geographic factors.

2.5.5 Publication Bias.

Publication bias was estimated visually by funnel plots and Begg and Egger test. The funnel plot analysis and statistical tests were presented in **Appendix 2.4** and showed no indication of potential publication bias.

Table 2.5 Results of meta-regression of univariate meta-analyses.

Characteristic	Trails	logit coefficient	P value	Characteristic	Trails	logit coefficient	P value
Male Gender				***Current smoker***			
male	9	<0.002	0.53	male	6	0.002	0.43
Age	9	0.005	0.23	Age	6	-0.004	0.63
BMI	6	-0.037	0.03	BMI	5	0.020	0.58
SBP	7	-0.014	0.12	SBP	5	-0.011	0.23
DBP	5	-0.001	0.88	DBP	3	0.022	0.15
Follow-up years	9	0.013	0.08	Follow-up years	6	0.005	0.61
current smoker	6	0.006	0.57	current smoker	6	0.006	0.57
diabetes duration	5	0.034	0.11	diabetes duration	4	0.005	0.94
fasting blood glucose	3	-0.025	0.16	fasting blood glucose	3	-0.025	0.16
HbA1c	5	0.131	0.43	HbA1c	3	-0.044	0.86
creatinie	4	-0.035	0.32	creatinine	3	-0.044	0.30
ACEI use	3	0.002	0.79	ACEI use	3	0.002	0.79
insulin use	4	-0.006	0.38	hypertension	3	-0.001	0.93
coronary heart disease	4	0.011	0.01				
hypertension	4	0.007	0.22				
Hypertension				***Insulin use***			
male	5	0.001	0.72	male	4	0.010	0.32
Age	5	0.006	0.34	Age	4	0.014	0.01
BMI	4	-0.005	0.90	BMI	3	-0.047	0.01
SBP	4	-0.001	0.93	SBP	3	0.024	0.46
DBP	3	0.002	0.97	DBP	3	-0.006	0.51
Follow-up years	5	0.018	0.23	Follow-up years	3	0.039	0.02
current smoker	4	0.001	0.93	insulin use	3	-0.052	<0.05
HbA1c	4	0.125	0.44	coronary heart disease	3	0.021	<0.05
creatinie	3	-0.034	0.33				
ACEI use	3	0.002	0.79				
insulin use	3	<-0.001	1.00				
coronary heart disease	3	0.005	0.31				
hypertension	4	0.007	0.22				
Cardiac protective drugs(β-blockers, ACEI, Calcium channel blockers, diuretics)							
male	3	<-0.001	0.97				
Age	3	0.001	0.89				
BMI	3	-0.004	0.91				
Follow-up years	3	<-0.001	1.00				
current smoker	3	-0.001	0.93				
diabetes duration	3	0.009	0.90				

Abbreviations: BMI, body mass index;HbA1c,hemoglobin A1c;MI,myocardial infarction; ESRD, end-stage renal disease; Hb, blood haemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; UAC, urinary albumin concentration; eGFR, estimate glomerular filtration rate.

2.6 Discussion

The results of this study show that five common clinical risk variables (coronary artery disease, glycaemic control (HbA1c and fasting glucose), insulin use and increasing age) are associated with incident HF in T2DM. These findings supplement the association of older age, hypertension, atherosclerotic vascular disease and diabetes with incident HF in the general population.

2.6.1 Preclinical diabetic cardiomyopathy.

In undiagnosed patients with preclinical diabetic cardiomyopathy, treatment is not initiated until the development of symptoms (stage C or D HF).[48] At this stage, changes may be irreversible and the ability to change the trajectory of the illness may be limited. Asymptomatic patients with cardiac structural changes are considered to have stage B HF, and have a greater risk of developing HF [15].

Numerous epidemiological and clinical studies have supported the existence of diabetic cardiomyopathy, which is defined as left ventricular (LV) dysfunction and/or left ventricular hypertrophy (LVH) independent of hypertension and coronary disease, that appears to result in cardiovascular complications and congestive HF.[51] Echocardiography has been the most widely used technique determine the prevalence of these LV structural or functional changes. Diastolic dysfunction in T2DM has been reported in between 27-75% in different populations and with different definitions.[53,66, 67] LVH is also prevalent in older and/or hypertensive T2DM populations; Kiencke et al [53] reported that 24% older diabetic subjects without evidence of heart disease had LVH while Dawson et al [54] reported 43% in an unselected older cohort using the same criteria of LVH. Thus, structural evidence of preclinical diabetic cardiomyopathy is common in older subjects with DM, ranging from 36-48% [52, 53]. Although the cost-effectiveness of screening tests for early HF screening of asymptomatic T2DM patients still

needs to be defined, a feasible and practical risk score would help physicians to identify high-risk individuals for preventive programs.

2.6.2 Risk factors for HF in T2DM.

While the association of coronary artery disease and increasing age with incident HF are expected from the general population, the importance of glycaemic control (HbA1c and fasting glucose) and therapy are specific to DM. Although weight gain and oedema have been recognised as complications of TZDs [132], in our meta-analyses, the strong association between TZD and incident HF in T2DM disappeared after fully adjusting for confounders. However, this literature is inconsistent, with the reported association of rosiglitazone with the increased risk of incident HF [133] being preceded by negative retrospective cohort studies [128]. Unfortunately, the systematic review approach does not lend itself well to distinction of study quality and avoidance of undocumented confounders in retrospective studies.

For HbA1c, our results confirm previous evidence that poor glycemic control is a predictor of incident HF in T2DM. The mechanism of this process is likely multifactorial, including both 1) higher HbA1c as a marker of poor adherence to not only diabetic therapy, but also antihypertensive therapy and lipid lowering medication; 2) worse glycaemic control as a true risk for incident HF. It is possible that the poor glycaemic control reflects insulin resistance – a contributor to both diabetic cardiomyopathy and atherosclerosis. [104]

Coronary artery disease (CAD) is a well-known risk factor of HF in not only diabetes but also non-diabetes patients. In this systematic review and meta-analysis, 21 studies were included and coronary artery disease was reported as a risk variable ≥3 times, so it was selected into the meta-analysis. In the analysis, CAD was also found having strong association with incident HF in patients with T2DM even after adjustment for confounders (HR 1.77; 1.31, 2.39). However, the downside is that screening for CAD is attended by many false positives[134] and it has not

been shown to be beneficial in any studies to date[135]. Moreover, even if CAD is identified, many large scale clinical trials have failed to show the long-term prognostic benefit from any intervention over optimal medical therapy. In BARI-2D, in diabetic patients with stable CAD, the 5-year survival rate was not statistically different between prompt revascularization group (either CABG or PCI) and optimal medical therapy group[136]. Similarly, COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) also failed to show the benefit of early PCI to optimal medical therapy can reduce the risk of cardiac event and death in diabetes[137].

The development of a risk score is an important step in estimating individuals' risk of incident HF in T2DM. Such method would facilitate the identification and classification of asymptomatic subjects with sufficient risk to provide detection from screening and other targeted public health interventions. The effect sizes of the risk factors in this systematic review may help clinicians to make decisions about screening the diabetic population. These results are analogous to a previously-described risk score for HF hospitalization in diabetes [120], with the benefit of derivation from a larger group. The risk variables in our findings were derived from a large number of patients, and could be expected to perform well in general populations.

2.6.3 Limitations.

Like all meta-analyses, this work is limited by variations in the original studies, although all involved at-risk individuals. Likewise, the constituent observational studies may be limited by biases in the recruitment process. The apparent paradoxical effects of cardio-protective medication are likely due to association with other cardiovascular diseases which might lead to HF, and therefore reflect confounding by indication.

2.7 Conclusion

This systematic review shows that among 507,637 patients with T2DM, five common clinical variables are associated with significantly increased risk of incident HF in T2DM.

2.8 Postscript

In this chapter, we have used a systematic review and meta-analysis to identify clinical, laboratory and echocardiographic predictors of incident HF in T2DM. The overall results of this meta-analysis showed that among patients with T2DM, 5 common clinical variables are associated with significantly increased risk of incident HF. The combination of these risks may be estimated for HF prediction in T2DM – a step that would be critical for effective HF screening.

As mentioned previously, numerous studies showed that intervention would be of benefit in the early stages of ischemic HF, but no evidence is available regarding early stage non-ischemic HF. It is also unclear as to whether CAD is a contributor to subclinical LV dysfunction, although previous studies in patients with DM have shown few positive stress test results and even fewer positive coronary angios. Therefore, we hypothesised that new echocardiographic measures – including strain imaging - can permit the recognition of asymptomatic early stage HF and permit the initiation of therapy that will reduce the development of HF.

In the forthcoming chapter, I will introduce the Tasmanian Study of Echocardiographic detection of Left ventricular dysfunction (Tas-ELF study), which integrates clinical and echocardiographic screening to permit early treatment of subclinical HF in the Tasmanian community. The next chapter will describe the study design and methodology that have been used in this study. The findings in the remainder of this thesis have been derived from this study.

2.9 Appendix

Appendix 2.1 Assessments - Newcastle-Ottawa Quality Assessment Scale.

Author	Study(Trial)	01_Representativeness of the exposed cohort	02_Selection of the non exposed cohort	03_Ascertainment of exposure	04_Outcome demonstration at start	05_Comparability	06_Assessment of outcome	07_Follow-up length long enough for outcome to occur	08_Follow-up adequacy	Total☆
Stratton, I; Adler, A	UKPDS	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Gerstein, H	HOPE study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Iribarren, C; Karter, A	KPMCP	☆	☆	☆	☆	☆	☆		☆	**7**
Nichols, G	KPNW	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Delea, T	U.S. PIOD	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Vaur, L	DIABHYCAR study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Rajagopalan, R	PMPCD	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Maru, S; Filion,K	U.K. GPRD	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Barzilay, J; Banerjee, D	CHS study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Held, C	ONTARGET/TRANSCEND	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Erdmann, E; Pfister, R	PROactive study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Lipscombe, L.L et al	ODBP	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Yang, X. et al	HKDR	☆	☆	☆	☆	☆	☆	☆	☆	**8**
McAlister, F; Leung, A	SHD study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Cheung, N; Pazin-Filho, A.	ARIC study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
From, A. M. et al	Olmsted County Study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Simone, G.et al	Strong Heart Study	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Komajda, M. et al	RECORD clinical trial	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Toprani, A. et al	VISN 16			☆	☆	☆	☆	☆	☆	**6**
Lind, M; Glogner, S	SNDR	☆	☆	☆	☆	☆	☆	☆	☆	**8**
Ebong, I. A. et al	MESA	☆	☆	☆	☆	☆	☆	☆	☆	**8**

01_Selection: No☆ is given to a)men or women only cohort; b) with age selection; c) with diabetes duration selection

05_Comparability: No☆ is given if not adjusted for confounders or without subgroup analysis

07_Follow-up length: No☆ is given if <24 months

08_Follow-up adequacy: No☆ is given if number of lost >20% or without description of those lost

Appendix 2.2 Frequency of risk variables reported

	Frequency n	%	KPNW	PROactive	U.K. GPRD	U.S. PIOD	VISN 16	HKDR	DIABHYCAR	Olmsted County study	RECORD	SHD	MESA	KPMCP	ARIC	SNDR	UKPDS	Strong Heart Study	ONTARGET/TRANSCEND	CHS	PMPCD	ODBP	HOPE
Age	11	53%	*	*	*	*	*	*	*	*	*	*		*									
HbA1c	9	43%	*	*			*	*	*					*	*	*	*						
TZDs(Rosigtzone, Pioglitazone)	8	38%	*	*P	*T,P,R	*	*				*R+M/S			*								*	
Hypertension	7	33%	*		*	*			*	*	*							*					
BMI	6	29%	*		*		*				*					*		*					
Systolic blood pressure	5	24%	*				*	*			*						*						
Insulin use	5	24%	*		*			*						*							*		
Albuminuria	4	19%	*						*		*												*
History of vascular disease	4	19%		*	*	*	*																
History of atherosclerotic disease	4	19%			*	*			*	*													
Sulfonyurea	3	14%	*		*							*											
Diabetes duration	3	14%	*	*				*															
Metformin	3	14%	*		*		*																
Gender	2	10%										*		*									
Smoking	2	10%			*				*														
Serum creatinine	2	10%	*	*																			
TG	2	10%					*						*										
LDL cholesterol	2	10%		*			*																
Antidiabeic oral agents	2	10%	*		*																		
Prior MI	2	10%		*	*																		
Diastolic blood pressure	1	5%	*																				

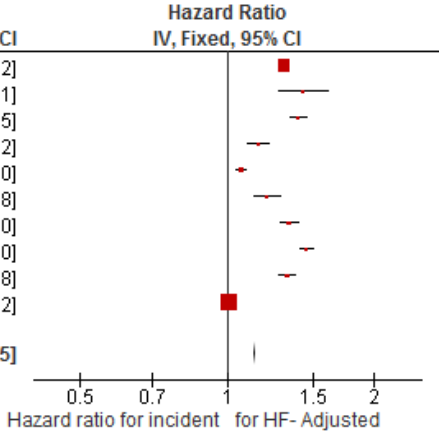
Fasting plasma glucose	1	5%																	*	*		
Fating insulin	1	5%																		*		
HDL-C	1	5%											*									
HDL-C or TC/HDL-C ratio	1	5%											*									
Non HDL-C	1	5%											*									
Beta-blockers	1	5%										*										
Diuretic use	1	5%		*																		
Nitrates use	1	5%										*										
Diabetic retinopathy	1	5%												*								
ECG signs																						
heart rate	1	5%		*																		
cQT-interval	1	5%		*																		
bundle branch blocks	1	5%		*																		
Echocardiographic signs																						
E/e'	1	5%								*												
Ejection Fraction	1	5%								*												
Left ventricular mass index	1	5%								*												
History of ischemic heart disease	1	5%	*																			
Stroke	1	5%				*																
Neurological	1	5%				*																
Cardiac arrhythmias	1	5%				*																
ESRD	1	5%	*																			

Appendix 2.3 Forest plot

Age (per 5 years) (Hazard Ratio – Adjusted)

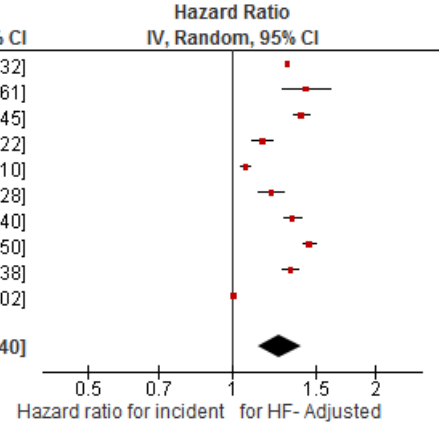
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
DIABHYCAR Vaur 2003	0.27	0.0039	36.8%	1.31 [1.30, 1.32]
HKDR Yang 2008	0.36	0.0593	0.2%	1.43 [1.28, 1.61]
KPNW Nichols 2004	0.3365	0.0186	1.6%	1.40 [1.35, 1.45]
Olmsted County Form 2010	0.1484	0.0252	0.9%	1.16 [1.10, 1.22]
PROactive Pfister 2011	0.0677	0.0126	3.5%	1.07 [1.04, 1.10]
RECORD Komajda 2010	0.1906	0.0304	0.6%	1.21 [1.14, 1.28]
SHD McAlister 2008	0.2927	0.0223	1.1%	1.34 [1.28, 1.40]
U.K. GPRD Maru 2005	0.3757	0.0149	2.5%	1.46 [1.41, 1.50]
U.S.PIOD Delea 2003	0.2852	0.0196	1.5%	1.33 [1.28, 1.38]
VISN 16 Toprani 2010	0.0114	0.0033	51.4%	1.01 [1.00, 1.02]
Total (95% CI)			**100.0%**	**1.14 [1.14, 1.15]**

Heterogeneity: Chi² = 3133.88, df = 9 (P < 0.00001); I² = 100%
Test for overall effect: Z = 56.19 (P < 0.00001)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
DIABHYCAR Vaur 2003	0.27	0.0039	10.2%	1.31 [1.30, 1.32]
HKDR Yang 2008	0.36	0.0593	9.1%	1.43 [1.28, 1.61]
KPNW Nichols 2004	0.3365	0.0186	10.1%	1.40 [1.35, 1.45]
Olmsted County Form 2010	0.1484	0.0252	10.0%	1.16 [1.10, 1.22]
PROactive Pfister 2011	0.0677	0.0126	10.2%	1.07 [1.04, 1.10]
RECORD Komajda 2010	0.1906	0.0304	9.9%	1.21 [1.14, 1.28]
SHD McAlister 2008	0.2927	0.0223	10.0%	1.34 [1.28, 1.40]
U.K. GPRD Maru 2005	0.3757	0.0149	10.1%	1.46 [1.41, 1.50]
U.S.PIOD Delea 2003	0.2852	0.0196	10.1%	1.33 [1.28, 1.38]
VISN 16 Toprani 2010	0.0114	0.0033	10.2%	1.01 [1.00, 1.02]
Total (95% CI)			**100.0%**	**1.26 [1.13, 1.40]**

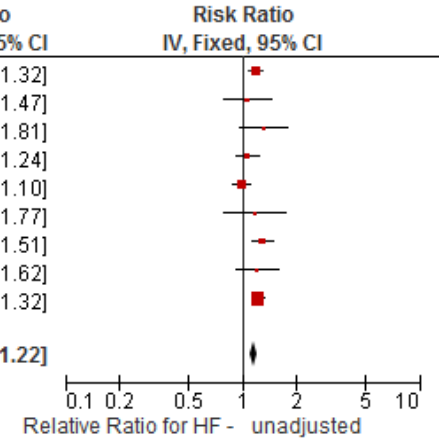
Heterogeneity: Tau² = 0.03; Chi² = 3133.88, df = 9 (P < 0.00001); I² = 100%
Test for overall effect: Z = 4.26 (P < 0.0001)

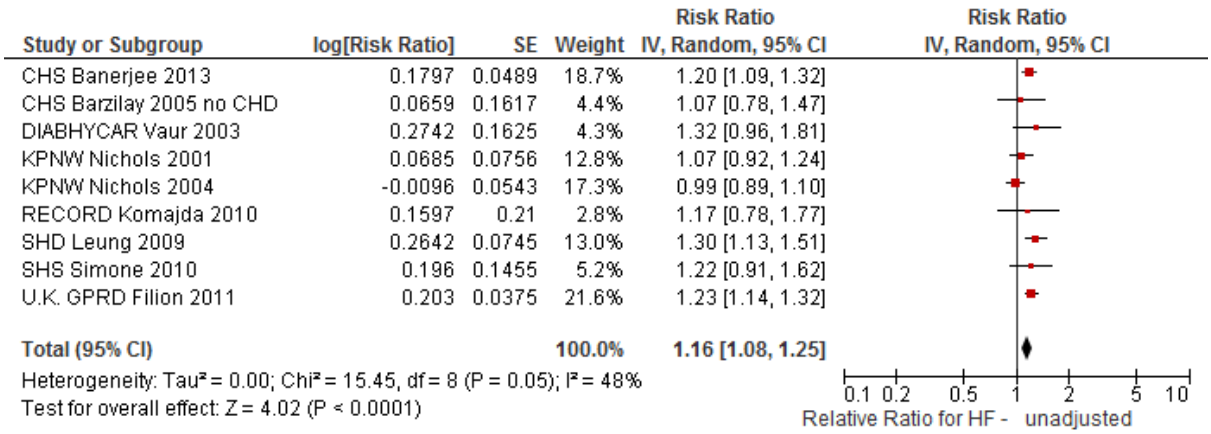


Male Gender (Relative Risk –unadjusted)

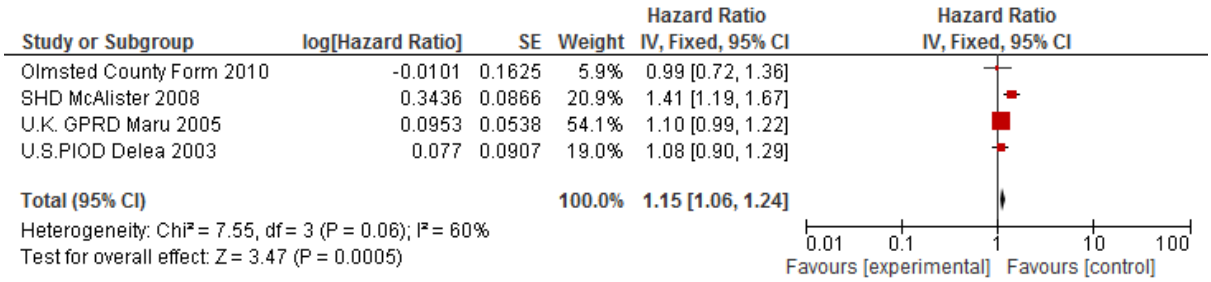
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
CHS Banerjee 2013	0.1797	0.0489	21.2%	1.20 [1.09, 1.32]
CHS Barzilay 2005 no CHD	0.0659	0.1617	1.9%	1.07 [0.78, 1.47]
DIABHYCAR Vaur 2003	0.2742	0.1625	1.9%	1.32 [0.96, 1.81]
KPNW Nichols 2001	0.0685	0.0756	8.9%	1.07 [0.92, 1.24]
KPNW Nichols 2004	-0.0096	0.0543	17.2%	0.99 [0.89, 1.10]
RECORD Komajda 2010	0.1597	0.21	1.2%	1.17 [0.78, 1.77]
SHD Leung 2009	0.2642	0.0745	9.1%	1.30 [1.13, 1.51]
SHS Simone 2010	0.196	0.1455	2.4%	1.22 [0.91, 1.62]
U.K. GPRD Filion 2011	0.203	0.0375	36.1%	1.23 [1.14, 1.32]
Total (95% CI)			**100.0%**	**1.17 [1.12, 1.22]**

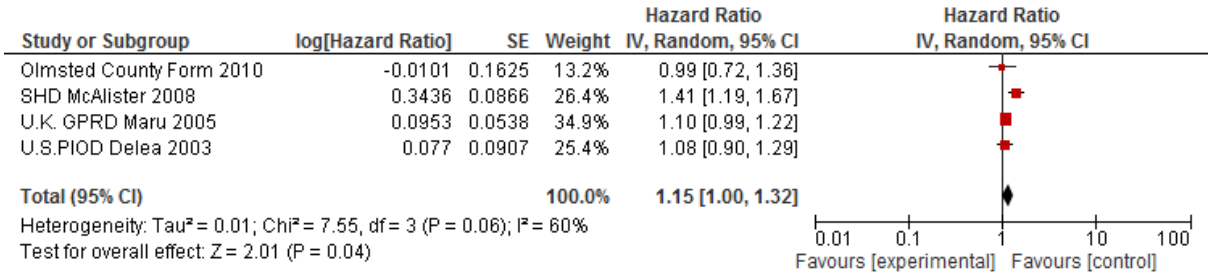
Heterogeneity: Chi² = 15.45, df = 8 (P = 0.05); I² = 48%
Test for overall effect: Z = 6.80 (P < 0.00001)



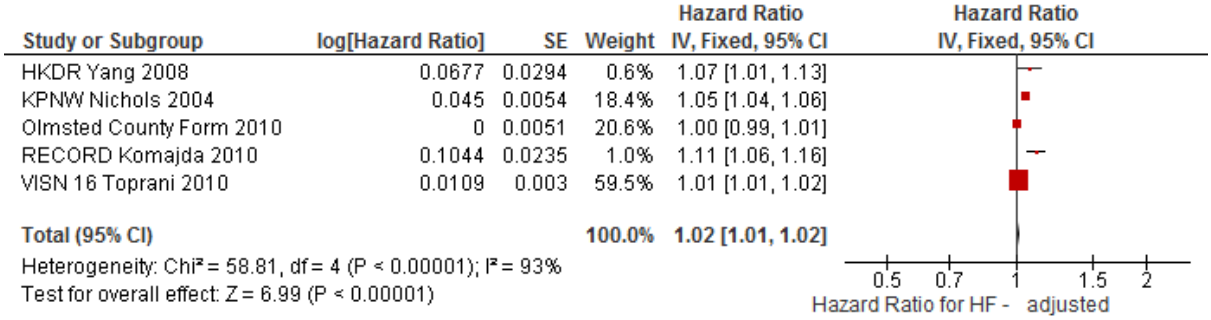


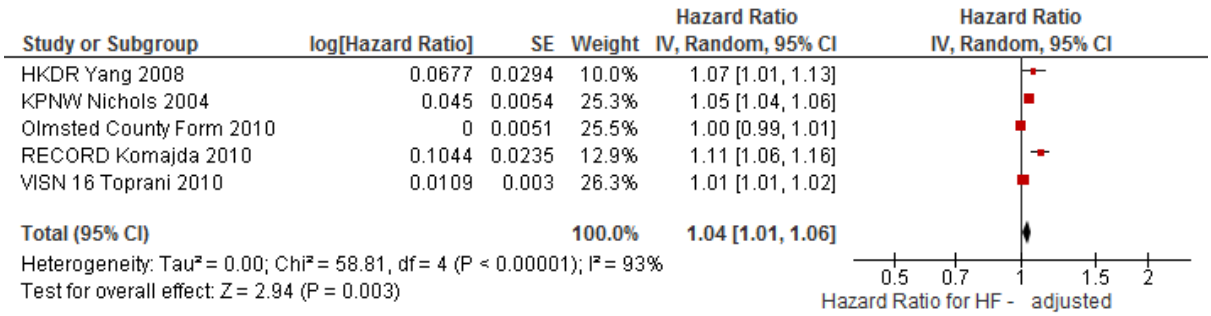
Male Gender (Hazard Ratio – adjusted)



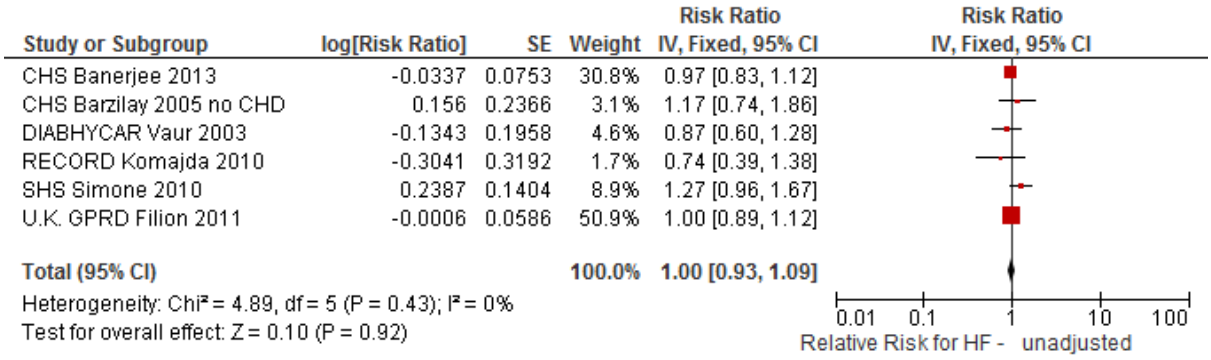


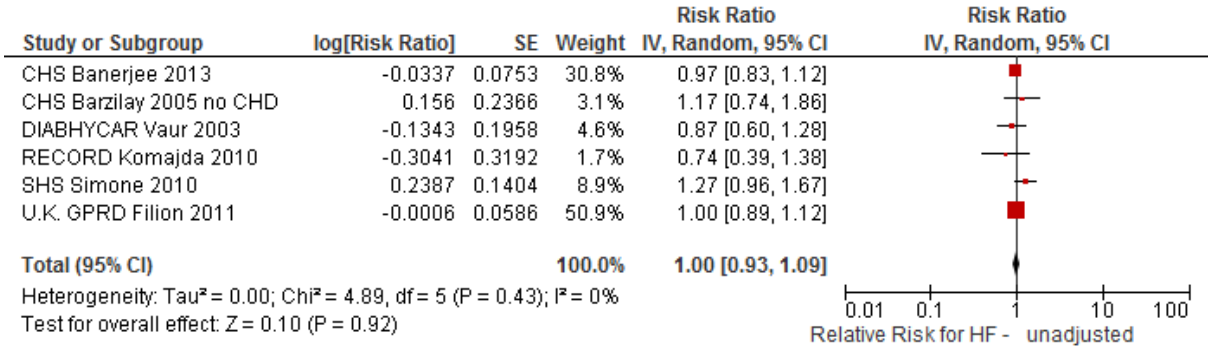
BMI (per 1 unit) (Hazard Ratio – adjusted)



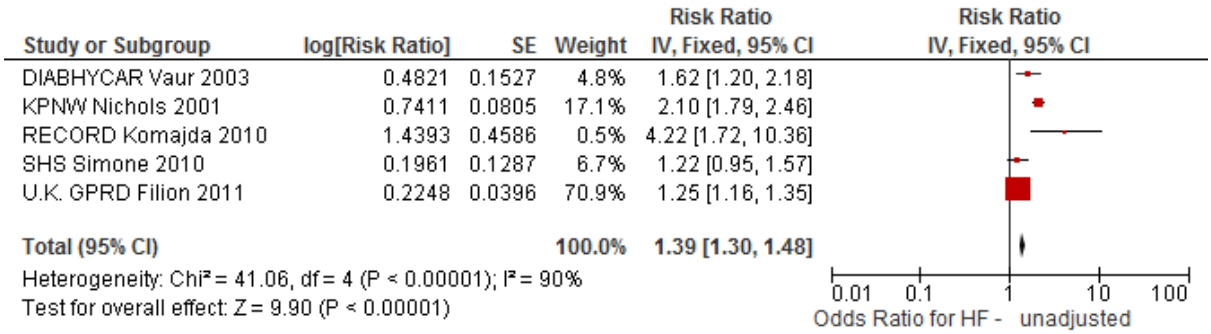


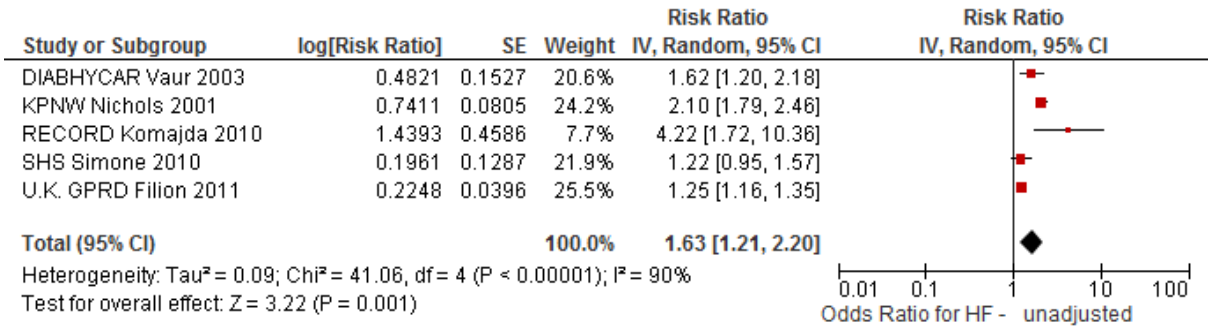
Current Smoker (Relative Risk – unadjusted)



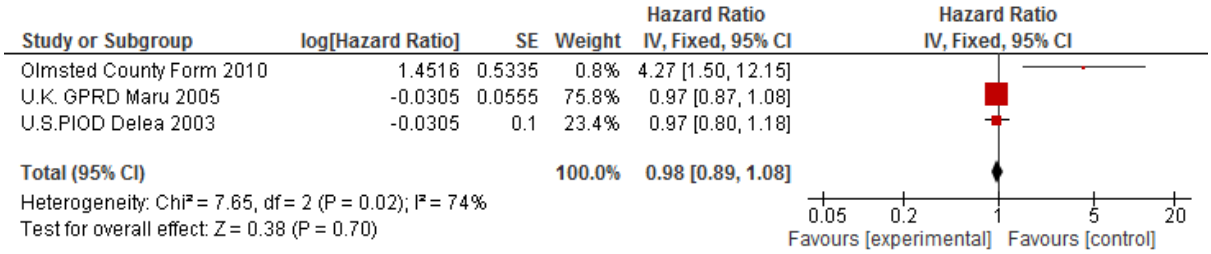


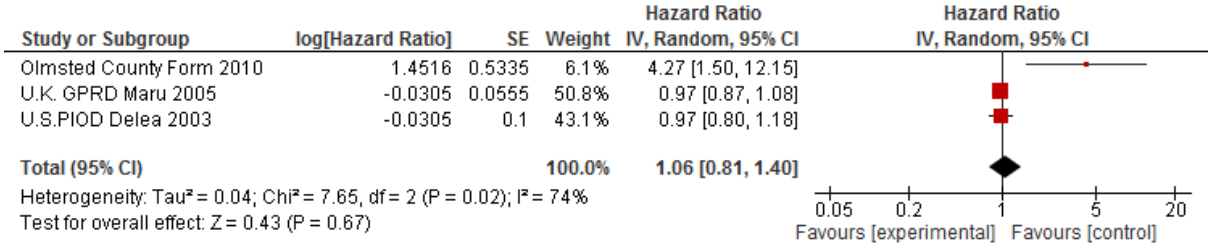
Hypertension (Relative Risk– unadjusted)



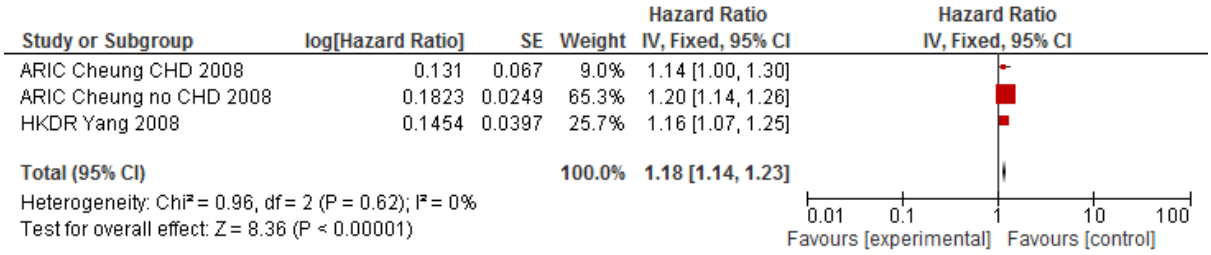


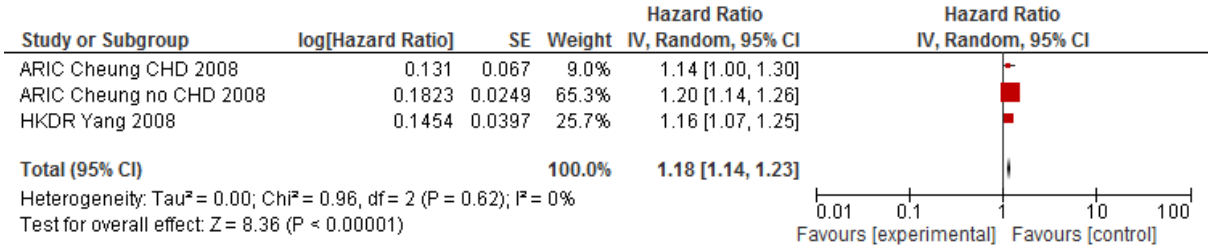
Hypertension (Hazard Ratio – adjusted)





HbA1c (per 1%) (Hazard ratio – unadjusted)

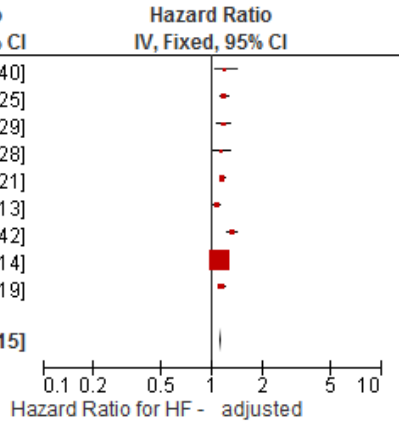




HbA1c (per 1%) (Hazard ratio – adjusted)

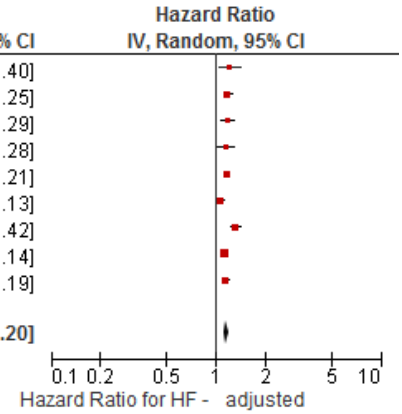
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
ARIC Cheung CHD 2008	0.1878	0.0758	0.9%	1.21 [1.04, 1.40]
ARIC Cheung no CHD 2008	0.1638	0.0303	5.3%	1.18 [1.11, 1.25]
DIABHYCAR Vaur 2003	0.1658	0.0453	2.4%	1.18 [1.08, 1.29]
HKDR Yang 2008	0.1398	0.0562	1.5%	1.15 [1.03, 1.28]
KPMCP Iribarren 2001Men	0.1484	0.0225	9.7%	1.16 [1.11, 1.21]
KPMCP Iribarren 2001Women	0.071	0.0261	7.2%	1.07 [1.02, 1.13]
KPNW Nichols 2004	0.2776	0.036	3.8%	1.32 [1.23, 1.42]
SNDR Lind 2012	0.1133	0.009	60.4%	1.12 [1.10, 1.14]
VISN 16 Toprani 2010	0.1293	0.0234	8.9%	1.14 [1.09, 1.19]
Total (95% CI)			**100.0%**	**1.13 [1.12, 1.15]**

Heterogeneity: Chi² = 28.23, df = 8 (P = 0.0004); I² = 72%
Test for overall effect: Z = 18.06 (P < 0.00001)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
ARIC Cheung CHD 2008	0.1878	0.0758	4.1%	1.21 [1.04, 1.40]
ARIC Cheung no CHD 2008	0.1638	0.0303	11.9%	1.18 [1.11, 1.25]
DIABHYCAR Vaur 2003	0.1658	0.0453	8.2%	1.18 [1.08, 1.29]
HKDR Yang 2008	0.1398	0.0562	6.3%	1.15 [1.03, 1.28]
KPMCP Iribarren 2001Men	0.1484	0.0225	14.2%	1.16 [1.11, 1.21]
KPMCP Iribarren 2001Women	0.071	0.0261	13.1%	1.07 [1.02, 1.13]
KPNW Nichols 2004	0.2776	0.036	10.4%	1.32 [1.23, 1.42]
SNDR Lind 2012	0.1133	0.009	17.8%	1.12 [1.10, 1.14]
VISN 16 Toprani 2010	0.1293	0.0234	13.9%	1.14 [1.09, 1.19]
Total (95% CI)			**100.0%**	**1.16 [1.12, 1.20]**

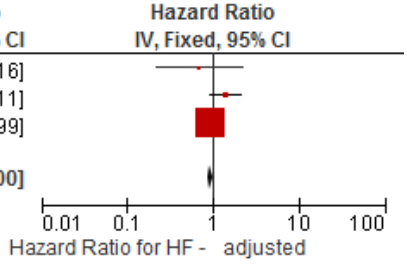
Heterogeneity: Tau² = 0.00; Chi² = 28.23, df = 8 (P = 0.0004); I² = 72%
Test for overall effect: Z = 8.45 (P < 0.00001)



HbA1c (6.0-7.0%) (Hazard Ratio – adjusted)

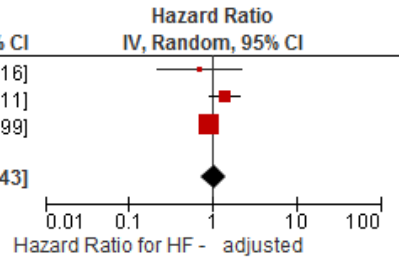
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
ARIC Cheung CHD 2008	-0.3711	0.5832	0.5%	0.69 [0.22, 2.16]
ARIC Cheung no CHD 2008	0.3365	0.2087	3.7%	1.40 [0.93, 2.11]
SNDR Lind 2012	-0.0943	0.0408	95.9%	0.91 [0.84, 0.99]
Total (95% CI)			**100.0%**	**0.92 [0.85, 1.00]**

Heterogeneity: Chi² = 4.35, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 2.00 (P = 0.05)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
ARIC Cheung CHD 2008	-0.3711	0.5832	7.6%	0.69 [0.22, 2.16]
ARIC Cheung no CHD 2008	0.3365	0.2087	32.3%	1.40 [0.93, 2.11]
SNDR Lind 2012	-0.0943	0.0408	60.1%	0.91 [0.84, 0.99]
Total (95% CI)			**100.0%**	**1.02 [0.73, 1.43]**

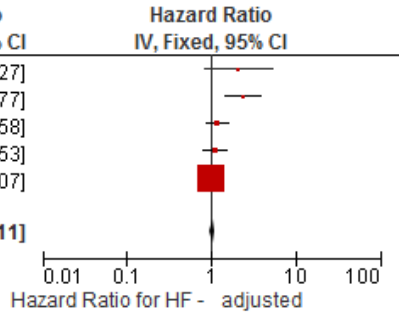
Heterogeneity: Tau² = 0.05; Chi² = 4.35, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 0.14 (P = 0.89)



HbA1c (7.0-8.0%) (Hazard Ratio – adjusted)

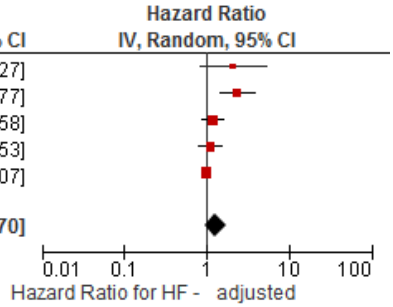
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
ARIC Cheung CHD 2008	0.7318	0.4746	0.6%	2.08 [0.82, 5.27]
ARIC Cheung no CHD 2008	0.8562	0.2403	2.5%	2.35 [1.47, 3.77]
KPMCP Iribarren 2001Men	0.1655	0.1497	6.5%	1.18 [0.88, 1.58]
KPMCP Iribarren 2001Women	0.1044	0.1637	5.4%	1.11 [0.81, 1.53]
SNDR Lind 2012	-0.0133	0.0413	85.0%	0.99 [0.91, 1.07]
Total (95% CI)			**100.0%**	**1.03 [0.96, 1.11]**

Heterogeneity: Chi² = 16.13, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 0.82 (P = 0.41)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
ARIC Cheung CHD 2008	0.7318	0.4746	7.0%	2.08 [0.82, 5.27]
ARIC Cheung no CHD 2008	0.8562	0.2403	16.7%	2.35 [1.47, 3.77]
KPMCP Iribarren 2001Men	0.1655	0.1497	23.4%	1.18 [0.88, 1.58]
KPMCP Iribarren 2001Women	0.1044	0.1637	22.3%	1.11 [0.81, 1.53]
SNDR Lind 2012	-0.0133	0.0413	30.6%	0.99 [0.91, 1.07]
Total (95% CI)			**100.0%**	**1.29 [0.97, 1.70]**

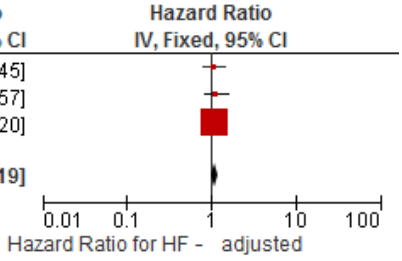
Heterogeneity: Tau² = 0.07; Chi² = 16.13, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 1.76 (P = 0.08)



HbA1c (8.0-9.0%) (Hazard Ratio – adjusted)

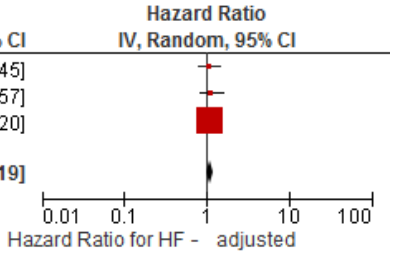
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
KPMCP Iribarren 2001Men	0.0677	0.1548	6.9%	1.07 [0.79, 1.45]
KPMCP Iribarren 2001Women	0.1222	0.1678	5.9%	1.13 [0.81, 1.57]
SNDR Lind 2012	0.0953	0.0436	87.2%	1.10 [1.01, 1.20]
Total (95% CI)			**100.0%**	**1.10 [1.02, 1.19]**

Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.33 (P = 0.02)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
KPMCP Iribarren 2001Men	0.0677	0.1548	6.9%	1.07 [0.79, 1.45]
KPMCP Iribarren 2001Women	0.1222	0.1678	5.9%	1.13 [0.81, 1.57]
SNDR Lind 2012	0.0953	0.0436	87.2%	1.10 [1.01, 1.20]
Total (95% CI)			**100.0%**	**1.10 [1.02, 1.19]**

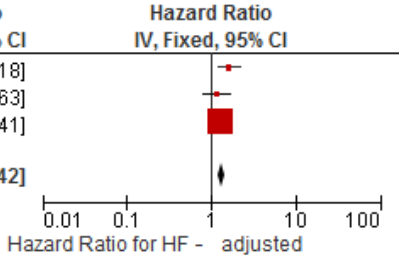
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.33 (P = 0.02)

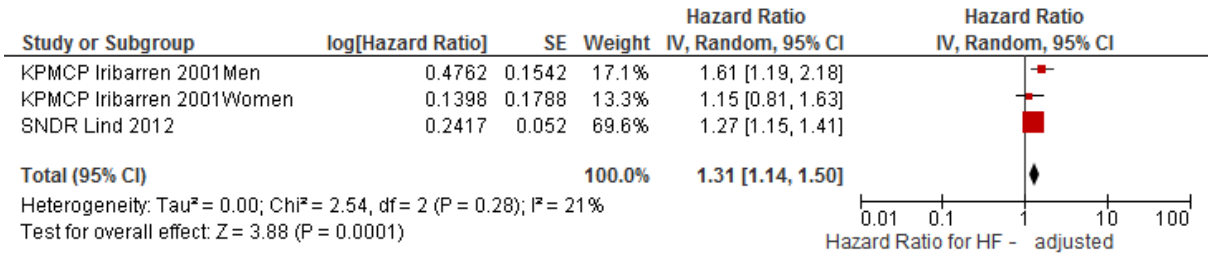


HbA1c (9.0-10%) (Hazard Ratio – adjusted)

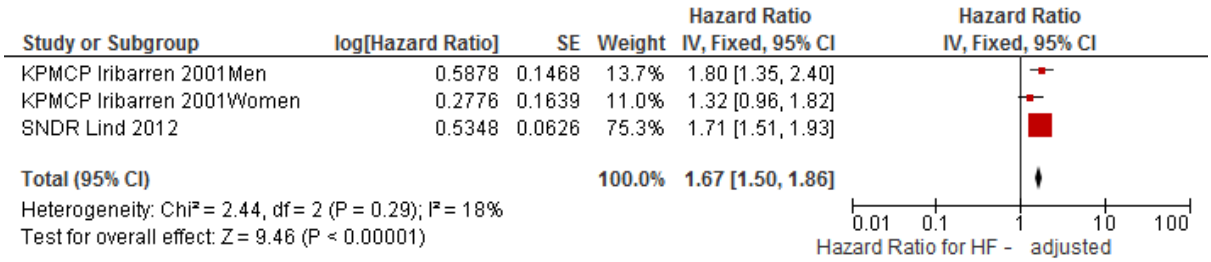
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
KPMCP Iribarren 2001Men	0.4762	0.1542	9.5%	1.61 [1.19, 2.18]
KPMCP Iribarren 2001Women	0.1398	0.1788	7.1%	1.15 [0.81, 1.63]
SNDR Lind 2012	0.2417	0.052	83.5%	1.27 [1.15, 1.41]
Total (95% CI)			**100.0%**	**1.29 [1.18, 1.42]**

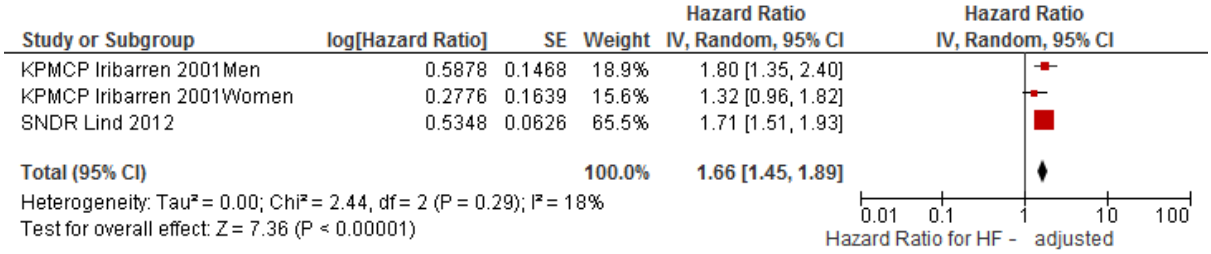
Heterogeneity: Chi² = 2.54, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 5.41 (P < 0.00001)



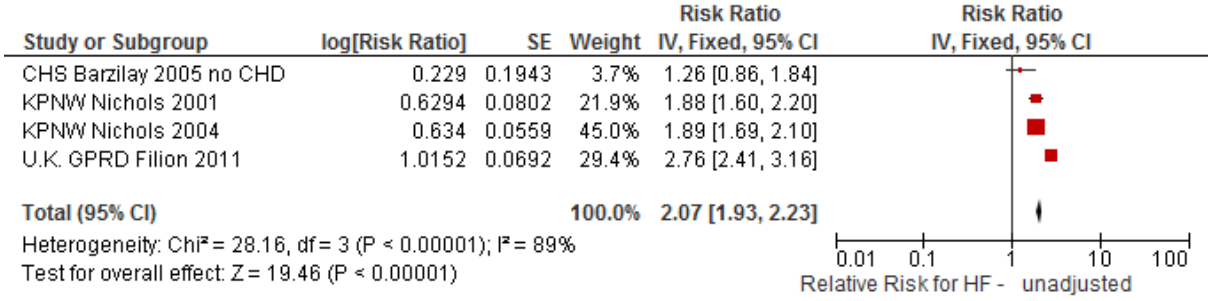


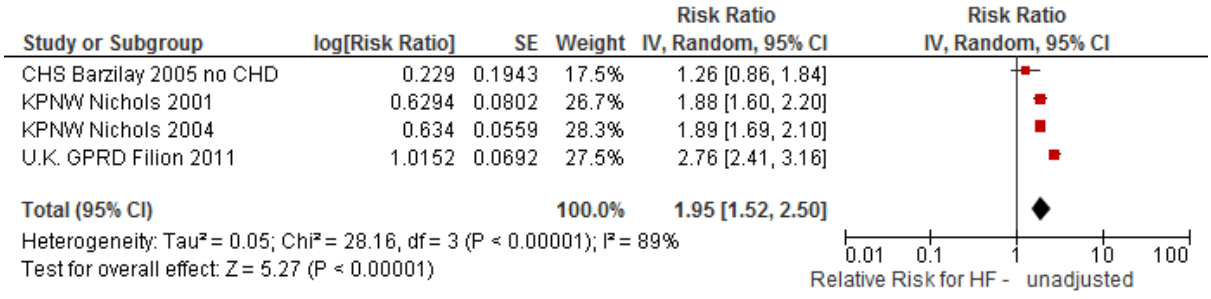
HbA1c (≥10%) (Hazard Ratio – adjusted)



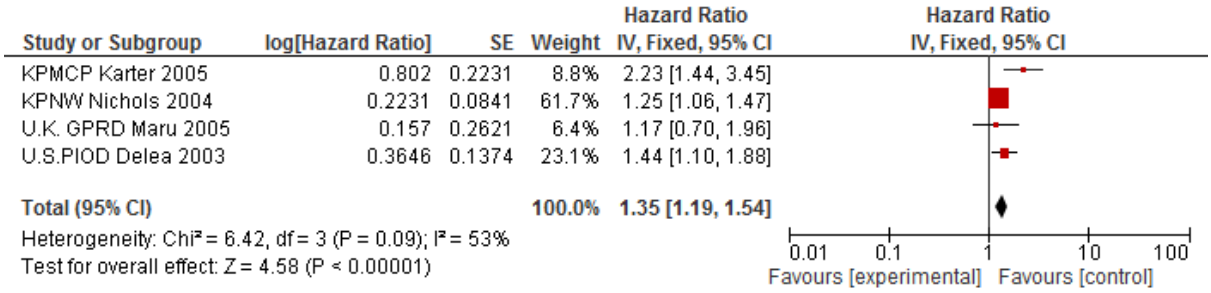


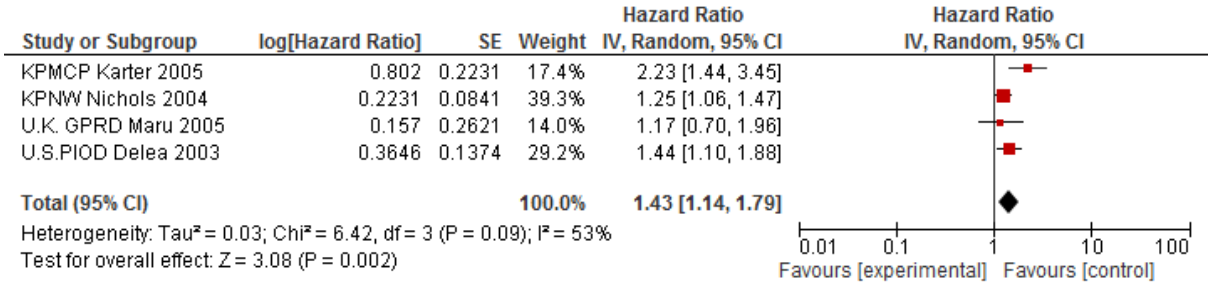
Insulin use (Relative Risk- unadjusted)



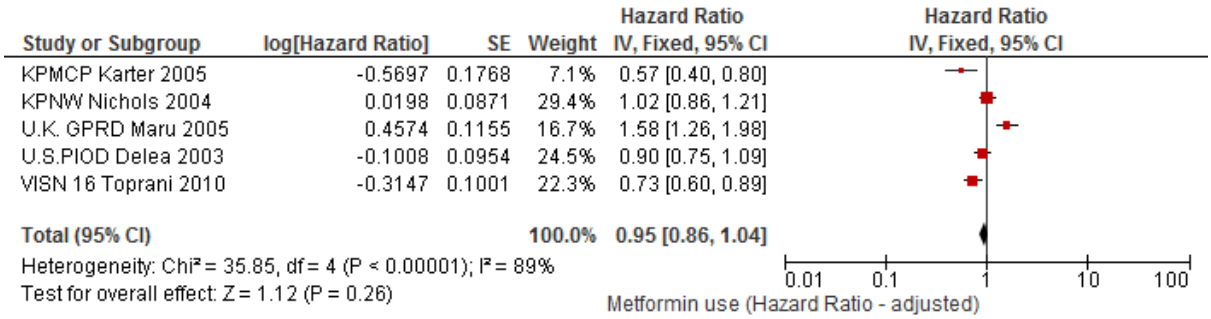


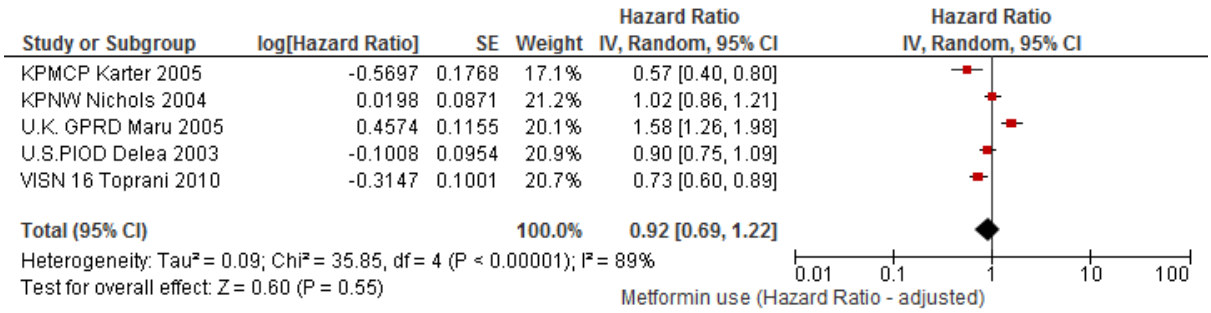
Insulin use (Hazard Ratio - adjusted)



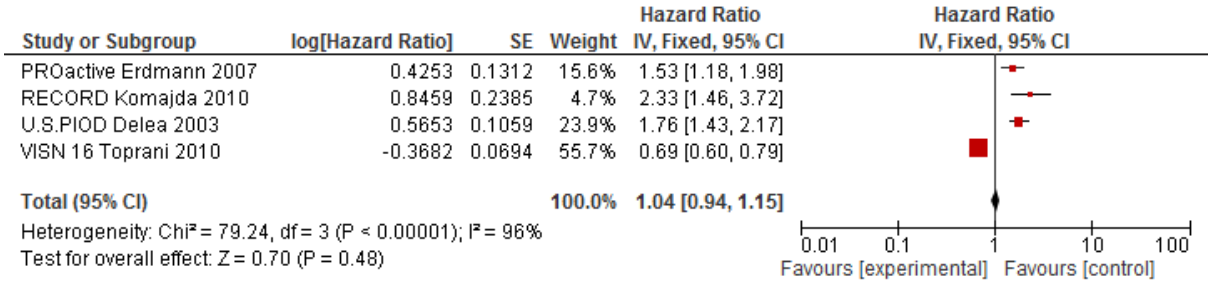


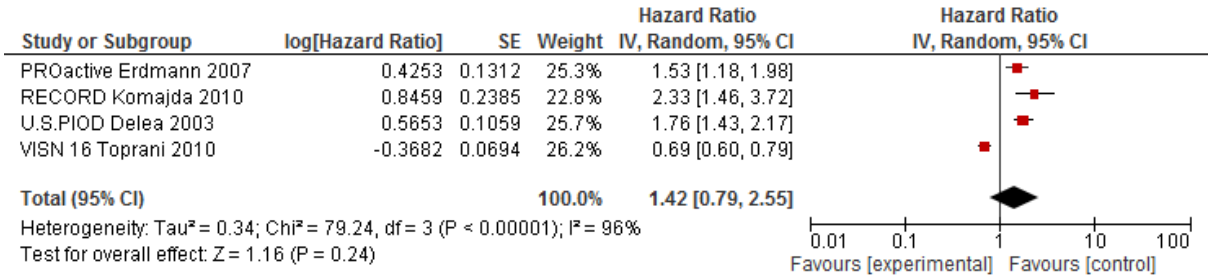
Metformin (Hazard Ratio - adjusted)



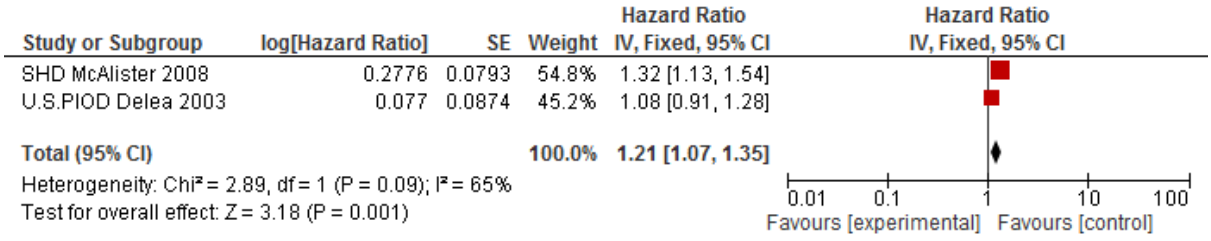


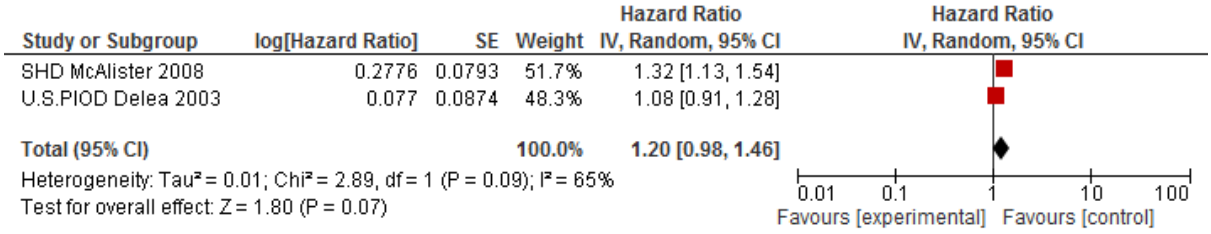
TZDs (Hazard Ratio – adjusted)



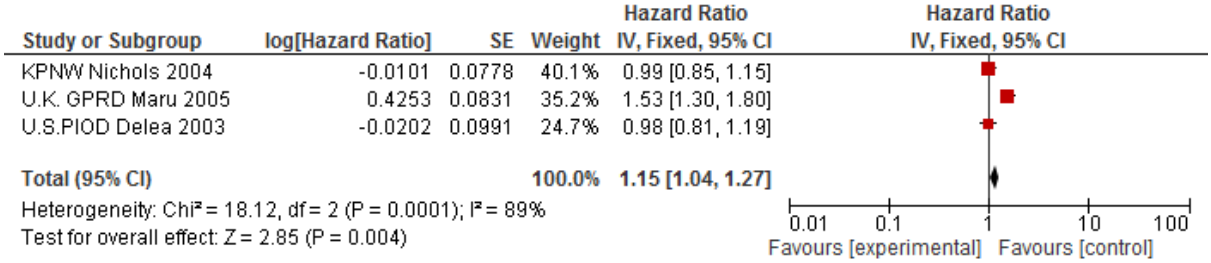


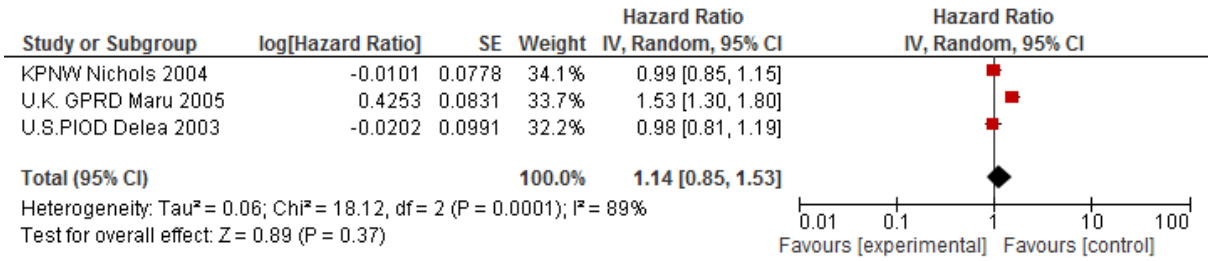
Sulfonylurea (Hazard Ratio – unadjusted)



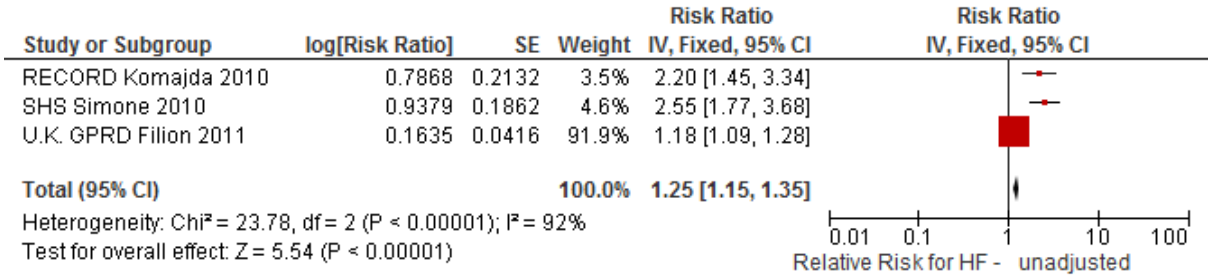


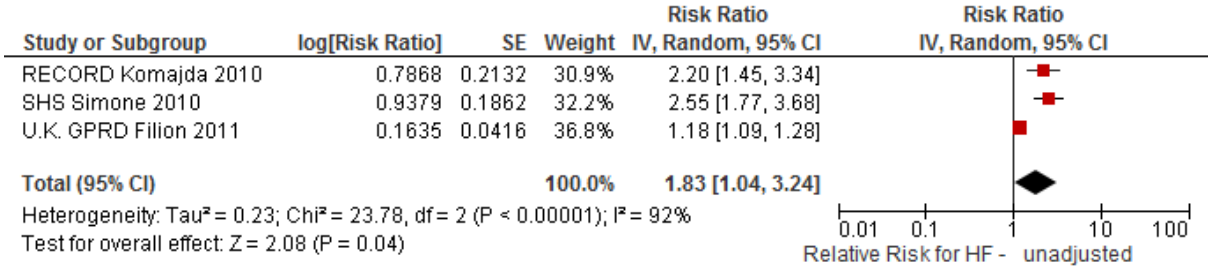
Sulfonylurea (Hazard Ratio – adjusted)



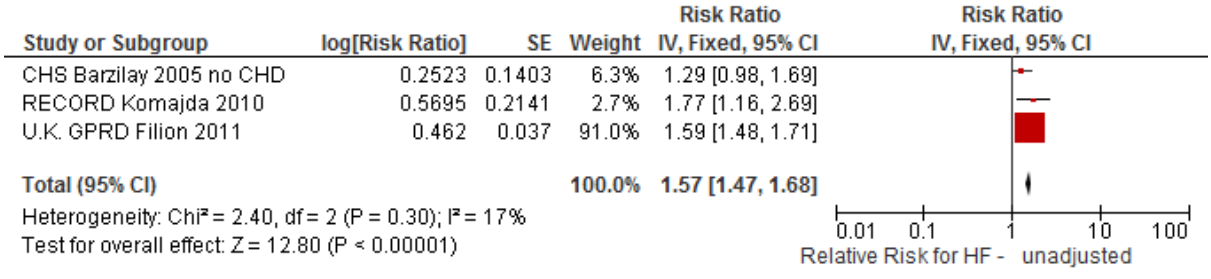


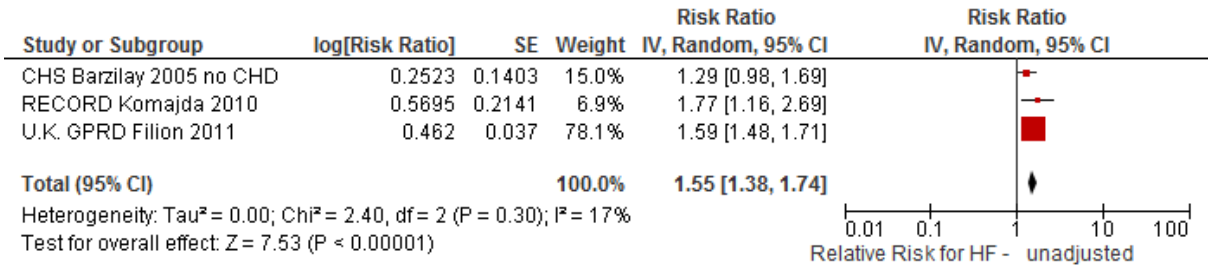
β-blocker (Relative Risk – unadjusted)



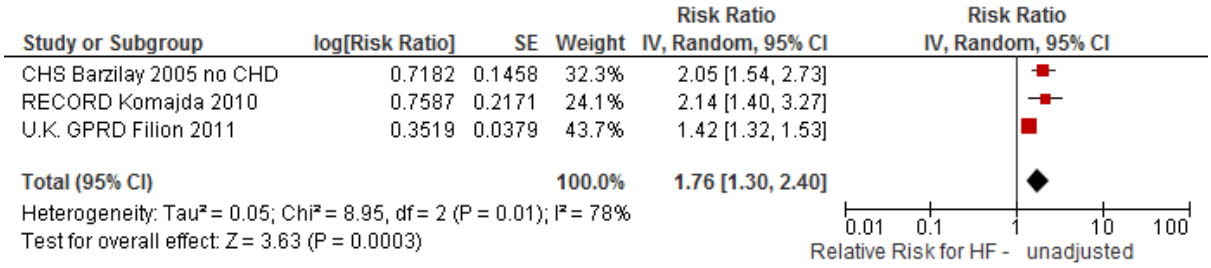


ACE-inhibitors (Relative Risk – unadjusted)

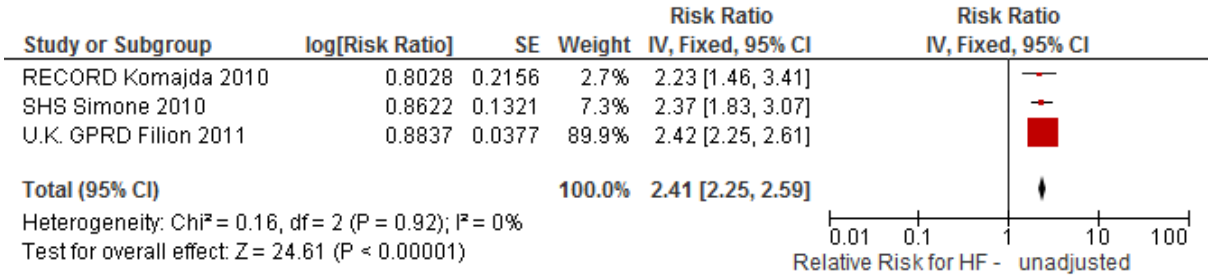


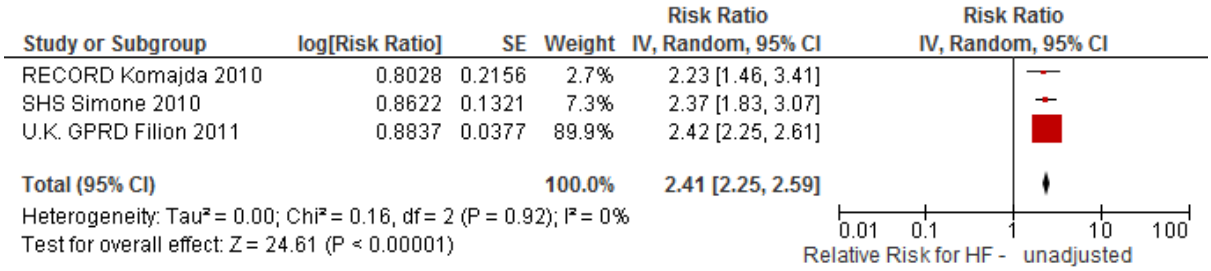


Calcium-channel blockers (Relative Risk – unadjusted)

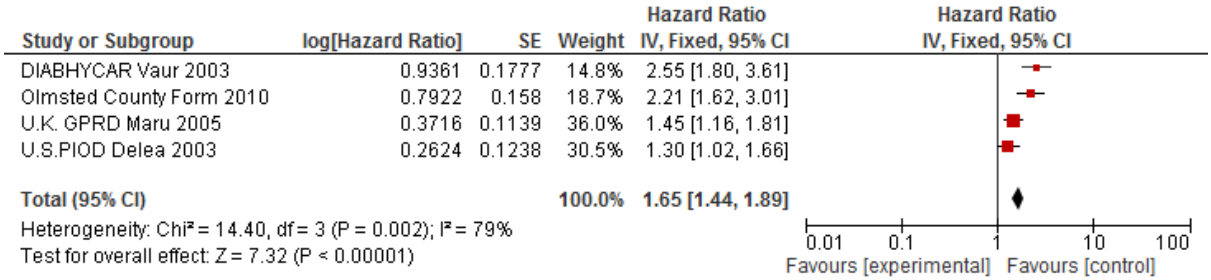


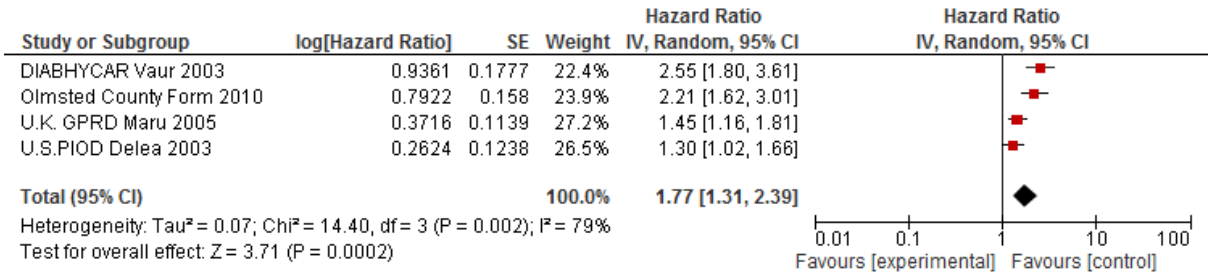
Diuretics (Relative Risk – unadjusted)



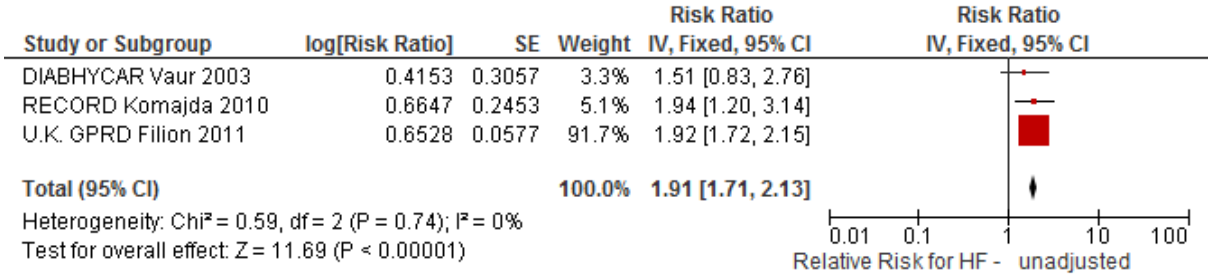


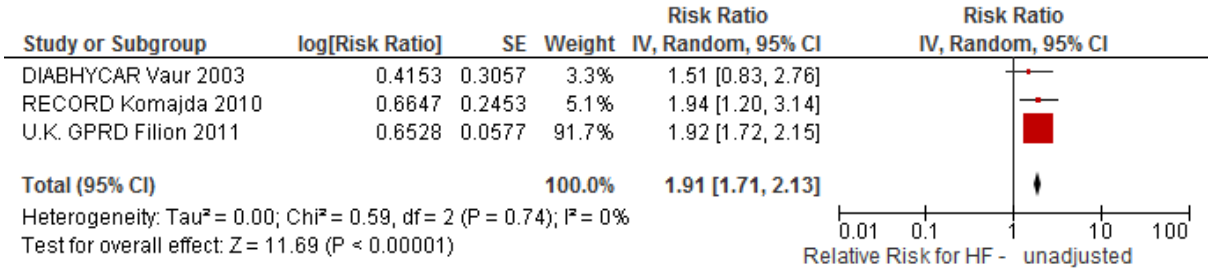
Coronary heart disease (Hazard Ratio – adjusted)



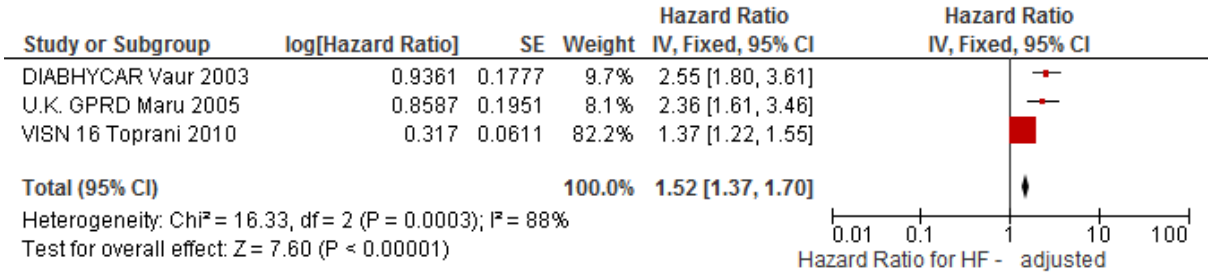


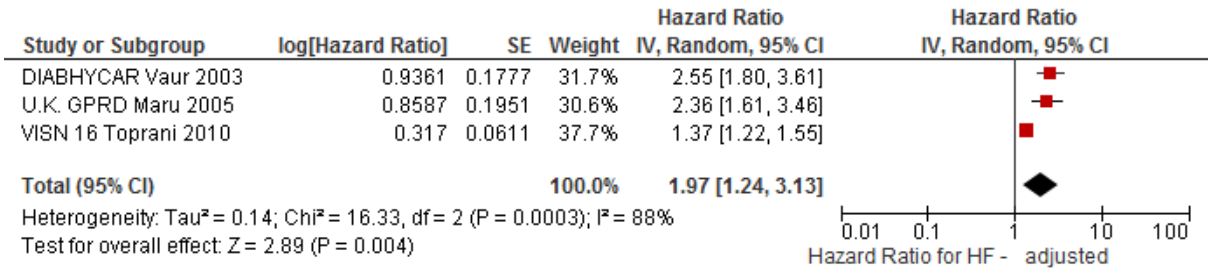
History of peripheral vascular disease (Relative Risk – unadjusted)



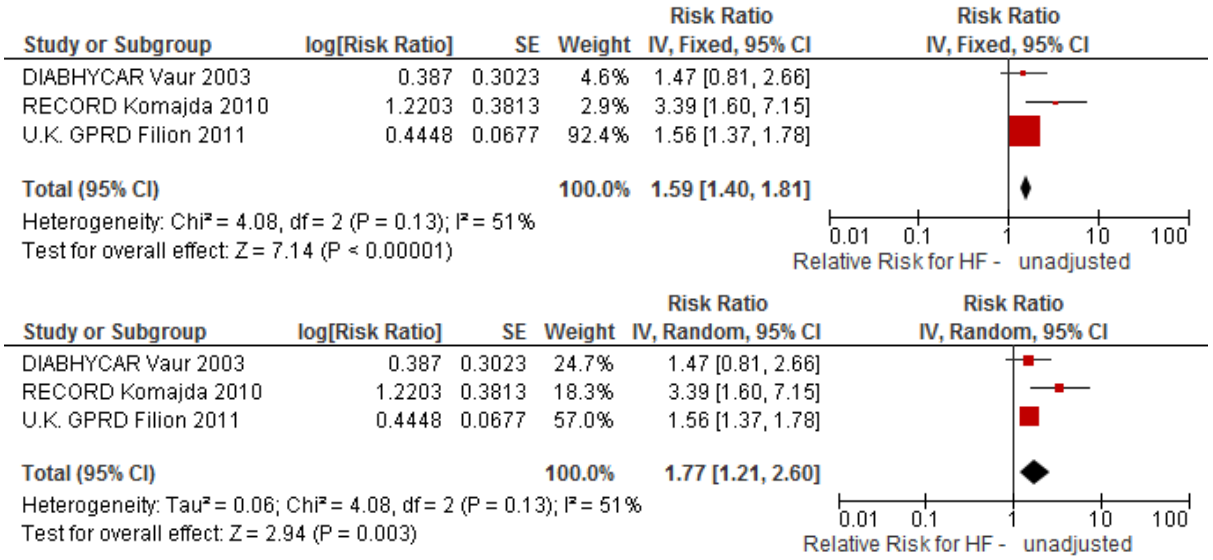


History of vascular disease (Hazard Ratio – adjusted)

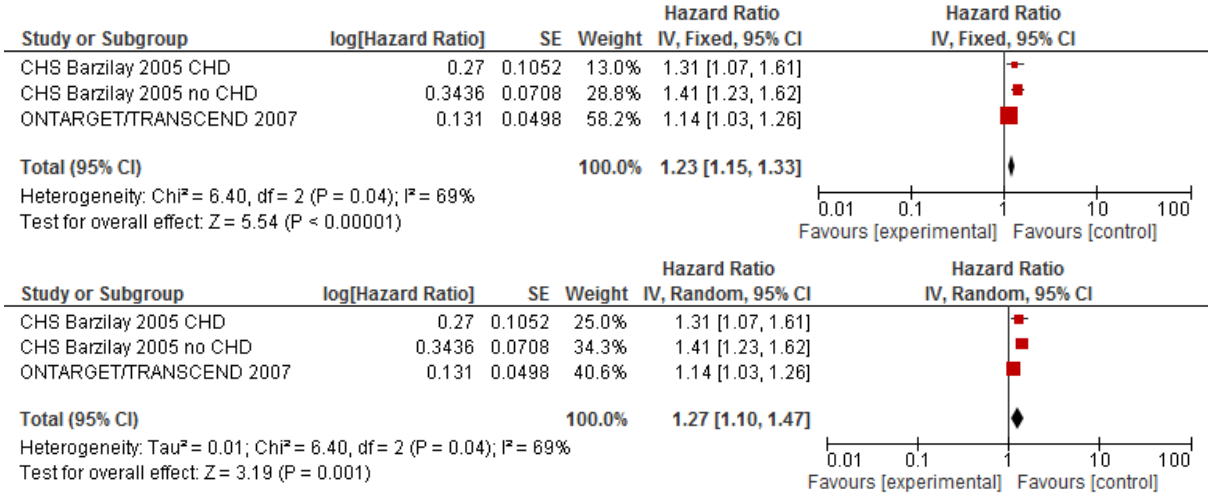




History of stroke (relative risk – unadjusted)

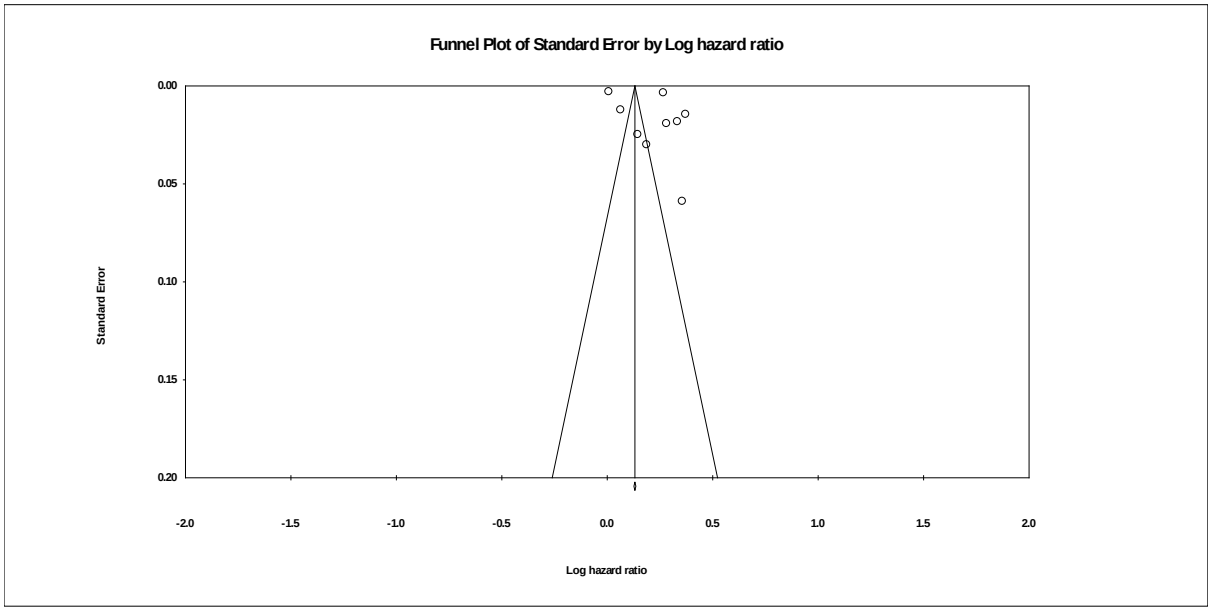


Fasting Glucose (1 SD increase) (Hazard Ratio - adjusted)



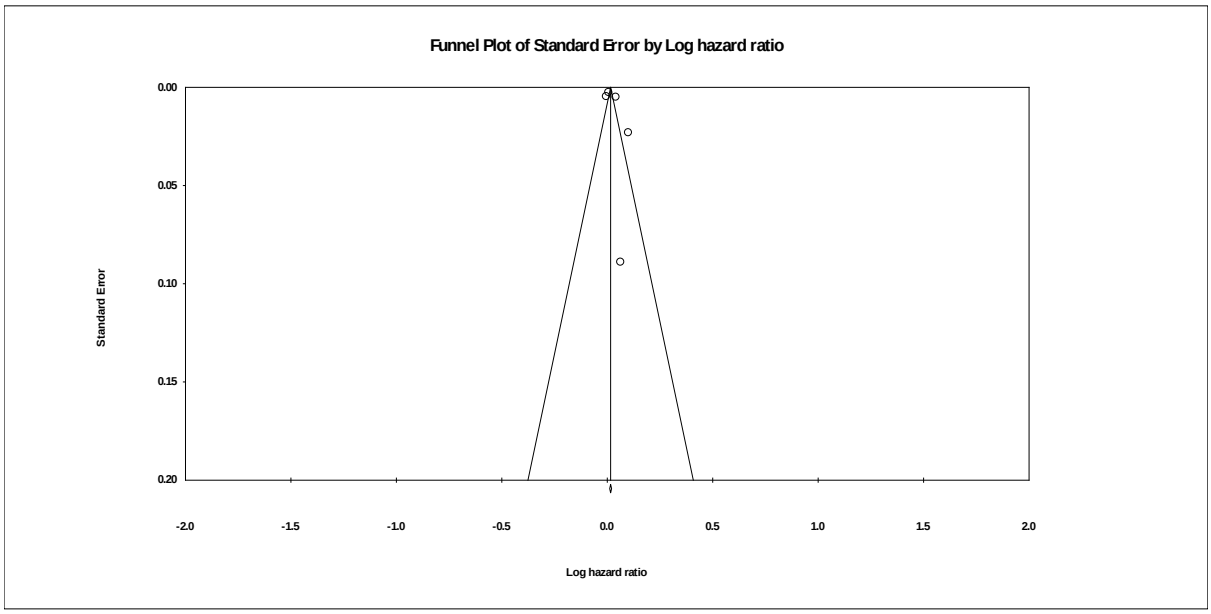
Appendix 2.4 Funnel plot

1) **Funnel plot: age.** The size of the data marker represents the weight of each trial.



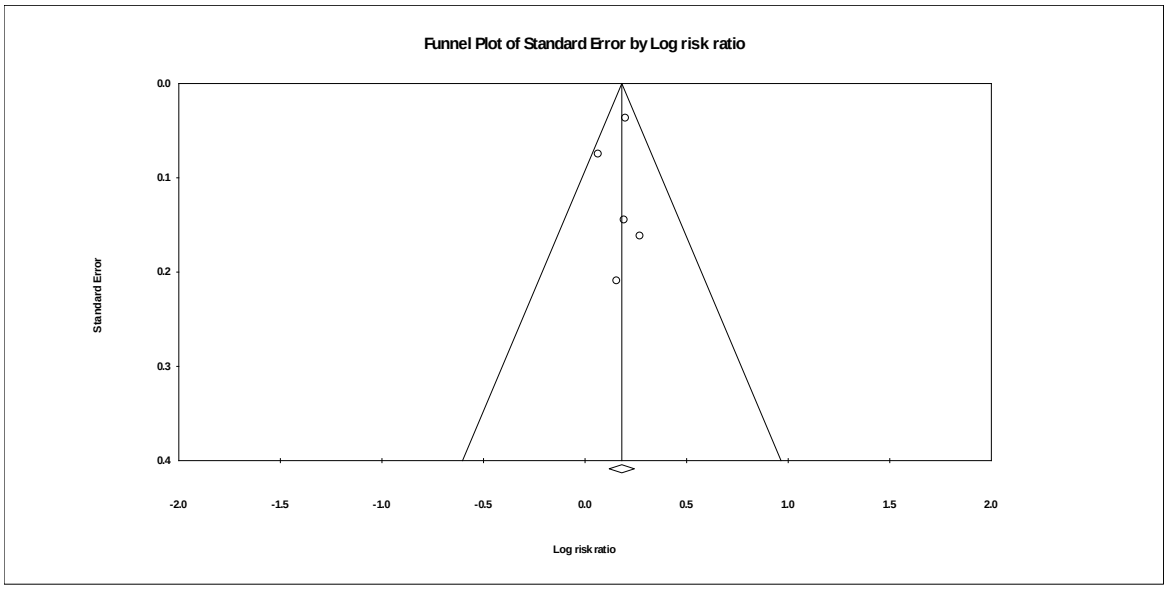
Egger's P-value= 0.42

2) **Funnel plot: BMI.** The size of the data marker represents the weight of each trial.



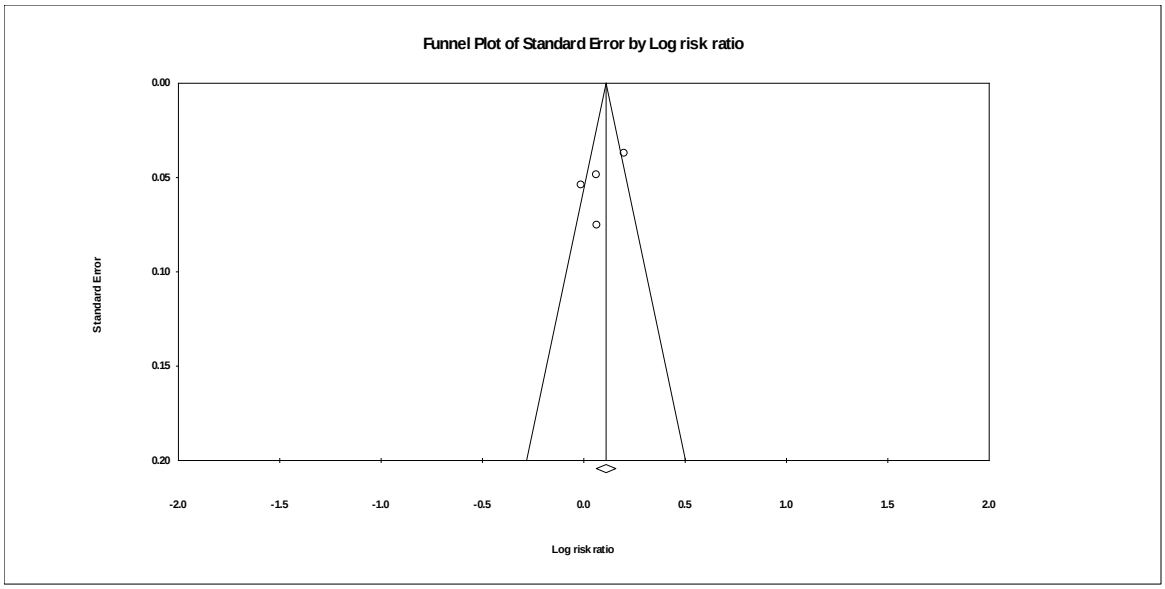
Egger's P-value= 0.40

3) **Funnel plot: hypertension.** The size of the data marker represents the weight of each trial.



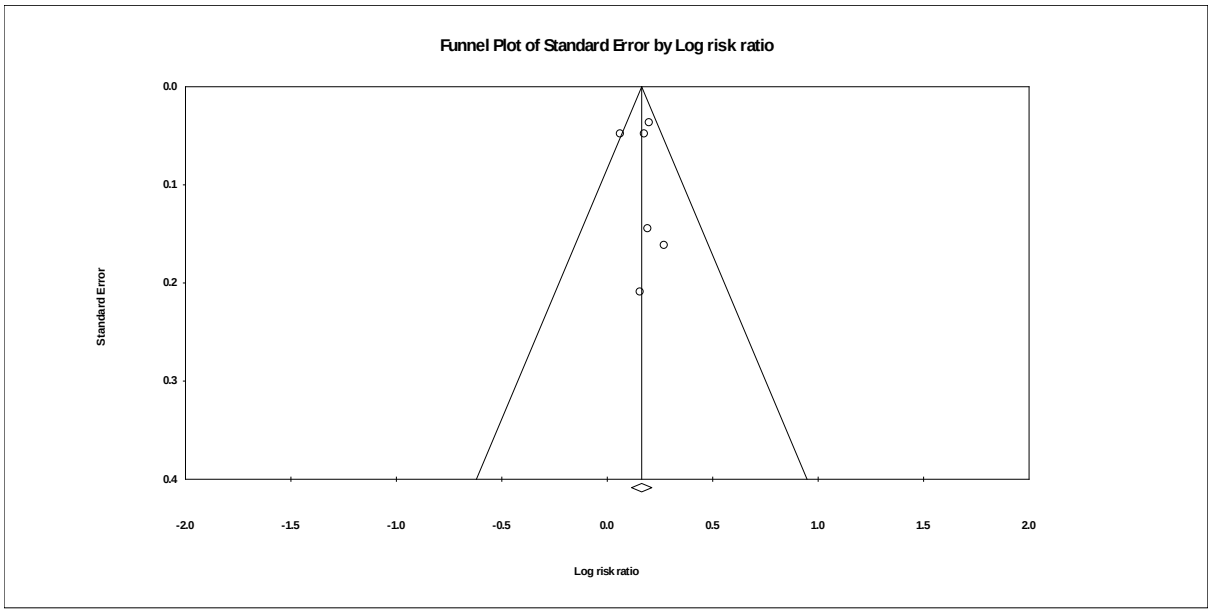
Egger's P-value= 0.92

4) **Funnel plot: insulin use.** The size of the data marker represents the weight of each trial.



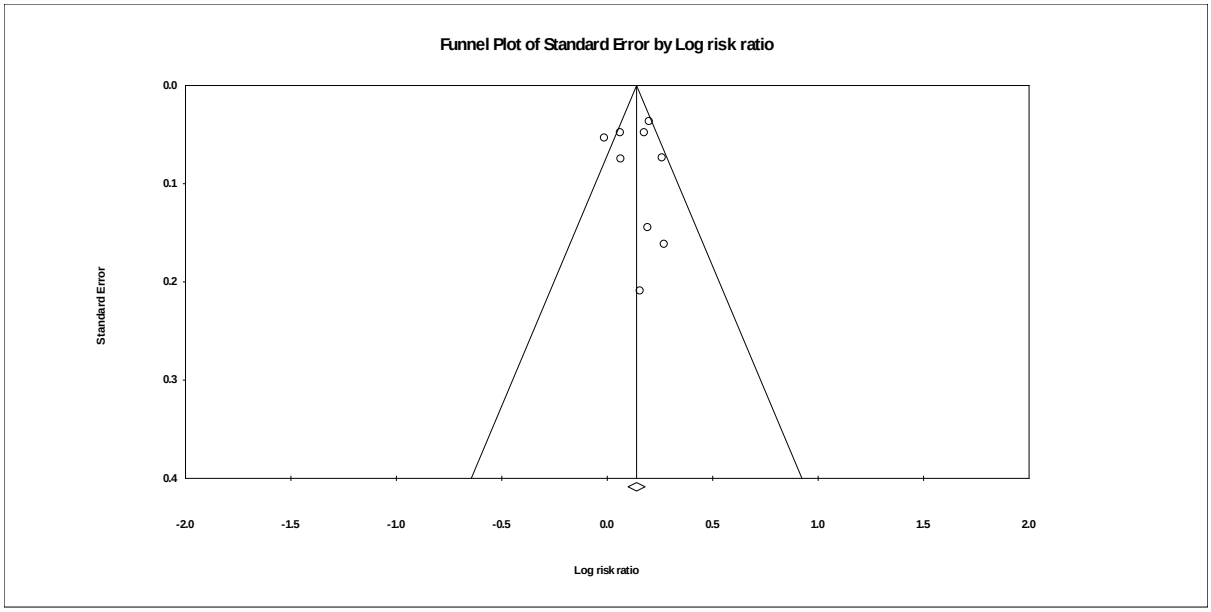
Egger's P-value= 0.29

5) **Funnel plot: smoking.** The size of the data marker represents the weight of each trial.



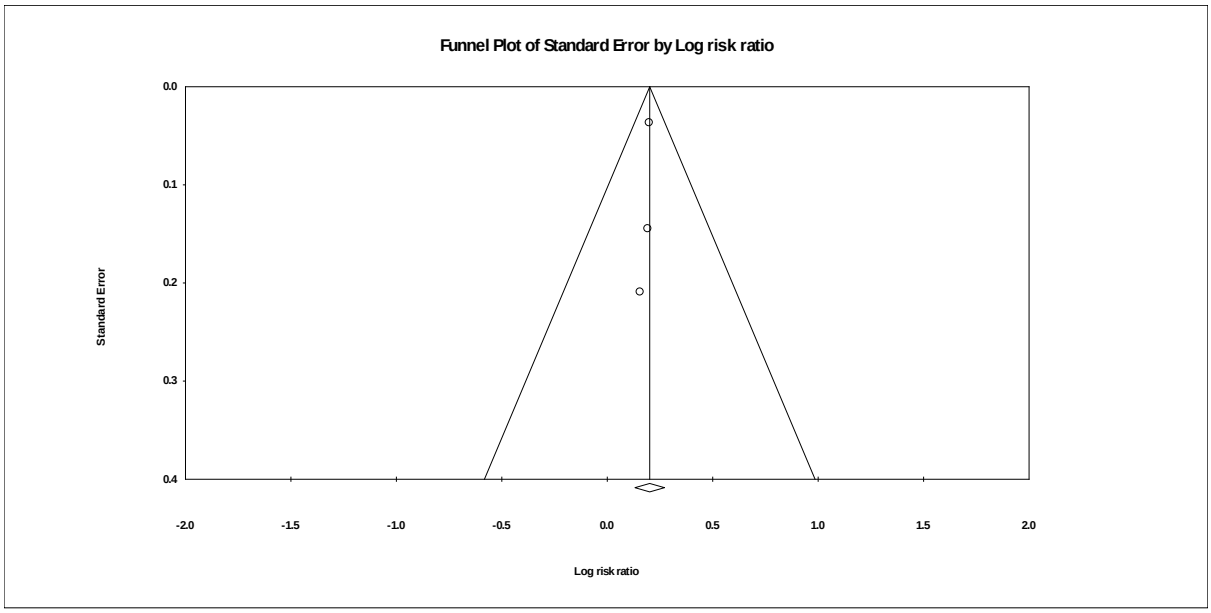
Egger's P-value= 0.86

6) **Funnel plot: male gender.** The size of the data marker represents the weight of each trial.



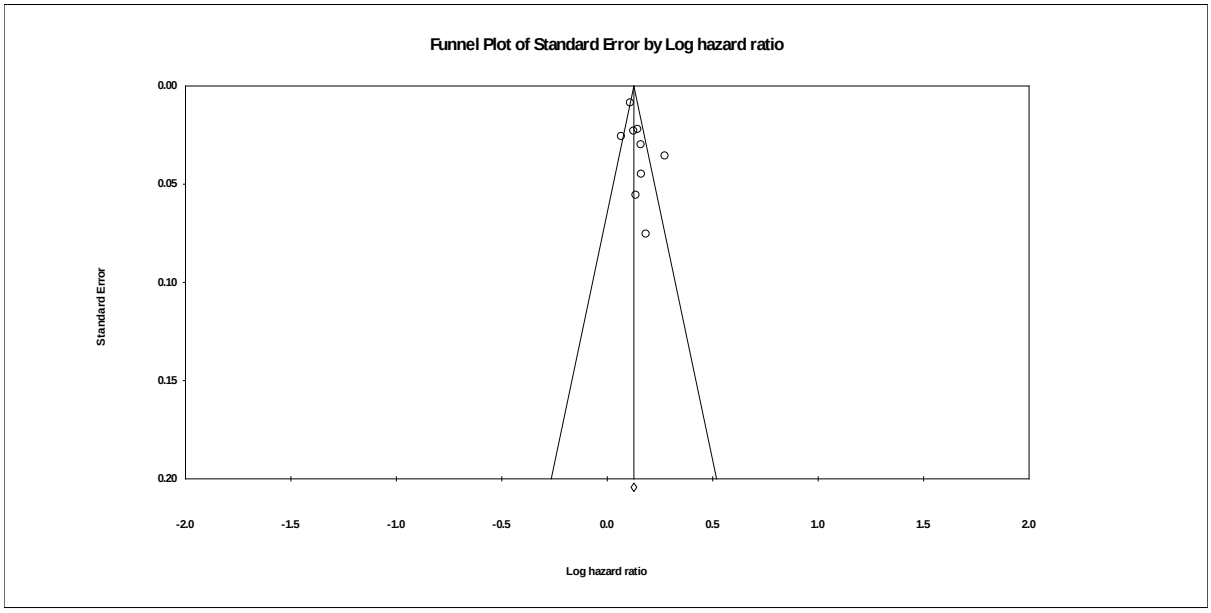
Egger's P-value= 0.68

7) **Funnel plot: cardiac protective medication.** The size of the data marker represents the weight of each trial.



Egger's P-value= 0.33

8) **Funnel plot: HbA1c.** The size of the data marker represents the weight of each trial.



Egger's P-value= 0.13

Chapter 3. Methodology

3.1 Preface

The research reported in this thesis is derived from the data collected on participants in the Tasmanian Study of Echocardiographic detection of Left ventricular dysfunction (Tas-ELF study). This chapter provides the study design, research rationale and the measurements used in this study. The specific details of each study are described in following chapters.

3.2Subjects

The Tasmanian Study of Echocardiographic detection of Left ventricular dysfunction was a prospective, randomized, open, blinded, end-point (PROBE) designed trial. The aim of this project was to reduce incident HF in the Tasmanian community, through implementation of a screening program for cardiac dysfunction and the use of cardio-protective therapy to limit the development of HF. Self-referred patients with at least one of the following risk factors for HF and aged≥ 65 years old from a community-based population in Tasmania were enrolled. The risk factors are T2DM, overweight, hypertension, family history of HF, cardiotoxin exposure and known cardiac disease (but not existing HF). Patients with symptoms of HF or existing HF or known ischaemic heart disease (CABG and/or AMI with regional scar) were excluded, as were patients with more than moderate valve disease, a history of HF and LV ejection fraction (LVEF) <40%, or life expectancy <12 months. In addition, as strain imaging was a requirement to assess subclinical cardiac dysfunction, patients with inability to acquire adequate echocardiographic images for speckle tracking imaging analysis at baseline were excluded. The target number of patients was 800 and the length of this study was 12 months for recruitment and 24 months for follow-up.

An overview of the study flow chart, updated to January 2017 is shown in Figure 3.1. Among 1,026 potentially eligible community participants volunteering for assessment, 378 were excluded due to failure to meet clinical inclusion criteria and 30 participants were excluded

after baseline echo screening, leaving 618 participants were included in the baseline analysis. After 2-years of follow-up, 4 participants lost contact and 39 participants were alive but unable to attend follow-up. Therefore the follow-up study was conducted in 576 remaining participants.

Among 618 patients included at baseline analysis, 310 (50%) had T2DM, 272 (44%) had obesity, 488 (79%) had hypertension, 229 (37%) had family history of HF, 74 (12%) had past chemotherapy, 52 (8%) had past heart disease. Among 310 patients with T2DM, 153 (49%) also had obesity, 236 (76%) had hypertension, 97 (31%) had family history of HF, 30 (24%) had past chemotherapy, and 22 (7%) had past heart disease. Among the non-diabetes group, hypertension was the most common risk factor, followed by family history of HF. Patients with past heart disease and cardiac sequelae of oncology management made up a relatively small percentage of the whole population and non-diabetic group.

The present thesis describes the subgroup of patients with T2DM. In the TasELF study, there were 310 T2DM patients were eligible for baseline analysis and 290 for follow-up analysis.

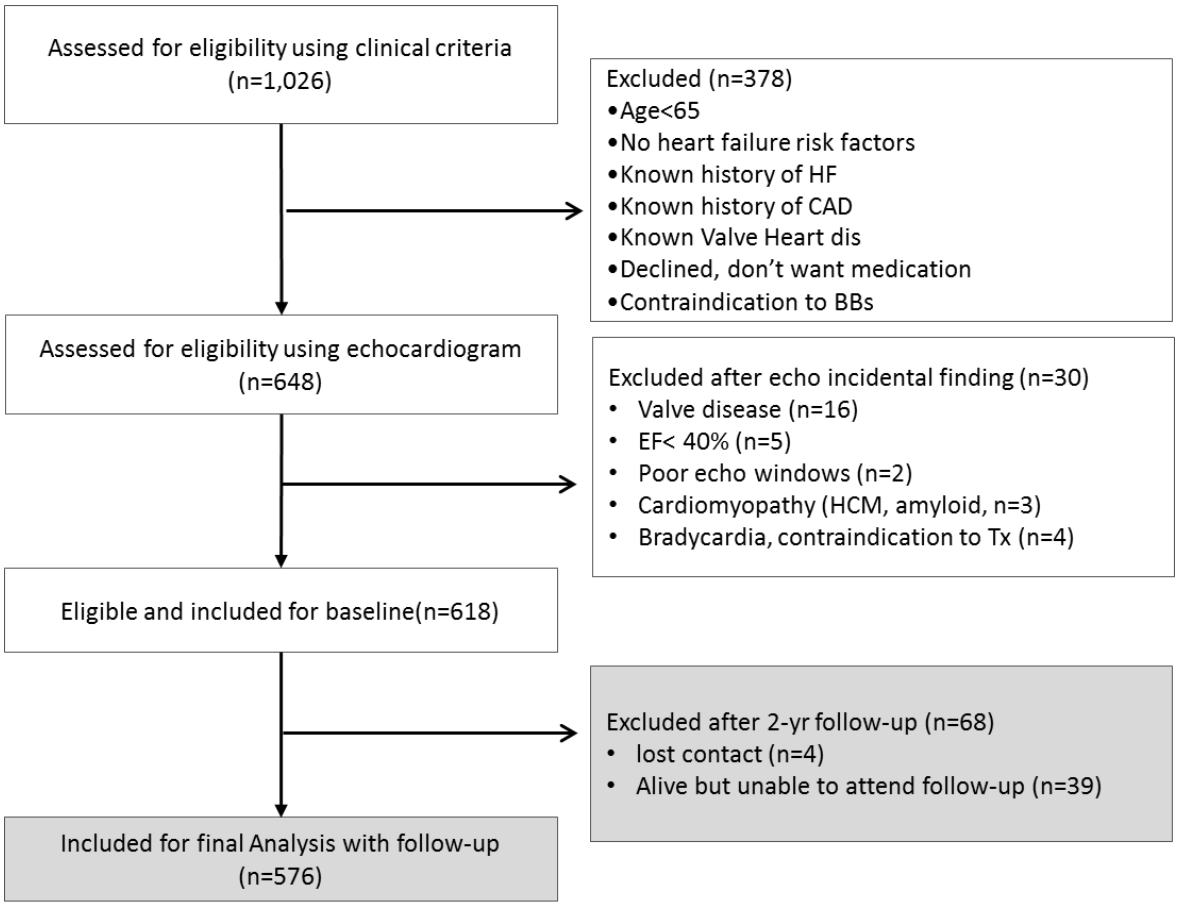
3.3 Clinical evaluation

3.3.1 Anthropometrics

Demographic characteristics, disease history, lifestyle factors, family history and medication use was collected using a standardized questionnaire. The questionnaire is provided in **Appendix 11.1**. Body weight was measured to nearest 0.1 in kilograms and height was measured to nearest 0.01 metres, both with shoes off. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. In addition to standardised weight and height measurements, waist circumference (WC) was measured with a tape measure to the nearest millimeter at the midpoint between the lower costal margin and the iliac crest by a

trained examiner. Supine resting blood pressure (BP) was measured twice and averaged in each patient after at least 5 minutes' rest.

Figure 3.1 Flow chart of study inclusion.



3.3.2 Questionnaires

EQ-5D questionnaire. The EuroQol-5 Dimensions (EQ-5D) questionnaire was used to assess the current general health status. The first part consists of five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. There are five levels of each dimension: 1) no problems; 2) slight problems; 3) some problems; 4) severe problems; 5) extreme problems. The second part EQ-5D visual analog scale (EQ-5D-VAS) is used as a quantitative measure of health status on a 20cm vertical with 0 to 100 points scale representing the 'worst imaginable health state' and 'best imaginable health state' [138].

DASI questionnaire. The Duke Activity Status Index Questionnaire (DASI) assessed the functional capacity of patients and the scores from DASI are expressed in metabolic equivalents (METs) which could be used to get a rough estimate of a patient's peak oxygen uptake. The questionnaire includes 12 items focused on daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs[139]. Each item had two answers - 'yes' and 'no' and each 'yes' corresponded to different values. The final value of DASI score (between 0 to 58.2 points)was obtained by adding all performed scores together – the highest score represents better functional capacity.

PHQ-9 questionnaire. The Patient Depression Questionnaire-9 (PHQ-9) was used to score for common mental disorders which scores each of the nine Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria as "0" (not at all) to "3" (nearly every day) [140, 141]. The total value of PHQ-9 score ranged from 0 (no depression) to 27(severe depression)[138].

All questionnaires used in the TasELF study are provided in **Appendix 11.2**.

3.3.3 Six-minute walk test (6MWT)

The six-minute walk test (6MWT) was conducted on a hard, flat 25-metre track to test the distance an individual is able to walk as far as possible over a total of six minutes. Patients were allowed to self-pace as needed as they traversed back and forth along the straight marked pathway [142].It was ensured that patients walked the same course on each re-test. At the end of the test, the total distance walked was recorded.

3.3.4 Echocardiographic evaluation

A comprehensive echocardiogram including standard transthoracic 2D, Doppler echocardiographic studies and speckle tracking echocardiogram (STE) using sensitive systolic and diastolic function parameters was performed using the same ultrasound machine (Siemens ACUSON SC2000, 4V1c and 4Z1c probes, Siemens Healthcare, Mountain View, CA) in

accordance with the American Society of Echocardiography guidelines [143, 144]. Images were saved in raw data format and analysed offline. LV internal dimensions and wall thickness, chamber volumes and valvular morphology were assessed. LV mass index (LVMi) was obtained from LV mass measurement using standard criteria and normalised for body surface area. LV hypertrophy (LVH) was defined as LVMi>115 g/m^2 in men and >95 g/m^2 in women. LVEF measurement was used the modified Simpson's biplane method. LV inflow was obtained using pulsed wave Doppler in the apical 4-chamber view; peak early (E) and late (A) diastolic velocities, deceleration time (DT) and E/A ratio were assessed. Peak early diastolic medial and lateral mitral annular velocity (e') and the ratio of mitral inflow early diastolic velocity to average e' velocity were obtained from pulsed-wave tissue Doppler and assessed at septal and lateral mitral annuli and averaged for calculation for E/e'; E/e'>13 was used as an indicator of diastolic dysfunction. For deformation analysis, standard grayscale 2-dimensional images were acquired in conventional 4-chamber, 2-chamber, 3-chamber, parasternal short-axis views at the mid, basal, and apical level. Global longitudinal strain (GLS) was calculated by average of three apical views using standard software. Although muscle shortening during a cardiac cycle is described as a negative number, for computational simplicity (and because there were no positive GLS), we express GLS in this thesis without this information in this thesis. Thus, GLS<18% was considered consistent with LV dysfunction [73, 74] while<18% was considered as impaired GLS.

3.3.5 Outcomes

The primary endpoint for the study was new-onset of HF and all-cause mortality. During the follow-up period, potential HF symptoms and signs were assessed through regular phone calls, followed by symptom surveillance questionnaires and clinical visits. Records of all-cause hospitalisation were obtained and collected. Suspicious HF symptoms and signs were reviewed

by three independent cardiologists. The diagnosis of HF was established according to Framingham heart failure criteria[4].

3.4 Ethical consideration

All participants provided written, informed consent prior to enrolment in the study, and all procedures in the TasELF study were approved by the Tasmanian Human Research Ethics Committee.

3.5 Data analysis

Descriptive data are presented as mean ± standard deviation (SD) and dichotomous data as subject number and percentage. Comparisons between the groups were performed by independent samples t test or analysis of variance (ANOVA) as appropriate; the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Linear or logistic regression was used to assess associations between one or more interested independent variables and dependent variables and reported as Relative Risk (RR) or Odds Ratio (OR) and 95% confidential intervals (CIs). Cox regression analysis was used in order to identify the strongest predictors of outcome among clinical, demographic, echocardiographic variables and other interested factors and reported as hazards ratio (HR) and 95% CIs. Analyses were performed with standard statistical computer software (SPSS 22, IBM, Chicago, IL); $p<0.05$ was deemed to be statistically significant. Non-normally distributed variables were normalised based on the Box-Cox transformation technique using STATA software (Stata/IC 12.1, StataCorp LP, Plano, TX, USA).

Chapter 4. Association of Insulin Resistance with Impaired Functional Capacity in T2DM

Published in part in[10]:

- Wang Y, Yang H, Nolan M, Negishi K, Burgess J, Marwick TH. Association of waist circumference with impaired six-minute walk in type 2 diabetes mellitus is independent of cardiac function. *J Diabetes Complications*. 2016.

4.1 Preface

Clinical and observational studies have determined that impaired functional capacity is a powerful predictor of cardiac and all-cause of death in patients with T2DM. Exercise intolerance assessed by six-minute walk test (6MWT)was commonly observed in patients with T2DM in the TasELF study. Diabetic patients often complain of limited exercise capacity with fatigue and although these symptoms may be due to other conditions such as coronary artery disease or hypertensive heart disease, the presence of diabetes itself is independently associated with limited functional capacity[145]. LV dysfunction is associated with impaired exercise capacity and adverse cardiac outcome in T2DM, but the causes of exercise intolerance in T2DM are not clearly understood. As insulin resistance (IR), which is linked to waist circumference (WC), is a characteristic feature of HF pathophysiology that affects prognosis, we hypothesised that insulin resistance might be a contributor to reduced functional capacity. We tested the hypothesis that WC is associated with the distance of 6MWT independently and incrementally to clinical, biochemical, therapeutic and echo variables in T2DM without overt HF.

4.2 Abstract

Subclinical left ventricular dysfunction has been associated with impaired exercise capacityin type 2 diabetes mellitus. In this community-based study of 274 asymptomatic T2DM patients (71±4 years, 55% men) with preserved ejection fraction, a comprehensive resting echocardiogram was performed to gather sensitive systolic and diastolic function parameters (including speckle tracking echocardiography), and a standard six-minute walk test was performed. Tertiles of increasing waist circumference were associated with worsening walk distance. In this community-based study, we found an association of waist circumference with impaired exercise capacity, independent of age, gender, diabetes duration, insulin and angiotensin blockade, LV mass, systolic and diastolic function.

Impaired exercise capacity is a powerful and independent predictor of increased risk of cardiac events in type 2 diabetes mellitus (T2DM)[146]. The mechanism of impaired exercise capacity is unclear, but appears to be associated with the presence of diabetes[145], as well as left ventricular (LV) dysfunction[147, 148]. LV ventricular dysfunction is common in T2DM; most of these patients lack symptoms of heart failure, and ejection fraction is preserved, so it is often described as "subclinical". As insulin resistance (IR) is linked to waist circumference (WC)[149, 150] as well as subclinical LV dysfunction, we sought whether the LV dysfunction was independently associated with impaired exercise capacity.

4.3 Patients and methods

We prospectively recruited 274 asymptomatic T2DM patients (71±4y, 55% men) with preserved ejection fraction from a community-based population. These patients were aged ≥65 years with ejection fraction ≥55% and without moderate or worse valve disease, history of heart failure and inability to acquire adequate echocardiographic images (**Table 4.1**). In

addition to standardized weight and height measurements, waist circumference (WC) was measured with a tape measure to the nearest millimeter at the midpoint between the lower costal margin and the iliac crest by a trained examiner. The age, gender, disease and family history of HF and medication use were obtained using a standardized questionnaire. Supine resting blood pressure (BP) was measured twice and averaged in each patient after at least 5 minutes rest. The EuroQol-5 Dimensions [EQ5D] questionnaire was used to assess the current general health status. A six-minute walk test (6MWT) was performed in a 25m indoor corridor with a hard, flat surface to test the greatest distance an individual was able to walk over a total of six minutes [142]. A comprehensive resting echocardiogram including speckle tracking echocardiography (STE) using sensitive systolic and diastolic function parameters was performed using the same ultrasound machine (SC200, Siemens, Mountain View, CA). Global longitudinal strain (GLS) was calculated by average of three apical views using standard software, and<18% was considered consistent with LV dysfunction[151, 152]. The study protocol was approved by the Tasmanian Human Research Ethics Committee, and all participants provided written consent.

4.4 Results

The baseline characteristics of the subjects are shown in **Table 4.1.**The mean 6MW distance (6MWD) was 451±106m (ranging from 100~667m) and mean WC was 103.9cm±13.4 (ranging from 70~155cm). Tertiles of increasing WC were associated with worsening 6MWD (1st:471±97m; 2nd:469±99m; 3rd:408±116m; $p<0.001$). In a univariable linear regression (**Table 4.1**), demographics, body habitus, diabetes duration, hypertension, insulin use and diastolic function parameters were associated with 6MWD. Age, gender, diabetes duration, systolic BP, EQ-5D score, insulin use, ARB use, E/e' ratio, LVMi, GLS and WC were entered into multivariable regression models, guided by clinical judgment and absence of colinearity.

WC was associated with reduced exercise capacity, independent of age, gender, diabetes duration, insulin and ARB use, E/e' ratio, $LVMi^{1.7}$ and GLS (model R^2=0.37). The association of clinical variables (age, sex, diabetes duration, insulin and ARB use) were not improved by adding E/e' (p=0.82), LVMi (p=0.01) or GLS (p=0.83), but significantly increased by adding WC (p<0.01) (**Table 4.2**).

Table 4.1 Clinical and echocardiography characteristics and their univariable association with 6MW distance.

Variables	Mean±SD (n=274)	R^2	β(95%CI)	P value
Age(years)	71±4	0.07	-6.6(-4.5,-3.8)	<0.01
Male Gender (n, %)	150(54.7)	0.04	45.5(20.2,70.8)	<0.01
Body Mass Index(kg/m^2)	30.6±6	0.19	-7.9(-9.9,-6.0)	<0.01
Diabetes Duration(years)	11±9	0.05	-2.6(-4.3,-1.0)	<0.01
Waist(cm)	103.9±13.4	0.14	-2.9(-3.9,-2.1)	<0.01
Hip(cm)	107.6±12.5	0.26	-4.3(-5.2,-3.5)	<0.01
Waist-Hip-Ratio	0.97±0.08	0.02	187(25.1,348.3)	0.02
Resting Heart Rate(n/min)	69±11	0.01	-0.7(-1.8,0.4)	0.19
Systolic BP(mmHg)	138±15	0.01	-0.7(-1.5,0.2)	0.11
Diastolic BP(mmHg)	81±10	0.05	2.4(1.1,3.7)	<0.01
Hypertension (n, %)	209(76.3)	0.01	-43.9(93.1,5.2)	0.08
Past chemotherapy(n, %)	22(8)	0.01	-38.7(-84.9,7.5)	0.10
Family history of HF(n, %)	85(31)	0.00	2.6(-25.2,30.4)	0.85
Insulin (n, %)	65(23.7)	0.07	-68.7(-97.8,-39.6)	<0.01
Metformin (n, %)	184(67.2)	0.00	14.7(-12.6,42.0)	0.29
ACE Inhibitor (n, %)	98(35.8)	0.00	6.4(-20.5,33.2)	0.64
Beta-Blocker (n, %)	13(4.7)	0.01	42.9(-17.4,103.2)	0.16
Calcium Antagonists (n, %)	76(27.7)	0.01	-19.5(-48.2,9.1)	0.18
Angiotensin II Receptor Blocker (ARB) (n, %)	108(39.4)	0.01	-25.8(-51.9,0.4)	0.05
Diuretic (n, %)	30(10.9)	0.01	-34.0(-75.0,7.0)	0.10
Lip Lowering medication (n, %)	201(73.4)	0.00	15.1(-13.9,44.1)	0.31
EQ-5D score	7±2	0.00	-0.6(-6.2,5.1)	0.85
Echocardiography				
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.66±0.17	0.06	-152.0(-224.3,-79.8)	<0.01
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.84±0.20	0.04	-105.3(-171.9,-38.9)	<0.01
E/A ratio	0.79±0.21	0.01	-45.8(-109.1,17.6)	0.16
Mitral valve deceleration time (ms)	248.2±52.9	0.01	0.2(-0.1,0.4)	0.41
Early diastolic mitral annular velocity (e') (m/s)	0.08±0.02	0.00	-158.5(-952.8,635.7)	0.70
Average E/e' ratio (E/e')	9.28±2.74	0.03	-7.1(-11.7,-2.6)	<0.01
LA maximal volume index (ml/m^2)	32.0±10.04	0.00	-0.01(-1.4,1.2)	0.85
LV mass index (g/m^2)	92.4±24.4	0.00	-0.1(-0.6,0.4)	0.71
LV mass index ($g/m^{1.7}$)	74.7±22.1	0.02	-0.7(-1.3,-0.2)	0.01
LV ejection fraction (%)	62.9±6.7	0.00	-0.3(-2.2,1.6)	0.75
GLS (%)	-17.6±2.7	0.00	-0.8(-5.7,4.0)	0.74

Table 4.2. A summary of regression models (dependent variable: 6MWD)

Model	Adjusted R^2	R^2 change	P value
Age + male gender + diabetes duration + SBP + EQ-5D score	0.18		
Age + male gender + diabetes duration + SBP + EQ-5D score **+ Insulin + ARB**	0.23	0.06	<0.01
Age + male gender + diabetes duration + SBP + EQ-5D score + Insulin + ARB **+ E/e' + LVMi* + GLS**	0.25	0.02	0.20
Age + male gender + diabetes duration + SBP + EQ-5D score + Insulin + ARB + E/e' + GLS **+** LVMi* **+ WC**	0.37	0.12	<0.01

*Normalization of left ventricular mass by height$^{1.7}$

4.5 Discussion

In this study of T2DM patients with preserved ejection fraction (arbitrarily designed on the basis of EF >55%), T2DM patients had shorter 6MWT than those published in healthy subjects (mean distance range 514~588).[153] The results also confirm the presence of resting diastolic dysfunction in T2DM[154, 155]. The major finding was that, on average, 6MWT in T2DM was reduced by 2.9 meters for every additional cm of WC. The association of WC with exercise capacity in T2DM was independent and incremental to diastolic dysfunction and other echocardiographic parameters and clinical and other demographic factors (age, sex, BMI, diabetes duration and medication use). This study confirms this finding with submaximal testing (6MW). The practical measurement of WC provides a simple tool to predict 6MWT that could be used to assess physical function, clinical condition and prognosis in cardiovascular diseases.

This study has confirmed the presence of resting diastolic dysfunction in a large proportion of apparently healthy individuals with T2DM. While 6MW distances in T2D are below the 25th percentile of published controls of similar age,[10] WC predicts 6MW, independent of changes in cardiac function. Thus, a simple measurement of WC can inform clinical practice, by leading to a heightened attention to functional capacity.

4.7 Conclusion

WC is an independent and incremental predictor of exercise capacity over clinical and echo information in asymptomatic patients with T2DM.

4.6 Postscript

This chapter focused on characterizing the relationship of clinical parameters, including state of deformation imaging and exercise function assessed by 6MWT, provided the clinical relevant finding that WC(a marker of IR)is a strong predictor of 6MWD. This finding was derived from a cross-sectional analysis of baseline data in the TasELF study. Whether baseline 6MWD and WC could predict the development of HF in the present cohort after 2-year follow-up was not determined. Accordingly, the next chapter addresses the incidence of HF and all-cause mortality in this cohort and the predictors of the endpoint.

Chapter 5. Subclinical LV Dysfunction, Function Capacity, Quality of Life and Outcomes in Stage A Heart Failure

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5.1 Preface

The early detection and prevention of symptomatic HF remains a major goal of cardiovascular research as the prevalence of HF is still increasing. In recognition of this concept, the American Heart Association and American College of Cardiology proposed the concept of HF stages to emphasize the progressive pathophysiology of HF – from risk factors to asymptomatic changes in cardiac function and structure to symptomatic HF to overt HF, disability and death. Longitudinal community studies are necessary to clarify the rate of progression through asymptomatic stage A to stage B HF, in order to define strategies for prevention of HF progression. Among the stage A HF risk factors listed in ACC/AHA guidelines, diabetes is one of the strongest risk factors, independent of hypertension and atherosclerosis. However, in the context of limited resources, the relative merit of screening in the context of diabetes and other risk factors has not been determined. In the following chapter, we seek to address this by better understanding the prevalence of stage B HF, functional capacity, quality of life and clinical outcomes among stage A HF of different aetiologies.

5.2 Abstract

Background. Patients with heart failure (HF) risk factors are described as being in stage A of this condition (SAHF). Management is directed towards prevention of HF progression, but to date, no evidence has been described to align the intensity of this intervention to HF risk. We sought to what extent SAHF of type 2 diabetes mellitus (T2DM) and other HF risks showed differences in subclinical LV function, exercise capacity and prognosis.

Methods. We recruited 551 elder asymptomatic SAHF patients (age 71±5 y, 49% men, 290 T2DM) with at least one risk factor from a community-based population with preserved ejection fraction. All underwent a comprehensive echocardiogram including global longitudinal strain (GLS) and a six-minute walk test (6MWT) and were followed for 2 years. The primary endpoints were new-onset HF and all-cause mortality.

Results. The T2DM group was associated with reduced 6MW distance (451±111 vs 493±87m, p<0.001), worse diastolic function (E/e' 9.2±2.7 vs 8.7±2.4, p=0.028) and impaired GLS (-17.7±2.6 vs -19.0±2.6%, p<0.001). Over a median follow-up of 1.6 years, 49 T2DM-SAHF and 27 other-SAHF met the primary endpoint. T2DM-SAHF had significantly worse outcome than other-SAHF (p=0.021). In Cox models, obesity (HR=2.46; p=0.007), atrial fibrillation (AF) (HR=2.39; p=0.028), 6MWD (HR=0.99; p=0.034) and GLS (HR=1.14; p=0.033) were independently associated with the primary endpoint in T2DM-SAHF, independent of age and glycemic control.

Conclusions. T2DM-SAHF has worse subclinical LV function, exercise capacity and prognosis than other-SAHF. Impaired GLS, AF, exercise capacity and obesity are associated with a worse prognosis in T2DM-SAHF but not in other-SAHF.

5.3 Background

The current ACC/AHA heart failure guidelines define Stage A heart failure (SAHF) as existing in subjects with risk factors for heart failure (HF), in the absence of structural heart disease or symptoms [156]. These risk factors include obesity, hypertension, atherosclerosis, diabetes mellitus (DM), exposure to cardiotoxins and family history of HF, and they may be present in up to a third of subjects aged ≥45 years. The natural history of SAHF is that patients may progress to functional or structural abnormalities without symptoms (stage B, SBHF), clinical manifestations of HF (stage C) and eventually, refractory or end-stage HF (stage D) [8, 157]. The identification of HF risk should stimulate efforts to identify SBHF, as therapeutic interventions in this setting may prevent the development of clinical HF and improve prognosis [8, 157]. However, an effective screening strategy necessitates an understanding of underlying risk[158].

A recent systematic review of the relative risk of a large range of HF risk factors, showed that type 2 diabetes mellitus (T2DM) had nearly double the risk of incident HF while the risk with hypertension was relatively lower [159]. The frequency of HF in patients with DM is even higher among elderly subjects [7]. The presence of T2DM adversely affects the prognosis of patients with HF, with contributions from coronary heart disease (CAD), diabetic cardiomyopathy, and hypertension [160, 161]. Even in the absence of ischemic heart disease, T2DM is over-represented in HF [24]. We hypothesized that non-ischemic SAHF due to T2DM would have more subclinical left ventricular (LV) dysfunction, and worse functional capacity and clinical outcomes, compared with other SAHF. This finding might justify a more aggressive stance towards screening for SBHF in T2DM.

5.4 Methods

5.4.1 Patient selection.

We prospectively recruited 551 asymptomatic patients aged ≥65 years, with preserved ejection fraction but at least one stage A risk factor for HF (DM, obesity, hypertension, known cardiac disease), from a community-based population in Tasmania. Patients with existing HF or known ischemic heart disease were excluded, as were patients with more than moderate valve disease, history of heart failure, LV ejection fraction (LVEF) <40%, inability to acquire adequate echocardiographic images for speckle tracking imaging analysis at baseline were excluded from recruitment. All participants provided written, informed consent, and the study protocol was approved by the Tasmanian Human Research Ethics Committee.

5.4.2 Clinical features.

T2DM was based on self-report of diagnosis including medication. Obesity was defined as body mass index (BMI) ≥30 kg/m^2. Demographics, disease and family history and medication use were obtained using a standardized questionnaire. BMI was calculated as weight in kilograms divided by height in meters squared. In addition to standardized weight and height measurements, waist circumference (WC) was measured with a tape measure to the nearest millimetre at the midpoint between the lower costal margin and the iliac crest by a trained examiner. Supine resting blood pressure (BP) was measured twice and averaged in each patient after at least 10 minutes rest in a quiet room. Active hypertension was defined by averaged systolic blood pressure (BP) ≥140 mmHg or a diastolic BP≥90 mmHg [162].International Federation of Clinical Chemistry (IFCC) standardized hemoglobin A1c (HbA1c) (cut-off 64 mmol/mol) level, estimated Glomerular Filtration Rate (eGFR) and creatinine were obtained from local pathology records. Missing values for HbA1c, eGFR and creatinine were estimated by imputation using linear regression.

5.4.3 Six-minute walk test.

The six-minute walk test (6MWT) was performed by traversing back and forth along a marked pathway on a hard, flat surface, to test the distance an individual was able to walk over a total of six minutes. Patients were allowed to self-pace, and the test was performed using a standardized protocol[142].

5.4.4 Echocardiography.

A comprehensive echocardiogram including standard transthoracic 2D, Doppler echocardiographic studies and speckle tracking echocardiogram (STE) using sensitive systolic and diastolic function parameters was performed using the same ultrasound machine (Siemens ACUSON SC2000, 4V1c and 4Z1c probes, Siemens Healthcare, Mountain View, CA) in accordance with the American Society of Echocardiography guidelines [143, 144]. Images were saved in raw data format and analysed offline. LV internal dimensions and wall thickness, chamber volumes and valvular morphology were assessed. LV mass index (LVMi) was obtained from LV mass measurement using standard criteria and normalized for body size (body surface area or height to the power of 1.7). LVEF measurement was used the modified Simpson's biplane method. LV inflow was obtained using pulsed wave Doppler in the apical 4-chamber view; peak early (E) and late (A) diastolic velocities, deceleration time (DT) and E/A ratio were assessed. Peak early diastolic medial and lateral mitral annular velocity (e') and the ratio of mitral inflow early diastolic velocity to average e' velocity were obtained from pulsed tissue Doppler; E/e'>13 was used as an indicator of diastolic dysfunction. For deformation analysis, standard grayscale 2-dimensional images were acquired in conventional 4-chamber, 2-chamber, 3-chamber, parasternal short-axis views at the mid, basal, and apical level. Global longitudinal strain (GLS) was calculated by average of three apical views using standard software and <18% was considered consistent with LV dysfunction [73, 74].

5.4.5 Outcomes.

Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. Records of all-cause hospitalization were obtained and collected. Suspicious heart failure symptoms and signs were reviewed by three independent cardiologists. The diagnosis of heart failure was established according to Framingham heart failure criteria[4]. The primary endpoint for study was new-onset of HF and all-cause mortality.

5.4.6 Statistical Analysis.

Descriptive data are presented as mean ± standard deviation (SD) and dichotomous data as subject number and percentage. Comparisons between the groups were performed by independent samples t test; the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Univariable Cox regression was used in order to identify the predictors with the primary endpoint among clinical, demographic and echocardiographic variables. Multivariable Cox proportional hazards model was performed to determine the independent predictors and reported as hazard ratio (HR) with 95% confidence interval (95%CI), guided by univariable analyses. Analyses were performed with standard statistical computer software (SPSS 22, IBM, Chicago, IL); $p<0.05$ was deemed to be statistically significant.

5.5 Results

5.5.1 Patient characteristics.

All 551 SAHF patients (age 71±5 years, 49% male) were eligible for inclusion in the final analysis. T2DM was present in 290 subjects (53%). The clinical and demographic characteristics of the SAHF patients according to T2DM status are listed in **Table 5.1**. T2DM-SAHF was characterized by more obesity as well as central obesity, higher heart rate, and lower diastolic blood pressure. The 6MW distance (6MWD) was significantly lower in T2DM-SAHF

patients compared with other-SAHF patients (451±111 vs 493±87m, p<0.001). Among T2DM-SAHF patients, 24% patients were treated with insulin and 68% with metformin. The mean HbA1c level is 53.7±10.3mmol/mol with 13% had impaired HbA1c level (>64mmol/mol); For eGFR, 14 % patients had eGFR>90 mL/min/1.73 m^2, 71% had eGRF 60~90 mL/min/1.73 m^2 and 15% had eGFR<60 mL/min/1.73 m^2; The mean creatinine value was 92±21 umol/L.

Table 5.1 Demographic and clinical characteristics of the SAHF population according to T2DM status.

	T2DM-SAHF(n=290)	**Other-SAHF(n=261)**	**P value**
Age (years)	71±4.4	71±5.1	0.877
Male gender (n, %)	163(56.2)	106(40.6)	**<0.001**
Weight (kg)	86.2±17.1	79.7±15.4	**<0.001**
Height (cm)	168.4±9.9	166.6±9.4	**0.027**
BMI ((kg/m^2)	30.4±5.9	28.6±4.7	**<0.001**
Waist circumference (cm)	103.7±13.3	96.8±13.7	**<0.001**
Obesity (n, %)	142(49.0)	108(41.4)	0.074
Heart rate (n/min)	69±11	66±11	**0.001**
Systolic blood pressure (mmHg)	139±15	141±18	0.143
Diastolic blood pressure (mmHg)	81±10	83±11	**0.021**
Hypertension (n, %)	222(76.6)	231(88.5)	**<0.001**
Active hypertension (n, %)	143(49.3)	132(50.6)	0.767
Past heart disease (n, %)	20(6.9)	24(9.2)	0.321
Family history of HF (n, %)	90(31.0)	115(44.1)	**0.002**
Past chemotherapy (n, %)	24(8.3)	25(9.6)	0.592
Atrial fibrillation (n, %)	29(10)	18(6.9)	0.224
6MWD (m)	451±111	493±87	**<0.001**
Biomarker			
HbA1c (mmol/mol)	53.7±10.3	-	-
Impaired HbA1c (>64mmol/mol)	38(13.1)	-	-
eGRR			
>90 mL/min/1.73 m^2	41(14.1)	-	-
60~90 mL/min/1.73 m^2	207(71.4)	-	-
<60 mL/min/1.73 m^2	42(14.5)	-	-
Creatinine (μmol/L)	91.8±21.4	-	-
Medication			
Insulin	69(23.8)	-	-
Metformin	196(67.6)	-	-
ACEi /ARB (n, %)	201(69.3)	190(72.8)	0.368
Beta-blockers (n, %)	16(5.5)	13(5.0)	0.778
Calcium antagonists (n, %)	68(23.4)	68(26.1)	0.108
Diuretics (n, %)	33(11.4)	42(16.1)	0.479
Lipid lowering meds (n, %)	148(51.0)	149(57.1)	0.155

Abbreviation: ACEI, Angiotensin-Converting-Enzyme Inhibitor; ARB, Angiotensin II Receptor Blocker.

5.5.2 Echocardiographic characteristics.

Table 5.2 shows the echocardiographic characteristics between T2DM-SAHF and the remaining SAHF group. Overall, the mean EF was 63±6% (range 40-80%) and only 2% and 1% had EF within 40~50% in T2DM-SAHF and other-SAHF patients respectively. Average GLS was -18.4±2.7% (range -10.4% to 26.0%). T2DM-SAHF had higher E/e' ratio, higher LVMi and worse GLS than the other-SAHF group. The T2DM group was associated with worse diastolic function (E/e' 9.2±2.7 vs 8.7±2.4, p=0.028) as well as impaired GLS (-17.7±2.6 vs -19.0±2.6%, p<0.001). T2DM-SAHF also had a much higher prevalence abnormal GLS (50% vs 28%, p<0.001) and abnormal E/e' (10% vs 5%, p=0.011).

Table 5.2 Echocardiographic characteristics of the SAHF population according to T2DM status.

	T2DM-SAHF (n=290)	**Other-SAHF (n=261)**	**P value**
LV ejection fraction (%)	62.9±6.5	63.9±5.5	**0.048**
40 - 50%	5(1.7)	3(1.1)	
>50%	285(98.3)	258(98.9)	
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.65±0.17	0.63±0.15	0.057
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.83±0.19	0.78±0.17	**0.001**
Early-to-late peak diastolic transmitral flow velocity ratio (E/A)	0.80±0.21	0.82±0.23	0.167
Early diastolic mitral annular velocity (e') (m/s)	0.08±0.02	0.08±0.02	0.306
Average E/e' ratio (E/e')	9.2±2.7	8.7±2.4	**0.028**
E/e' ratio >13 (n, %)	30(10.3)	12(4.6)	**0.011**
Deceleration time(DT) (s)	246.4±52.4	242.8±49.4	0.414
LV mass index (g/m^2)	92.4±23.8	92.7±22.1	0.912
LVH/LVMi	167(57.6)	179(68.6)	**0.009**
GLS (%)	-17.7±2.6	-19.0±2.6	**<0.001**
GLS<18% (n, %)	146(50.3)	74(28.4)	**<0.001**

Abbreviation: LVH, left ventricular hypertrophy

In order to determine the incremental impact of T2DM on subclinical systolic and diastolic function over hypertension, **Table 5.3** lists echocardiographic parameter comparisons between patients with isolated active hypertension (HT-SAHF) and patients with both active hypertension and T2DM (HT+T2DM-SAHF). HT+T2DM-SAHF had worse GLS than HT-

SAHF group. HT+T2DM -SAHF also had a much higher prevalence of abnormal GLS (52% vs 30%, p<0.001).

Table 5.3 Echocardiographic characteristics of the SAHF population according to T2DM and hypertension status.

	HT-SAHF* (n=132)	**HT+T2DM-SAHF** (n=143)**	**P value**
LV ejection fraction (%)	63.6±5.6	62.7±6.9	0.247
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.61±0.15	0.67±0.17	**0.008**
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.80±0.16	0.85±0.20	**0.016**
Early-to-late peak diastolic transmitral flow velocity ratio (E/A)	0.78±0.19	0.79±0.23	0.513
Early diastolic mitral annular velocity (e') (m/s)	0.07±0.02	0.08±0.02	0.220
Average E/e' ratio (E/e')	9.0±2.5	9.4±2.8	0.185
E/e' ratio >13 (n, %)	8(6.1)	18(12.6)	0.065
Deceleration time(DT) (s)	247.5±49.7	246.5±52.1	0.882
LV mass index (g/m^2)	93.4±21.5	95.1±25.1	0.547
LVH/LVMi	41(31.1)	44(30.8)	0.989
GLS (%)	-19.1±2.4	-17.7±2.5	**<0.001**
GLS<18% (n, %)	39(29.5)	74(51.7)	**<0.001**

**HT-SAHF: Patients had active hypertension without diabetes **Patients had both T2DM and active hypertension.*

5.5.3 Follow-up.

Over a median follow-up period of 1.6±0.6 years (range 0.6-3.2 years), 49 (16.9%) T2DM-SAHF and 27 (10.3%) other-SAHF met the primary endpoint of new-onset of HF and all-cause mortality. On examination of individual components of the primary endpoint, 46 T2DM-SAHF and 24 other-SAHF developed HF, and 3 T2DM-SAHF and 3 other-SAHF died. In the entire cohort, the annualized event rate of HF and all-cause of mortality was 8.8% - varying from 11.2% in T2DM-SAHF to 6.4% in other-SAHF.

Stepwise nested Cox models were constructed to determine the predictors of primary outcome in SAHF patients with and without T2DM. Hazard ratios (HRs) of the primary outcome from univariable and multivariable analyses are listed in **Table 5.4** Significant variables from univariable analyses were entered into the final age- and sex-adjusted model. Among T2DM-

SAHF patients, obesity (HR=2.46 [1.28 to 4.70]; p=0.007), AF (HR=2.39 [1.10 to 5.22]; p=0.028), 6MWD (HR=0.99 [0.99 to 1.00]; p=0.034) and GLS (HR=1.14 [1.01 to 1.30]; p=0.033) were independently associated with the primary endpoint after adjustment for age, gender and glycemic control. In the other-SAHF cohort, history of heart disease (HR=2.97 [1.19 to 7.4]; p=0.019) was predictive after adjustment for age (HR=1.08 [1.01 to 1.15]; p=0.022) and gender.

Kaplan-Meier survival curves were constructed for the primary endpoint, with log-rank testing for significance between strata. Among the whole cohort, T2DM-SAHF had significantly worse outcome than other-SAHF ($\chi 2$=5.36; p=0.021; **Figure 5.1**). Subclinical LV systolic dysfunction (LVSD) (defined as GLS<18%) was predictive of primary outcome (HF and all-cause of mortality) in T2DM-SAHF in Kaplan-Meier analysis **(**$\chi 2$=6.75; p=0.009; **Figure 5.2a)**. However, there was no statistically significant difference in survival when comparing other-SAHF with or without LVSD ($\chi 2$=2.68; p=0.101; **Figure 5.2b)**. There were significantly more events in T2DM-SAHF with obesity compared to those without ($\chi 2$=11.86; p=0.001; **Figure 5.3a)**, but there were no differences when other-SAHF were divided by obesity ($\chi 2$=0.09; p=0.770; **Figure 5.3b)**. In T2DM-SAHF patients, the most serious prognosis pertained to those with impaired GLS or obesity. However, as shown in **Figure 5.4**, in other-SAHF individuals, the most serious prognosis was seen in those with history of heart disease ($\chi 2$=12.49; p<0.001**)**.

5.6 Discussion

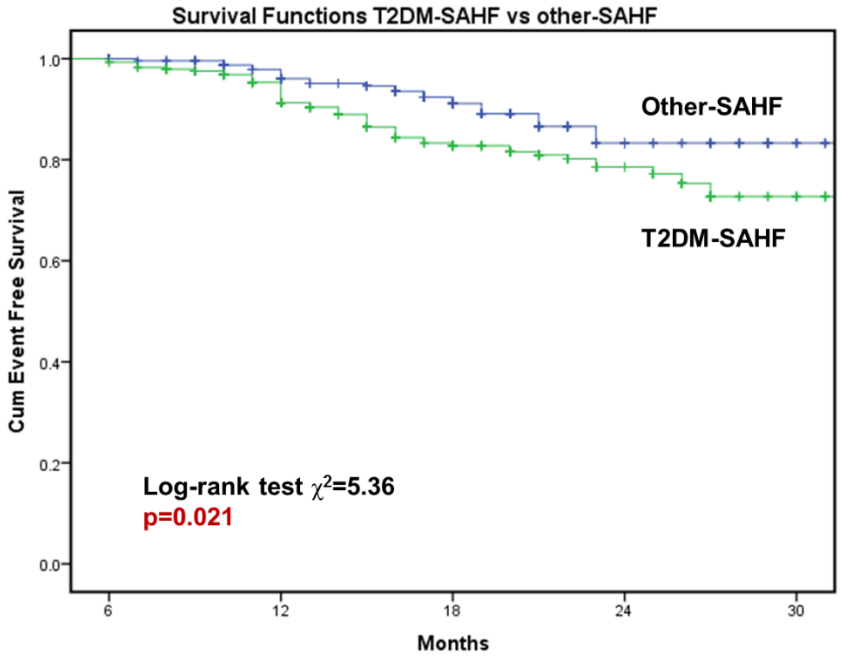
In these data from a prospectively-enrolled cohort, we examined the prevalence of subclinical LV dysfunction, impaired exercise capacity and prognosis in a community-based population with HF risk factors. The results suggest that SAHF due to T2DM has a worse echocardiographic manifestation, functional capacity and clinical outcome than other-SAHF. This work builds on previous reports of an association between increasing HF stage and worse

functional status and prognosis,[163] by adding evidence about clinical features and functional capacity within the early asymptomatic phases of HF.

Table 5.4 Prognostic value of baseline clinical and echocardiographic characteristics over time.

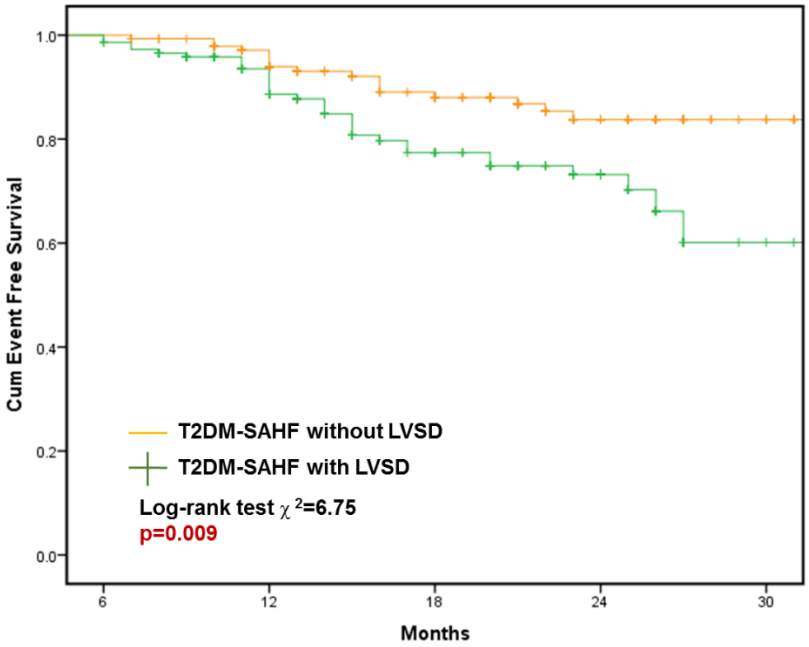
	Unadjusted				**Adjusted**			
	T2DM-SAHF		**Other-SAHF**		**T2DM-SAHF** (Chi-square=54.7)		**Other-SAHF** (Chi-square=25.8)	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age	1.06(0.99,1.12)	0.070	1.10(1.04,1.17)	**0.002**	1.02(0.96,1.09)	0.455	1.08(1.01,1.15)	**0.022**
Male gender	1.58(0.87,2.86)	0.136	1.47(0.69,3.13)	0.319	1.02(0.51,2.04)	0.946	1.51(0.65,3.51)	0.654
BMI	1.10(1.06,1.14)	**<0.001**	0.98(0.90,1.07)	0.651				
Waist	1.05(1.03,1.08)	**<0.001**	1.01(0.98,1.04)	0.548				
Heart rate	1.00(0.97,1.03)	0.856	0.98(0.95,1.02)	0.412				
Systolic blood pressure	1.00(0.98,1.02)	0.861	1.00(0.98,1.02)	0.776				
Diastolic blood pressure	1.00(0.99,1.03)	0.811	1.01(0.97,1.04)	0.732				
History of heart disease	1.93(0.82,4.56)	0.131	3.95(1.73,9.03)	**0.001**			2.97(1.19,7.4)	**0.019**
Obesity	2.77(1.51,5.10)	**0.001**	1.12(0.52,2.42)	0.771	2.46(1.28,4.70)	**0.007**		
Active hypertension	1.05(0.60,1.84)	0.866	0.87(0.41,1.85)	0.712				
Past chemotherapy	1.34(0.53,3.39)	0.537	1.01(0.24,4.28)	0.987				
Family history of HF	0.62(0.32,1.21)	0.164	0.78(0.36,1.70)	0.525				
Atrial fibrillation	3.96(2.06,7.63)	**<0.001**	2.22(0.77,6.44)	0.141	2.39(1.10,5.22)	**0.028**		
Dyslipidaemia	1.48(0.83,2.65)	0.187	1.14(0.54,2.45)	0.728				
Beta-blocker	2.89(1.23,6.81)	**0.015**	1.39(0.33,5.87)	0.654				
ACEi/ARB	1.37(0.71,2.63)	0.343	1.00(0.42,2.37)	0.998				
Insulin	1.57(0.86,2.86)	0.140	-	-				
Metformin	0.89(0.50,1.59)	0.688	-	-				
6MWD	0.996(0.994,0.999)	**0.003**	0.995(0.990,0.999)	**0.010**	0.997(0.995,1.000)	**0.034**	0.99(0.99,1.00)	0.237
Biomarker								
HbA1c	1.03(1.01,1.05)	**0.008**	-	-	1.01(0.99,1.04)	0.283		
HbA1c>64mmol/mol	2.83(1.52,5.27)	**0.001**	-	-				
eGRR	0.67(0.40,1.12)	0.666	-	-				
Creatinine (µmol/L)	1.01(1.01,1.02)	0.065	-	-				
Echocardiography								
GLS	1.27(1.15,1.41)	**<0.001**	1.17(1.03,1.32)	**0.016**	1.14(1.01,1.30)	**0.033**	1.04(0.90,1.20)	0.586
GLS<18%	2.13(1.18,3.84)	**0.012**	1.87(0.87,4.04)	0.109				
E/e’	1.06(0.96,1.17)	0.251	1.08(0.93,1.25)	0.295				
E/e’ ratio >13	1.35(0.58,3.18)	0.489	0.84(0.11,6.16)	0.860				
LVMi	1.03(1.01,1.04)	**<0.001**	1.02(1.00,1.04)	0.052	1.01(0.99,1.02)	0.087		
LVH/ LVMi	3.52(2.00,6.18)	**<0.001**	1.02(0.45,2.32)	0.969				

Figure 5.1 Comparison of primary outcomes between patients with T2DM-SAHF and other-SAHF. SAHF patients with T2DM had significantly worse outcome than those without T2DM.



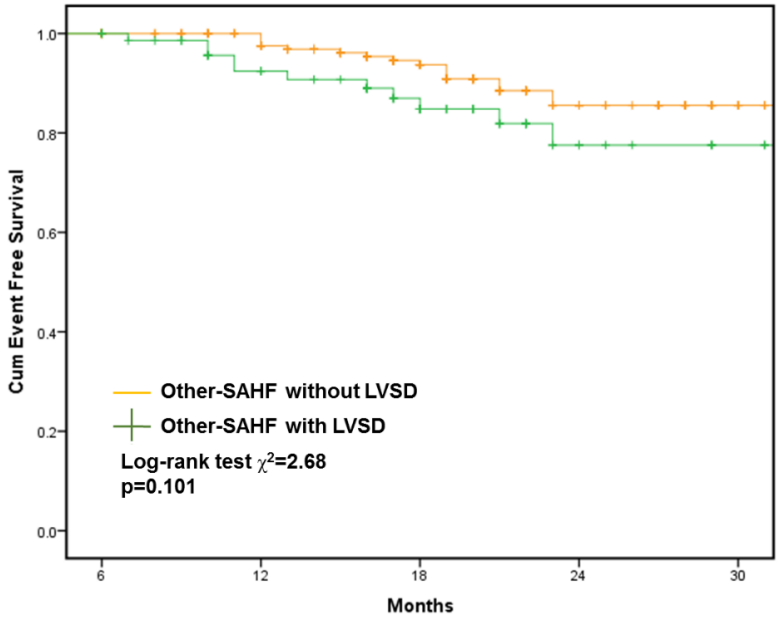
No. at risk					
Other-SAHF	261	251	242	234	234
T2DM-SAHF	290	267	250	244	241

Figure 5.2 Prognostic implications of T2MD-SAHF and other-SAHF and the role of left ventricular systolic dysfunction.



No. at risk in T2DM-SAHF					
Without LVSD	144	136	130	127	127
With LVSD	146	131	120	117	114

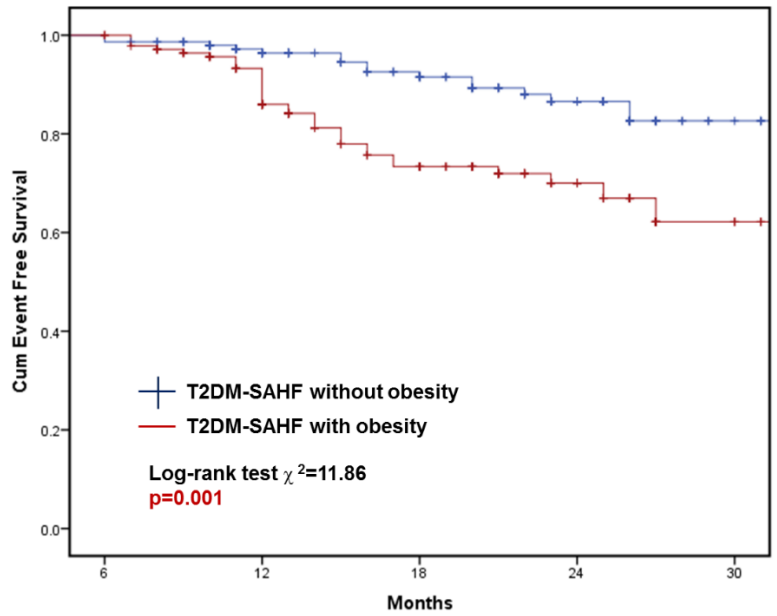
(a)



No. at risk in other-SAHF					
Without LVSD	187	183	178	171	171
With LVSD	74	69	65	63	63

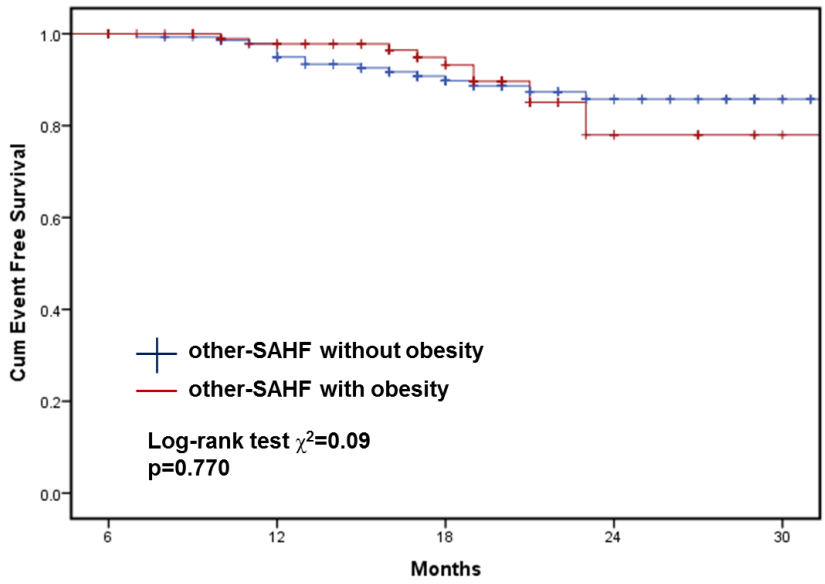
(b)

Figure 5.3 Prognostic implications of T2MD-SAHF and other-SAHF and the role of obesity.



No. at risk in T2DM-SAHF					
Without obesity	148	144	139	134	133
With obesity	142	137	112	110	108

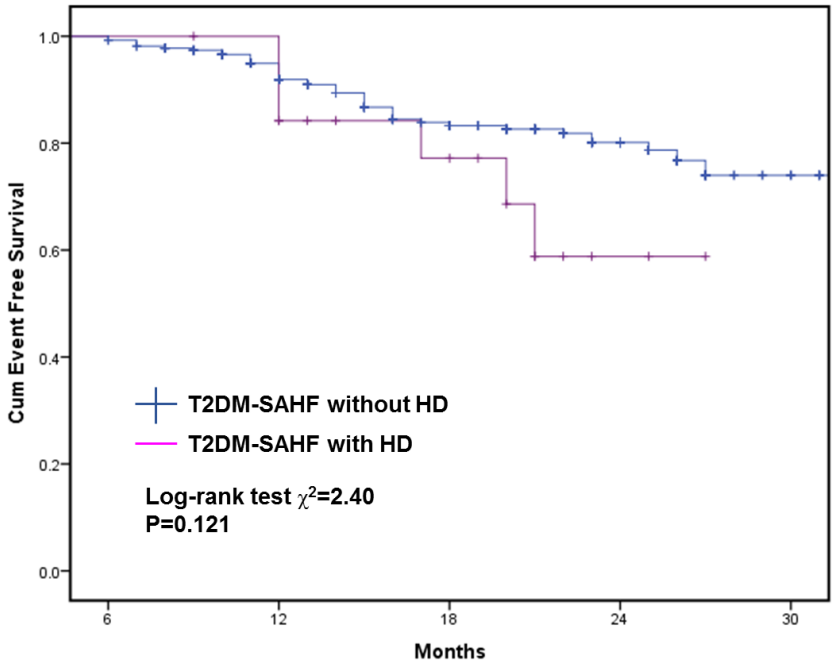
(a)



No. at risk in other-SAHF					
Without obesity	153	150	140	137	137
With obesity	108	106	103	97	97

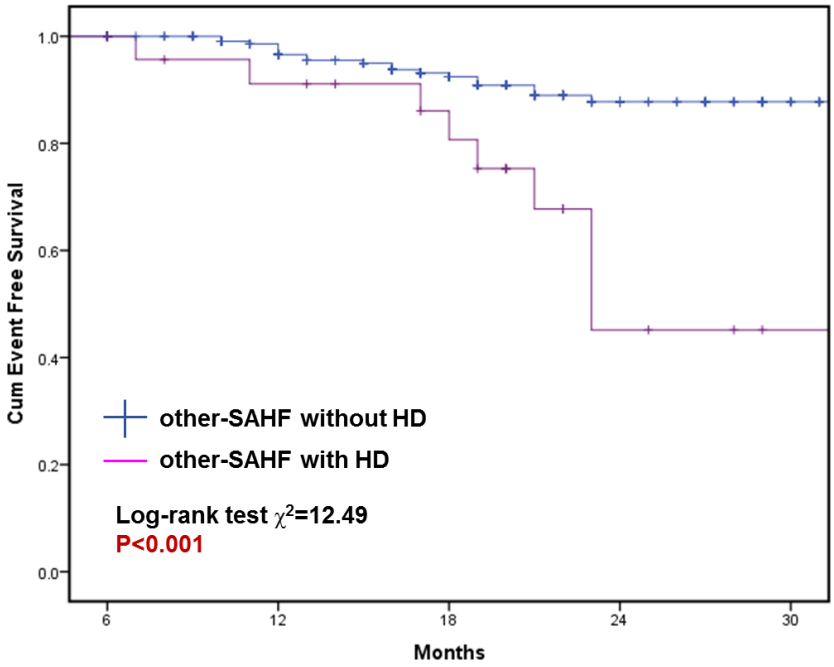
(b)

Figure 5.4 Prognostic implications of T2MD-SAHF and other-SAHF and the role of heart disease history.



No. at risk in T2DM-SAHF					
Without HD	270	250	235	230	227
With HD	20	17	15	14	

(a)



No. at risk in other-SAHF					
Without HD	237	230	223	218	218
With HD	24	22	20	16	16

(b)

5.6.1 LV mechanics in Stage A Heart Failure.

Previous studies have shown that changes of subclinical LV longitudinal systolic and diastolic function begin before structural LV changes in asymptomatic patients with HF risk factors [164-167]. However, comparisons of the degree of LV myocardial dysfunction in early diabetic cardiomyopathy compared with other-SAHF have not been documented previously. Our results show that abnormalities of diastolic function are more common in T2DM than other SAHF groups, as are disturbances of LV longitudinal systolic function (GLS:-17.7±2.6% vs -19.0±2.6%, p<0.001). In the current study, we report that the prevalence of systolic longitudinal dysfunction is 50% among community population-based T2DM-SAHF and 28% among other SAHF. Alterations of systolic strain may exist despite normal diastolic function [88]. Importantly, impaired GLS as a marker of stage B HF is associated with an increased risk of further transition to symptomatic stage C HF with preserved EF in diabetes [157]. However, in real life few asymptomatic SAHF patients have done tests of cardiac morphology and functions. It

seems like many of them develop into stage C/D directly without receiving a diagnosis of SBHF. Indeed, many SBHF 'hide' in SAHF and our results highlight the importance of identifying potential SBHF using echocardiogram among SAHF cohorts for preventing further transition.

These findings highlight the fact that the severity of the early LV function impairment is not necessarily analogous within different aetiologies of SAHF. Despite rigorous adjustment for covariables, each unit decrement of GLS in subjects with T2DM showed a 1.14 fold-higher risk of HF and mortality, whereas in subjects with other risks, the predictive value of GLS was not found. The worse LV function in T2DM-SAHF may be attributable to diabetic complications and associated co-morbidities as well as the presence of a distinct diabetic cardiomyopathy.[158, 164] The pathogenesis of the latter is complex and likely multifactorial, involving cardiac autonomic neuropathy, altered myocardial metabolism, small and large vessel damage, insulin resistance and myocardial fibrosis [164]. Additionally, in our study patients with active hypertension showed relatively preserved GLS, but a combined group with active hypertension and T2DM had more abnormal GLS (-19.1±2.4% vs -17.7±2.5%, p<0.001; **Table 5.3**), as well as a higher prevalence of abnormal GLS than in T2DM without hypertension (52% vs 30%). Although hypertension and T2DM are the two leading aetiologies of early HF, impaired GLS is more likely due to diabetic cardiomyopathy than hypertensive heart disease [168].

5.6.2 Functional capacity in Stage A Heart Failure.

In this study, functional capacity at submaximal stress was assessed using 6MWT is a simple, safe test of functional capacity that is a well-established diagnostic procedure in cardiovascular and pulmonary disease, which has prognostic value [169]. A systematic review [170] that is performed via 8 database to investigate the reliability between 6MWT and other methods to

assess functional capacity defined as peak VO_2 level in patients with chronic HF showed that 6MWT has moderate to good ability to predict VO_2 level, good reliability and a significant ability to predict functional capacity in those patients particularly in patients who do not walk more than 490 meters. Compared with healthy controls, patients with T2DM have lower 6MWD [171]. The results of this study show that, compared with other-SAHF, functional capacity was more impaired in T2DM-SAHF.

The determinants of functional capacity are complex and depend on both psychological and physical factors. Although it might be considered that the association of T2DM with functional capacity could be driven by obesity– and indeed, advanced age and obesity had strong associations with functional capacity - our results suggest that the association of T2DM with functional capacity was independent of these features. Subclinical cardiac dysfunction, which is often present in both T2DM-SAHF and other-SAHF, could influence functional capacity but cannot fully explain the difference of exercise capacity between the two SAHF subgroups. Previous work has shown that exercise intolerance in T2DM is independent of obesity and even presents with good glycemic control and without clinically apparent cardiovascular disease [172]. The presence of endothelial dysfunction, decreased myocardial perfusion, decreased muscle mitochondrial function, abnormal tissue haemoglobin oxygen saturation and insulin resistance may be mediators in the relationship between diabetic oxidative dysfunction and defects in functional capacity [172]. In addition, good evidence was found that in diabetes both components of the autonomic nervous system dysfunction - cardiac sympathetic and cardiac parasympathetic nervous system dysfunction is involved [173]. Vagal tone inhibits and subsequent sympathetic activates immediately after onset of exercise, while parasympathetic activates followed by sympathetic inhibition when recovery starts. Parasympathetic control may be weakened by persistent hyperglycemia that may also enhance sympathetic activity[174].Heart rate recovery is associated with vagal tone and T2DM is associated with poor

heart rate recovery and chronotropic incompetence[175]. However, this association in diabetes is only found when subjects have both poor physique and autonomic dysfunction[175]. Previous research have shown that cardiac autonomic dysfunction is associated with reduced cardiac output response to functional capacity in diabetes, which is probably due to hemodynamic instability during exercise [176]. Left atrial (LA) dysfunction is also common in patients with heart failure with preserved EF and asymptomatic T2DM and contributes to exercise intolerance, however, data on the specific influence of diabetes contributing to LA dysfunction is limited. LA enlargement in diabetes is an independent predictor of LA dysfunction, probably due to a combination of diastolic dysfunction and diabetic atrial myopathy [177].

5.6.3 Prognosis in Stage A Heart Failure.

Despite current epidemiological evidence of the greater risk of development of HF in patients with diabetes, the natural history of asymptomatic subjects at risk of HF remains poorly identified [178, 179]. This study extends present knowledge about the prognosis of the entire SAHF cohort in 2 years, based on a community (as opposed to a clinic-based) population. In the entire SAHF cohort, the annualized event rate of incident HF and all-cause of mortality was 8.8%. The rate in T2DM-SAHF (11.2%) was almost twice that of other-SAHF (6.4%).

T2DM was associated with more serious outcome, irrespective of whether or not other risk factors were present. A recent systematic review of 15 observational studies indicated that diabetes (HR=2.0) showed the strongest predictive value for incident HF among the non-ischaemic SAHF risks, followed by hypertension (HR=1.61) and BMI (per 5kg/m^2) (HR=1.15) [159]. In patients with T2DM in the present study, the prognosis was associated with obesity, exercise capacity and abnormal GLS independent of glycemic control and renal function. Among patients with T2DM, poor glycemic control and related hyperglycemia may be associated with the process of developing HF, however, the association between intensive

glycemic control and the reduction of cardiovascular complications still remains controversial [180]. Although a large cohort study reported an HbA1c≥10%, relative to HbA1c<7% was associated with 1.6 fold risk of incident HF in diabetes, several large clinical trials reported no significant benefit for primary cardiovascular events with intensive glycemic control [180]. The interpretation of our finding is poor glycemic control (HbA1c>64mmol/mol) may not be a marker of composite endpoint (HF and all-cause of death) in this elderly asymptomatic diabetes cohort. We found a negative association between renal function and outcomes in T2DM-SAHF. Previous research showed that reduced eGFR is a risk factor of cardiovascular events and death in diabetes patients without advanced renal disease, but the risks are small when considering other risk factors[181]. Although in our study the association is negative, it still has important implication to require further research with longer follow-up to examine the impact of sub-clinical renal dysfunction in patients with diabetes. AF is a strong risk factor for HF. In our study the presence of AF shows independent association with increased risk of new-onset of HF and all-cause of mortality in T2DM-SAHF but not in other-SAHF. The result is not entirely consistent with the recent systematic review and meta-analysis that included 15 cohort studies and reported AF seems to predict myocardial infarction, HF and all-cause of mortality [182]. The inconsistent result in other-SHAF cohort may due to the relatively low prevalence of AF (7%) and the exclusion of ischemic heart disease at baseline.

Although the staging system serves as a reminder to clinicians of the importance of early detection and prevention of patients at risks of transitioning to higher stages of HF, these results highlight the notion that SAHF associated with diabetes is clinically different from other cause of SAHF, and perhaps should have different targets for prevention. These findings have important implications for awareness and identification of high-risk individuals and optimal management to prevent or delay progression to adverse outcome in SAHF.

5.6.4 Limitation.

The population of the present study was selected from the community, based on the presence of at least one known non-ischemic HF risk factor and excluding patients with known HF or established asymptomatic LV systolic dysfunction. This limits external validity to the primary prevention group. In addition, the prevalence of T2DM is relatively high in this SAHF population as in order to acquire sample size that adequate to better justify the hypothesis of this study, we had pooled a bigger number of diabetic patients into the present study. The high proportion of patients with diabetes in the study population means relatively low classification rates within other-SAHF risks and smaller pool sizes. Consequently the study lost a lot of information about the clinical heterogeneity between each SAHF group that underlines the need for identifying high – risk among the SAHF cohort. In other words, if each SAHF risk factor were equally represented in the sample, we may be able to explore the differences among different risk groups in more detail and obtain more information about the long-term outcomes in each group.T1DM were excluded from our study due to the different mechanism of affecting the heart from T2DM. We did not record circumferential and radial strain, which would have provided additional details about myocardial mechanics, although longitudinal strain is the most robust of these myocardial deformation parameters. Additionally, we do not have data on biomarkers, which may also be used as a potential predictor of HF and adverse outcome. Their absence may have weakened the ability to predict HF. Moreover, different biomarkers may play different roles in T2DM-SAHF and other-SAHF, and provide evidence of the differences between two SAHF groups and be potential targets of interventions.

5.7 Conclusion.

In this community cohort of patients with HF risks, T2DM-SAHF had worse subclinical LV function, functional capacity and adverse outcome than other causes of SAHF. Impaired GLS, worse exercise capacity, the presence of obesity or AF were independently associated with

prognosis in T2MD-SAHF, whereas a history of heart disease was the driver of subsequent HF and mortality in other causes of SAHF. The clinical application of this study provides an important caveat that not all types of SAHF are the same. Better targeting of interventions at the most vulnerable SAHF group – those with T2DM – seems appropriate.

5.8 Postscript.

The results of this study combine data on cross-sectional prevalence with longitudinal prognostic data to truly capture the burden of preclinical HF and symptomatic HF in elderly individuals in the community. The findings justify our hypothesis that among SAHF patients, SAHF due to diabetes is associated with worse prognosis and less well-being. These findings underscore the potential benefit of targeting prevention efforts at the T2DM-SAHF group. The next chapter will explore how this might be accomplished.

Chapter 6. Use of Echocardiographic Markers to Predict Heart Failure in T2DM

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6.1 Preface

The prevention of HF remains a major goal of cardiovascular research, and diabetes is one of the strongest risk factors of incident HF, independent of hypertension and atherosclerosis. A number of studies have shown that the presence of asymptomatic LV dysfunction is independently associated with the risk of developing HF in diabetes. Treatment strategies of more intensive targeting of high-risk but asymptomatic individuals may be an effective way to prevent symptomatic HF and future cardiac events in diabetes. Asymptomatic diabetic subjects with LV dysfunction (classified as stage B HF) – lie between stage A HF (those with diabetes as a HF risk factor) and symptomatic stage C and D HF. Previous studies have demonstrated that reduced ejection fraction (EF) as a marker of stage B HF successfully predicts new-onset of HF in diabetes. However, although strategies for improving survival have now been established for HF patients with reduced EF,[183] EF is not a sufficient screening tool to detect early myocardial changes in diabetes. This is because HF in diabetes is commonly associated with preserved EF. In this chapter, different echocardiographic markers including increased LV mass index, left atrial enlargement, LV diastolic dysfunction and impaired global longitudinal strain (GLS) were evaluated as potential echocardiographic features of stage B HF in T2DM. We hypothesized that GLS would be the optimal echocardiographic feature of stage B HF in T2DM for community screening.

6.2 Abstract

Background. Stage B heart failure (SBHF), is a precursor to the development of HF, and its recognition justifies initiation of cardioprotective therapy. However, original definitions of non-valvular, non-ischemic SBHF was based on LV hypertrophy and impaired ejection fraction (EF). We sought whether impaired global longitudinal strain (GLS),LV diastolic dysfunction (LVDD) or left atrial enlargement (LAE) should be added to SBHF criteria in asymptomatic patients with type 2 diabetes mellitus (T2DM).

Methods. Asymptomatic T2DM ≥65 years old (age 71±4 y, 55% men) with preserved EF and no ischemic heart disease underwent a comprehensive echocardiogram, including assessment of LVH, LVE, LVDD(abnormal E/e') and GLS (<16%), and standard clinical evaluation were recruited from a community-based population. Over a median follow-up of 1.5 years (range 0.5-3), 20 patients were lost to follow-up, and 290 individuals were entered into the final analyses.

Results. The prevalence of SBHF was 10% by LVDD, 23% by LVH, 35% by LAE and 23% by impaired GLS. Over a median follow-up of 1.5 years, 45 of 290 patients developed new-onset HF and 4 died, giving an event rate of 112/1000 person-years. In a competing-risks regression analysis that controlled for glycaemic control, LVH (HR=2.90; p<0.001) and GLS<16% (HR=2.26; p=0.008), but not LVDD and LAE were associated with incident HF and had incremental predictive power to clinical variables.

Conclusion. Subclinical LV systolic dysfunction is prevalent in asymptomatic elderly patients with T2DM, and both LVH and impaired GLS are independent and incremental predictors of incident HF.

6.3 Background

Type 2 diabetes mellitus (T2DM) is a potent risk factor for the development of non-ischemic heart failure (HF) [157, 158]. The development of HF may be preceded by stage B HF (SBHF), defined on the basis of valvular disease, evidence of previous infarction, LV hypertrophy and impaired ejection fraction (EF) [184]. The recognition of this entity is important because cardio-protective medication may prevent or retard the progression of HF. However, epidemiologic studies show that 83% of elderly patients with T2DM and newly diagnosed HF have HF with preserved EF (HFpEF) [185], so EF-based criteria seem unsuited to this group. Moreover, LVD is highly prevalent in T2DM, with up to half of the patients involved [186].

Myocardial deformation (strain) may now be readily measured using speckle-tracking echocardiography [187]. Global longitudinal strain (GLS) is the most robust LV strain parameter, which is more sensitive and specific than conventional 2D-EF as a measure of systolic function, and can be used to identify subclinical systolic LV dysfunction (LVD) in cardiomyopathies [188]. Previous studies have has demonstrated that early detection of subclinical LVD by strain imaging is independently associated with long-term adverse outcome in asymptomatic patients with T2DM [189, 190]. However, whether the presence of impaired systolic strain in asymptomatic patients with T2DM without reduced EF predicts incident HF is uncertain. We sought whether impaired global longitudinal strain (GLS),LV diastolic dysfunction (LVDD) or left atrial enlargement (LAE) should be added to SBHF criteria in asymptomatic patients with type 2 diabetes mellitus (T2DM).

6.4 Methods

6.4.1 Patient selection.

Three-hundred and ten asymptomatic T2DM patients aged ≥65 years with preserved LVEF were prospectively recruited from a community-based population in Tasmania from 2013 and

2015. The recruitment exclusion criteria were existing HF or known ischemic heart disease, more than moderate valve disease, history of HF or LVEF <40%, and inability to acquire adequate echocardiographic images for speckle tracking imaging analysis at baseline. All participants provided written, informed consent, and the study protocol was approved by the Tasmanian Human Research Ethics Committee.

6.4.2 Clinical features.

The diagnosis ofT2DM was based on self-report including diabetes treatment. Socioeconomic status, demographics, medical history, family history and use of medication including diabetes treatment were obtained from a baseline survey. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and obesity was defined as BMI ≥30 kg/m^2. Waist circumference (WC) was measured to the nearest millimeter by a trained examiner using a tape measure at the midpoint between the lower costal margin and the iliac crest. Supine resting blood pressure (BP) was measured twice and averaged in each patient after at least 10 minutes rest in a quiet room. Hypertension was defined by averaged systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥90 mmHg . International Federation of Clinical Chemistry (IFCC) standardized hemoglobin A1c (cut-off 64 mmol/mol) level were obtained from local pathology records. Missing values for HbA1c were estimated by imputation using linear regression. The ARIC (Atherosclerosis Risk In Communities) HF risk scores were used to estimate the absolute risk of HF at 3 years. The online ARIC Heart Failure Risk Calculator was used and 10 common clinical variables were included (age, gender, race, systolic BP, heart rate, BMI, smoking status, previous coronary heart disease, current use of blood pressure-lowering medication and diabetes [80].

6.4.3 Echocardiography.

Patients all underwent a comprehensive echocardiogram including standard transthoracic 2D, Doppler echocardiographic studies and speckle tracking echocardiogram (STE) in accordance with the American Society of Echocardiography (ASE) guidelines (Siemens ACUSON SC2000, 4V1c and 4Z1c probes, Siemens Healthcare, Mountain View, CA) [143, 144]. LV internal dimensions and wall thickness, chamber volumes and valvular morphology were assessed. LVEF measurement was used the modified Simpson's biplane method. LA volumes were calculated using the Simpson biplane method and LA enlargement (LAE) defined as LA volume index [LAVi, LA volume indexed to body surface area (BSA)] ≥34 mL/m^{2}[143]. LV mass index (LVMi) was obtained from LV mass measurement using standard criteria and normalized for body size [BSA or height to the power of 1.7 or 2.7]. LV hypertrophy (LVH) was defined as LVMi (normalized for BSA) >115 g/m^2 for men and >95 g/m^2 for women. LV inflow was obtained using pulsed wave Doppler in the apical 4-chamber view; peak early (E) and late (A) diastolic velocities, deceleration time (DT) and E/A ratio were obtained. Peak early diastolic medial and lateral mitral annular velocity (e') and the ratio of mitral inflow early diastolic velocity to average e' velocity were obtained from pulsed tissue Doppler; E/e'>13 was used as a cut-off of LV diastolic dysfunction (LVDD) [154]. For deformation imaging, standard grayscale 2-dimensional images were acquired in conventional 4-chamber, 2-chamber, 3-chamber, parasternal short-axis views at the mid, basal, and apical level. Global longitudinal strain (GLS) was calculated by average of three apical views using standard software [73, 74]. Although in deformation analysis, shortening is described as a negative number, for computational simplicity (and because there were no positive GLS), we express GLS in this paper without this information. Our laboratory uses cut-offs of 16% to designate impaired GLS and 18% to designate abnormal GLS, and we evaluated both cut-offs.

Accordingly, SBHF was defined by;

1) Diastolic dysfunction (E/e' >13);

2) LA enlargement (LAE>34 mL/m^2;

3) LVH (>115 g/m^2 for males, >95 g/m^2 for females;

4) Impaired GLS (cut-off 16%).

6.4.4 Outcomes.

Regular phone calls and surveys were performed to identify potential HF symptoms during follow-up, and symptom surveillance questionnaires and clinical visits were followed. Records of all-cause hospitalization were obtained and collected. Suspicious HF symptoms and signs were reviewed by three independent cardiologists. Incident HF diagnosis was validated according to Framingham heart failure criteria [4]. The primary composite endpoint for study was new-onset of HF and all-cause mortality. The primary endpoint was incident HF, and all-cause mortality was considered as a competing risk.

6.4.5 Statistical Analysis.

Continuous variables are presented as mean ± standard deviation (SD) and categorical data as frequencies and percentages. Cox regression models were used to model time to composite endpoint and reported as hazard ratio (HR) and 95% confidence interval (95%CI) [191]. The cumulative survival free of HF incidence and death during the follow-up period was estimated using the Kaplan–Meier method and survival curves were compared with the log-rank test. Univariable Cox regression was used to assess the predictive power of composite endpoint among clinical, demographic, biochemical and echocardiographic variables. Significant variables and echocardiographic parameters of interest were selected for entry into multivariate analyses to determine independent correlates. To account for the competing risk of all-cause death during follow-up, competing risk methods were used to generate hazard ratios (HR) and 95% confidence intervals (CI) for the associations between each echocardiographic parameter and incident HF [191]. The cumulative incidences (CIF) of HF were calculated and graphically

displayed separately for patients with and without impaired GLS. Gray's K-sample test was to compare the cumulative incidence estimates of HF between patients with and without impaired GLS [192]. All data were analyzed using standard statistical computer software (SPSS 22, IBM, Chicago, IL and Stata, V.12.0, Stata Corp, College Station, Texas, USA); $p<0.05$ was deemed to be statistically significant.

6.5 Results

6.5.1 Patient characteristics.

Of 310 eligible asymptomatic T2DM patients ≥65 years old with preserved EF from the community and underwent baseline tests, 2 (0.7%) were lost to follow-up and 18 participants (5.8%) were alive but unable to attend for clinic review, after a median follow-up time of 1.5 years (range 0.5-3 years) (**Figure 6.1**). This group was no different from the remaining 290 individuals who completed follow-up (**Appendix 6.1**). The baseline clinical and echocardiographic characteristics of 290 individuals with and without events are summarized in **Table 6.1**. In the remaining 290 T2DM participants (age 71±4 years, 56% male), the mean HbA1c level was 53.7±10.3 mmol/mol. HF risk factors were prevalent among these patients – 77% had hypertension, 49% had obesity, 31% had family history of HF, 8% had exposure to chemotherapy and 7% had history of heart disease.

Figure 6.1. Flow chart of study inclusion.

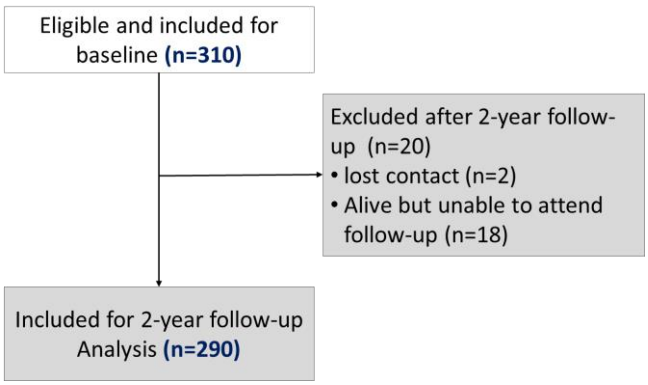


Table 6.1 Baseline clinical and echocardiographic characteristics of 290 elderly asymptomatic patients with T2DM.

Demographic and clinical characteristics	
Age (years)	70.9±4.3
Male gender (n, %)	163(56.2)
Weight (kg)	85.9±17.0
Height (cm)	168.0±10.3
BMI (kg/m^2)	30.3±5.9
Waist circumference (cm)	103.4±13.0
HbA1c (mmol/mol)	53.7±10.3
Poor HbA1c (n, %)$^{\Diamond}$	38(13.1)
Obesity (n, %)	142(49.0)
Heart rate (n/min)	69±11
Systolic blood pressure (mmHg)	139±14
Diastolic blood pressure (mmHg)	81±10
Hypertension (n, %)	222(76.6)
Family history of HF (n, %)	90(31.0)
Past chemotherapy (n, %)	24(8.3)
Past heart disease (n, %)	20(6.9)
ARIC HF risk score (3 year) (%)	7.5±6.4
Medication	
Insulin (n, %)	69(23.8)
Metformin (n, %)	196(67.6)
ACEi / ARB (n, %)	201(69.3)
Beta-blockers (n, %)	16(5.5)
Calcium antagonists (n, %)	68(23.4)
Diuretics (n, %)	33(11.4)
Lipid lowering meds (n, %)	148(51.0)
Echocardiography	
LV ejection fraction (%)	62.9±6.5
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.65±0.17
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.83±0.19
Transmitral diastolic flow velocity ratio (E/A)	0.80±0.21
Early diastolic mitral annular velocity (e') (m/s)	0.08±0.02
Average E/e' ratio (E/e')	9.2±2.7
Deceleration time(DT) (s)	246.4±52.4
LA volume (mL/m^2)	32.3±10.1
LV mass index (g/m^2)	92.4±23.8
LV mass index (g/m$^{1.7}$)	74.7±21.4
LV mass index (g/m$^{2.7}$)	44.4±12.6
GLS (%)	17.7±2.6
Echocardiography categorical variables	
E/e' ratio >13 (n, %)	30(10.3)
LA enlargement (n, %) $^{\Delta}$	102(35.2)
LV hypertrophy (n, %)*	68(23.4)
GLS<18% (n, %)	146(50.3)
GLS<16% (n, %)	68(23.4)
Presence of any SBHF features (n, %) †	169(58.3)

$^{\Diamond}$ Poor HbA1c, ICFFstd-HbA1c>64mmol/mol;$^{\Delta}$ LA enlargement was defined as LA volume>34 mL/m^2; *LV hypertrophy was defined as LVMi>115 g/m^2 for males, >95 g/m^2 for females. † The presence of at least one the following: LVH, GLS<18%, E/e'>13, LAE

6.5.2 Prevalence of Stage B heart failure.

The prevalence of conventionally-defined SBHF was 23%, based on the presence of LVH. Subclinical LV dysfunction was identified in 10% by abnormal E/e', 35% by LAE, 50% by abnormal GLS (cut-off 18%) and 23 by impaired GLS (cut-off 16%) (**Figure 6.2**). In the entire cohort, 97 (33%) had only one echocardiographic abnormality, 48 (17%) had two, 21 (7%) had three and 3 (1%) had four and in total 58% had any feature. The distribution of patients with multiple features is shown in **Figure 6.3**.

Figure 6.2. Prevalence of SBHF features in elderly asymptomatic patients with T2DM (n=290). More than half diabetic patients have abnormal strain (GLS<18%), 23% have impaired strain (GLS<16%) and LVH (cut-off >115g/m^2 for males, >95 g/m^2 for females); LAE (cut-off 34 mL/m) was prevalence in 35% subjects and abnormal E/e' (cut-off 13) was prevalence in 10% subjects.

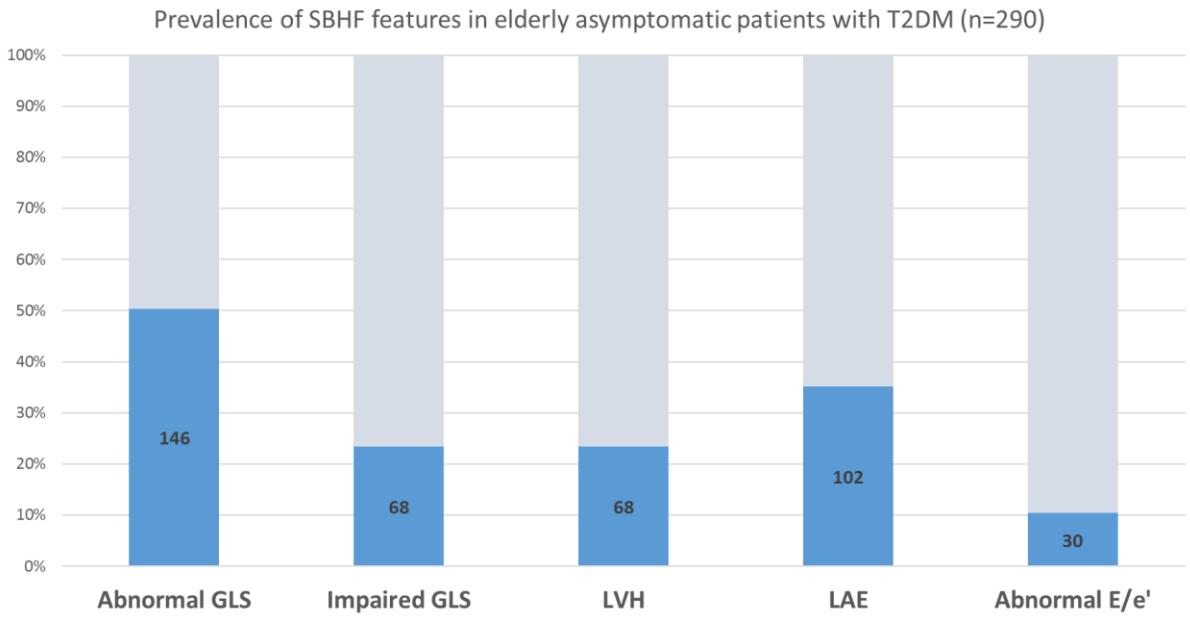
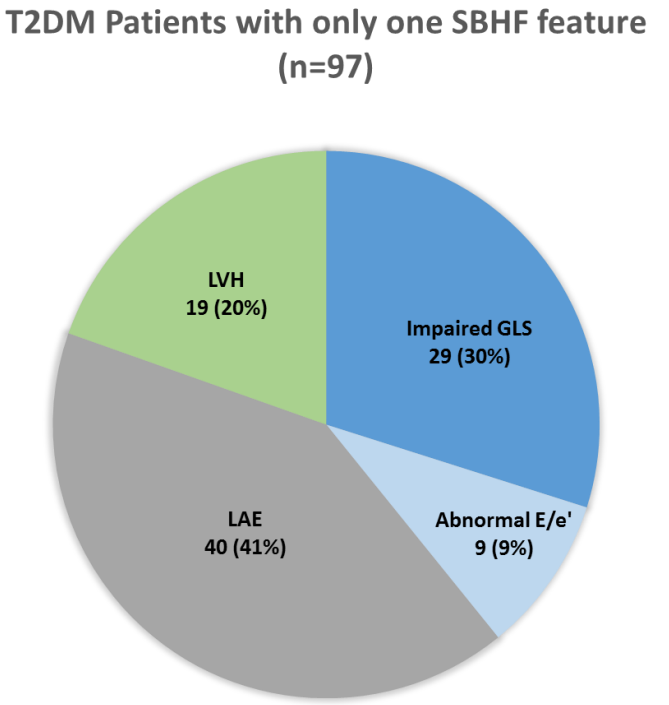
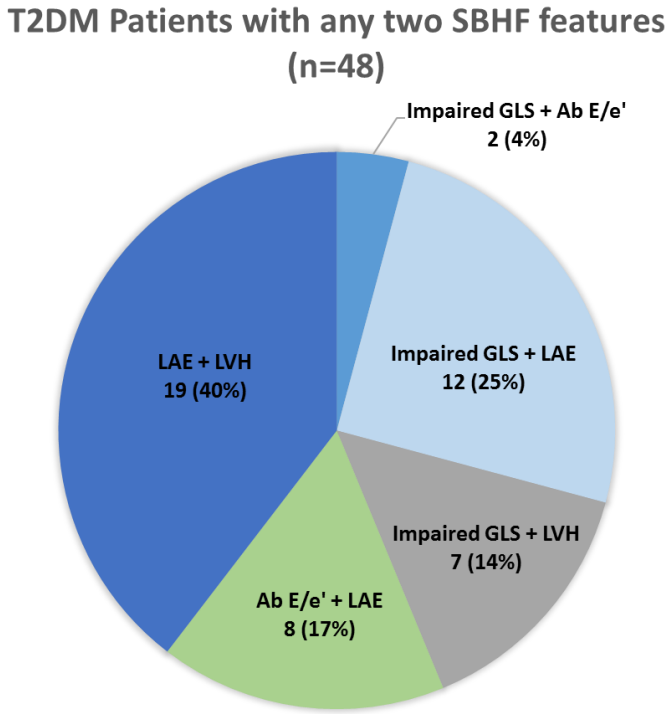


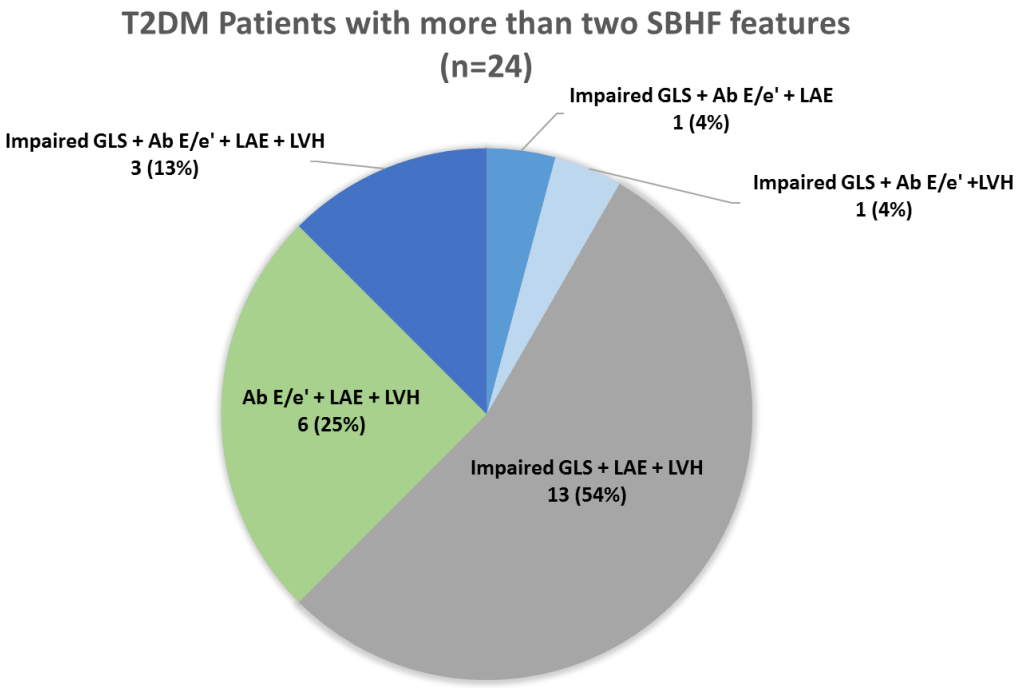
Figure 6.3 Distribution of patients with SBHF features (LVH, LAE, abnormal E/e' and impaired GLS) among elderly asymptomatic patients with T2DM (n=169).



(a)



(b)



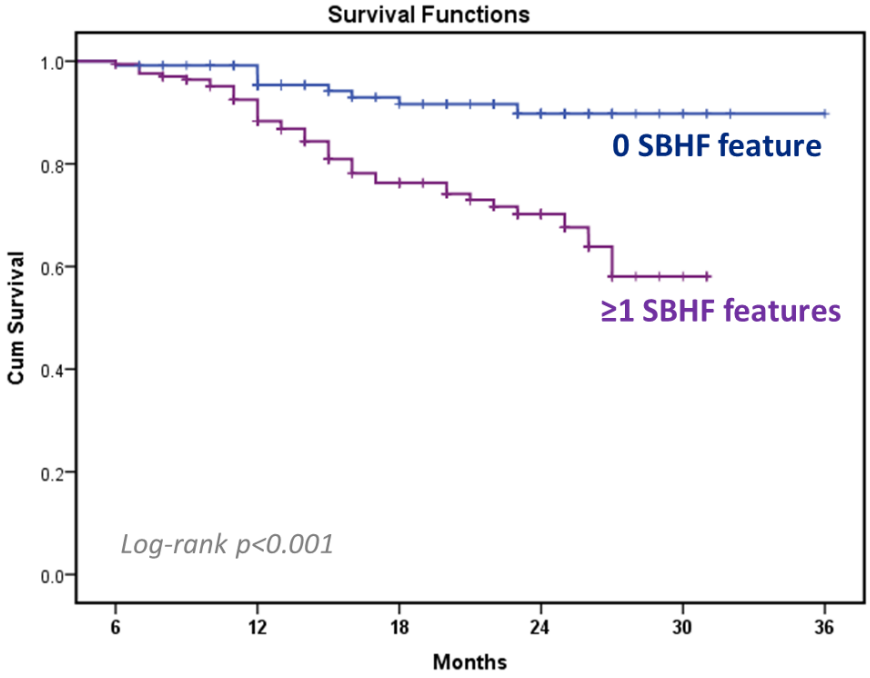
(c)

6.5.3 Follow-up.

Over a median follow-up of 1.5 years, 45 patients developed new-onset HF and 4 died, giving an event rate of 112/1000 person-years. Patients who had events we more commonly men, and showed greater levels of obesity (especially central obesity), worse glycemic control, higher LVMi and LA volume and worse GLS. EF and E/e' ratio showed no difference between the two groups (p=0.096). Of the 49 individuals having events, 82% had any of the echocardiographic features. The conventional diagnosis of SBHF was made in 47%, on the basis of LVH. In contrast, the diagnosis of subclinical dysfunction was 12% by abnormal E/e', 61% by LAE, 65% by GLS <18% and 45% by GLS <16%.

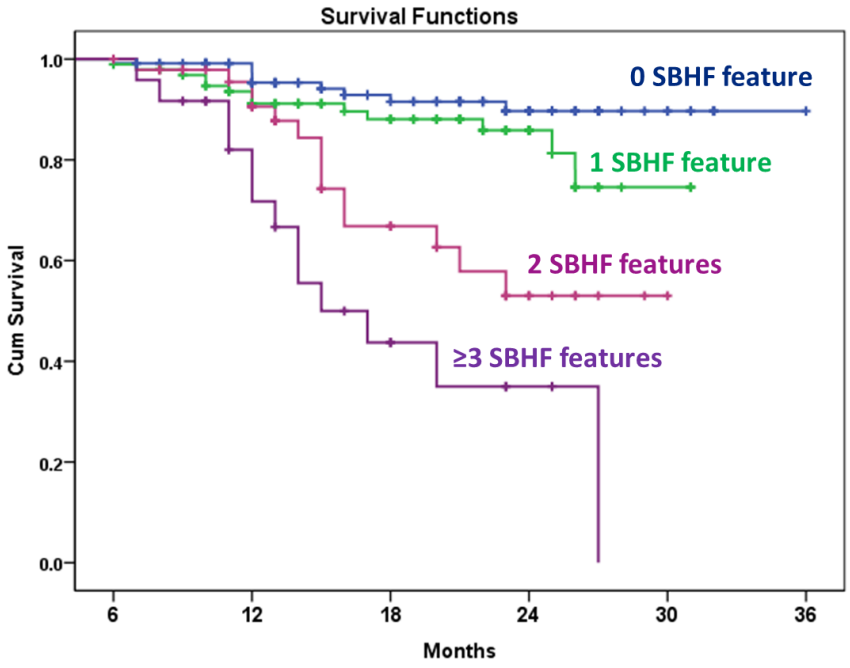
Survival free of the composite endpoint (HF and death) was about 1.5-fold higher in patients without any SBHF feature compared with patients with the presence of any SBHF features (**Figure 6.4a**). The proportion of cumulative event-free survival was less with increasing numbers of echocardiographic features of SBHF (**Figure 6.4b**).

Figure 6.4. Comparison of primary outcomes between diabetic patients with (a) and without SBHF features. (b)There is decreasing survival rate with increasing numbers of SBHF echocardiographic features.



0 SBHF feature	120	116	113	112	112	112
≥1 SBHF feature	168	151	137	132	129	129

(a)



0 SBHF feature	119	115	112	111	111	111
1 SBHF feature	96	92	87	87	85	85
2 SBHF features	47	43	37	34	34	34
≥3 SBHF features	23	18	13	11	11	11

(b)

6.5.4 Predictors of the HF and death.

Cox regression analysis was performed to analyze the association between clinical variables and echocardiographic parameters of interest and the time to the primary composite endpoint (**Table 6.2**). Multivariable Cox regression models were constructed to determine whether impaired GLS and other echocardiographic SBHF features of interest were associated with composite endpoint controlled for ARIC risk score and glycemic control. Significant univariable parameters of interest (ARIC risk score, HbA1c >64 mmol/mol, E/e' >13, LAE, LVH and GLS<16%) were entered into the model (**Table 6.3**). LVH, LAE and GLS<16% were associated with increased risk of the composite endpoint, independent of ARIC risk score and HbA1c, but abnormal E/e' was not. Multivariable models were also used to assess the measures as continuous variables; LA volume (adjusted HR=1.05, p=0.001) and GLS (adjusted HR=1.16, p=0.008) were predictors of the primary endpoint, independent of HbA1c (adjusted HR=1.03, p=0.039) (**Appendix 6.2**).

Table 6.2 Baseline clinical and echocardiographic characteristics of patients with T2DM who met primary composite outcome.

	Event (n=49)	No Event (n=241)	HR (95%CI)	p-value
Demographic and clinical characteristics				
Age (years)	71.9±4.7	70.7±4.2	1.06(0.99,1.12)	0.070
Male gender (n, %)	33(67.3)	130(53.9)	1.58(0.87,2.86)	0.136
Weight (kg)	95.4±19.7	84.1±15.7	1.04(1.02,1.05)	**<0.001**
Height (cm)	169.2±10.4	168.3±9.7	1.01(0.98,1.04)	0.673
BMI (kg/m^2)	33.6±7.7	29.7±5.2	1.10(1.06,1.14)	**<0.001**
Waist circumference (cm)	110.6±13.5	101.9±12.5	1.05(1.03,1.08)	**<0.001**
HbA1c (mmol/mol)	57.5±11.6	52.9±9.9	1.03(1.01, 1.05)	**0.008**
Poor HbA1c (n, %)$^{\lozenge}$	14(28.6)	24(10.0)	2.82(1.52,5.24)	**0.001**
Obesity (n, %)	34(69.4)	108(44.8)	2.77(1.51,4.09)	**0.001**
Heart rate (n/min)	68±12	69±10	0.99(0.97,1.03)	0.856
Systolic blood pressure (mmHg)	139±15	139±14	1.00(0.98,1.02)	0.860
Diastolic blood pressure (mmHg)	81±9	81±10	1.00(0.98,1.03)	0.811
Hypertension (n, %)	39(79.6)	183(75.9)	1.27(0.63,2.54)	0.505
Family history of HF (n, %)	11(22.4)	79(32.8)	0.62(0.32,1.21)	0.163
Past chemotherapy (n, %)	5(10.2)	19(7.9)	1.34(0.53,3.39)	0.536
Past heart disease (n, %)	6(12.2)	14(5.8)	1.94(0.82,4.56)	0.456
ARIC HF risk score (3 year) (%)	11.1±8.9	6.8±5.4	1.08(1.05,1.11)	**<0.001**
Medication				
Insulin (n, %)	16(32.7)	53(22.0)	1.57(0.86,2.86)	0.140
Metformin (n, %)	31(63.3)	165(68.5)	0.89(0.50,1.59)	0.688
ACEi / ARB (n, %)	37(75.5)	164(68.4)	1.37(0.72,2.63)	0.344
Beta-blockers (n, %)	6(12.2)	10(4.1)	2.89(1.23,6.81)	**0.015**
Calcium antagonists (n, %)	7(14.3)	61(25.3)	0.50(0.22,1.11)	0.089
Diuretics (n, %)	6(12.2)	27(11.2)	1.08(0.46,2.54)	0.858
Lipid lowering meds (n, %)	31(63.3)	117(48.5)	1.48(0.83,2.65)	0.186
Echocardiography				
LV ejection fraction (%)	61.2±7.9	63.2±6.1	0.95(0.91,0.99)	**0.026**
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.69±0.21	0.65±0.16	4.35(0.88,21.44)	0.071
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.87±0.27	0.82±0.18	2.67(0.62,11.55)	0.190
Transmitral diastolic flow velocity ratio (E/A)	0.79±0.24	0.80±0.20	0.96(0.20,4.59)	0.960
Early diastolic mitral annular velocity (e') (m/s)	0.08±0.02	0.08±0.01	1.06(0.89,1.27)	0.502
Average E/e' ratio (E/e')	9.6±3.1	9.1±2.6	1.06(0.96,1.17)	0.251
Deceleration time(DT) (s)	247.5±57.5	246.1±51.4	1.00(0.99,1.01)	0.757
LA volume (mL/m^2)	38.0±11.5	31.1±9.3	1.06(1.03,1.08)	**<0.001**
LV mass index (g/m^2)	104.0±27.1	90.1±22.5	1.02(1.01,1.03)	**<0.001**
LV mass index (g/m$^{1.7}$)	87.0±25.2	72.2±19.7	1.03(1.02,1.04)	**<0.001**
LV mass index (g/m$^{2.7}$)	51.6±14.9	42.9±11.6	1.05(1.03,1.07)	**<0.001**
GLS (%)	16.3±2.9	18.0±2.4	1.27(1.15,1.41)	**<0.001**
Echocardiography categorical variables				
E/e' ratio >13 (n, %)	6(12.2)	24(10.0)	1.35(0.58,3.18)	0.488
LV hypertrophy (n, %)*	23(46.9)	45(18.7)	3.52(2.00,6.18)	**<0.001**
LA enlargement (n, %)$^{\Delta}$	30(61.2)	72(29.9)	3.29(1.85,5.86)	**<0.001**
GLS<18% (n, %)	32(65.3)	114(47.3)	2.13(1.18,3.84)	**0.012**
GLS<16% (n, %)	22(44.9)	46(19.1)	3.24(1.94,5.69)	**<0.001**
Any presence of SBHF features (n, %)†	40(81.6)	129(53.5)	4.09(1.62,10.33)	**0.003**

$^{\lozenge}$ *Poor HbA1c, ICFFstd-HbA1c>64mmol/mol;*

$^{\Delta}$ *LA enlargement was defined as LA volume>34 mL/m^2;*

**LV hypertrophy was defined as LVMi>115 g/m^2 for males, >95 g/m^2 for females.*

† *The presence of at least one the following: LVH, GLS<18%, E/e'>13, LAE*

Table 6.3 Independent associations of death and HF in elderly asymptomatic patients with T2DM. Cox regression analysis for primary composite endpoint.

Variable	Unadjusted HR (95%CI) P value	E/e' Adjusted HR(95%CI)* P value	LAE Adjusted HR(95%CI)* P value	LVH Adjusted HR(95%CI)* P value	GLS Adjusted HR(95%CI)* P value	All except LAE. Adjusted HR(95%CI)* P value	All except E/e'. Adjusted HR(95%CI)** P value
ARIC HF risk score(3 year)	1.08(1.05,1.11) **<0.001**	1.08(1.04,1.11) **<0.001**	1.06(1.03,1.10) **<0.001**	1.06(1.02,1.09) **0.001**	1.07(1.04,1.11) **<0.001**	1.06(1.02,1.10) **0.002**	1.05(1.01,1.09) **0.007**
Poor HbA1c	2.83(1.52,5.27) **0.001**	2.72(1.45,5.07) **0.002**	2.79(1.50,5.19) **0.001**	2.34(1.24,4.40) **0.008**	2.26(1.20,4.26) **0.011**	1.97(1.01,3.81) **0.045**	2.11(1.10,4.04) **0.025**
Abnormal E/e'	1.35(0.58,3.18) 0.488	1.11(0.47,2.66) 0.810	-	-	-	0.86(0.34,2.16) 0.746	-
LAE	3.29(1.85,5.86) **<0.001**	-	2.80(1.55,5.05) **0.001**	-	-	-	2.34(1.27,4.32) **0.007**
LVH	3.52(2.00,6.18) **<0.001**	-	-	2.34(1.26,4.35) **0.007**	-	2.04(1.08,3.84) **0.027**	1.62(0.84,3.14) 0.149
Impaired GLS	3.24(1.84,5.69) **<0.001**	-	-	-	2.67(1.51,4.75) **0.001**	2.46(1.36,4.45) **0.003**	2.29(1.26,4.15) **0.007**

Abbreviations: HR=hazard ratio; CI=confidence interval;Poor HbA1c, ICFFstd-HbA1c>64mmol/mol; abnormal E/e', cutoff 13; LAE, left atrial enlargement, cutoff>34 mL/m^2; LVH, left ventricular hypertrophy, cutoff >115 g/m^2 for males, >95 g/m^2 for females; GLS, global longitudinal strain, cutoff -16%.

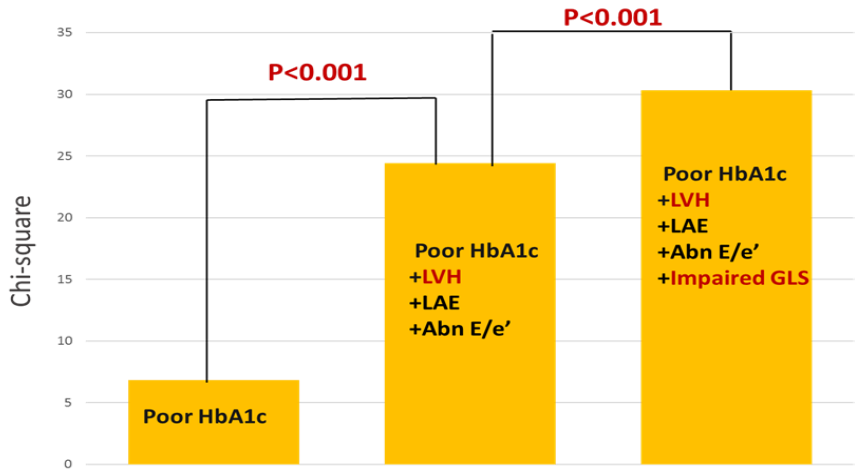
** In the multivariate cox model, poor HbA1c, abnormal E/e', LAE, LVH and impaired GLS were entered into the model.*

*** In the multivariate cox model, poor HbA1c, LAE, LVH and impaired GLS were entered into the model.*

6.5.5 Prediction of HF.

A competing risk analysis that controlled for HbA1c was performed to assess whether impaired GLS and other echocardiographic SBHF features of interest were associated with incident HF in elderly asymptomatic patients with T2DM (**Figure 6.5**). The baseline model, showing a significant effect of poor glycemic control (p=0.009) on incident HF, was improved by LVH (p=0.042). However, the addition of impaired GLS (p=0.008) had incremental predictive power to biochemical and other echocardiographic SBHF features for the prediction of incident HF (**Figure 6.5**).

Figure 6.5 Prediction of incident HF in elderly asymptomatic patients with T2DM (competing risk analysis). LVH and impaired GLS showed incremental value over glycaemic control for incident HF.

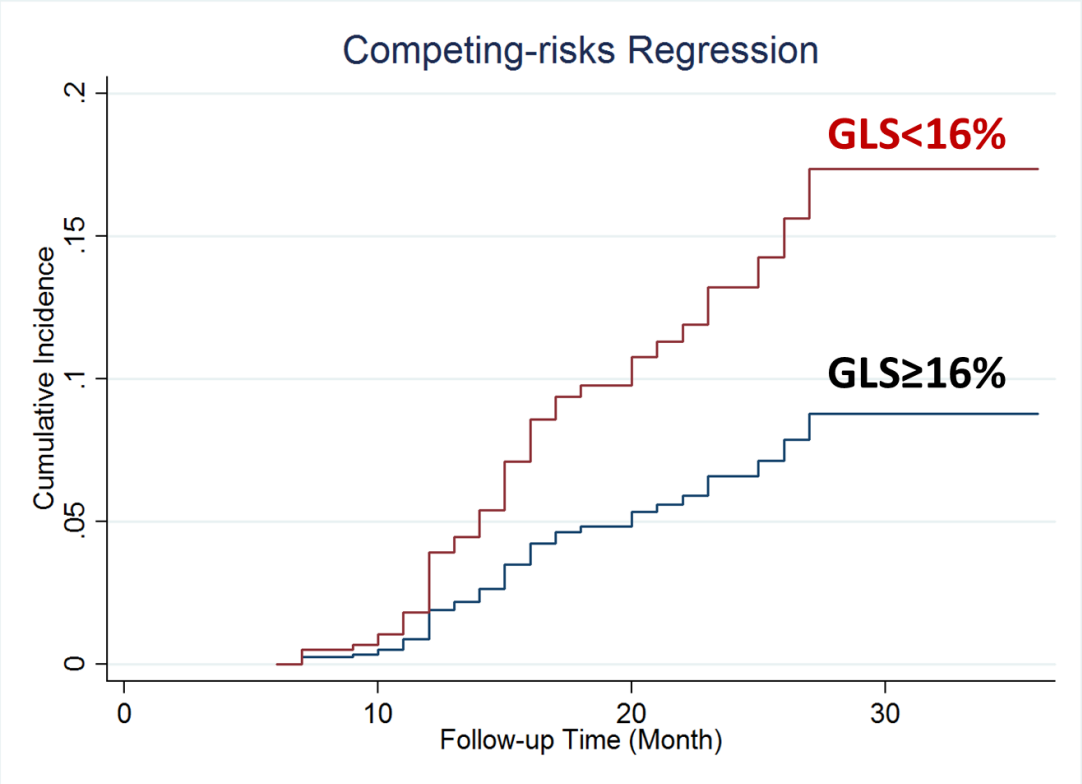


	Model 1	Model 2	Model 3
Chi-square **P for chi-square change**	6.81	24.42 P<0.001	30.30 P<0.001
	HR (95% CI) **P value**	**HR (95% CI)** **P value**	**HR (95% CI)** **P value**
Poor HbA1c	2.37(1.24,4.53) **0.009**	2.04(1.03,4.05) **0.042**	1.76(0.86,3.61) 0.121
LVH		3.33(1.87,5.93) **<0.001**	2.90(1.61,5.25) **<0.001**
LAE		1.23(0.69,2.19) 0.483	1.29(0.69,2.19) 0.401
Abnormal E/e'		1.49(0.67,3.29) 0.329	1.31(0.55,3.08) 0.541
Impaired GLS			2.26(1.24,4.15) **0.008**

Abbreviations: HR=hazard ratio; CI=confidence interval; Poor HbA1c, ICFFstd-HbA1c>64mmol/mol; LVH, left ventricular hypertrophy, cutoff >115 g/m2 for males, >95 g/m2 for females; LAE, left atrial enlargement, cutoff>34 mL/m2;abnormal E/e', cutoff 13; GLS, global longitudinal strain, cutoff -16%.

The cumulative incidence of HF with time among elderly asymptomatic T2DM stratified by impaired GLS status is shown in **Figure 6.6**. By the end of the follow-up, considering the competing risk, the cumulative incidence (CIF) of HF was 0.17 in patients with GLS<16% and was 0.09 in patients with GLS≥16%. Gray's test also showed that the cumulative incidence (CIF) of HF was significantly lower in patients with GLS<16% than those patients with GLS≥16% (p<0.001).

Figure 6.6 Cumulative incidence estimates of HF in elderly asymptomatic T2DM stratified by patients with and without impaired GLS.



6.6 Discussion

In this prospectively enrolled community-based cohort, poor glycemic control, LVH, LAE and GLS<16% were independently associated with new-onset HF and death in elderly asymptomatic patients with T2DM who had no evidence of overt LVD. Although previous

studies have shown LVD to predict mortality, to our knowledge, this is the first study to show that echocardiographic parameters as SBHF markers are useful for screening for new-onset HF in asymptomatic patients with T2DM that accounts for all-cause of mortality as a competing risk. GLS <16% provides incremental prognostic information in patients with T2DM and preserved EF.

6.6.1 SBHF screening in T2DM.

T2DM is a risk factor of HF, independent of hypertension, coronary artery disease and other potential risk factors [4, 7]. The recognition of the pre-clinical stages of HF may permit the initiation of cardioprotection for these subjects, but the main functional marker for non-ischemic SBHF is LVEF. Although readily obtainable, this is not the optimal diagnostic parameter, as HFpEF is the most common manifestation of HF in T2DM. GLS is an effective means of detecting early changes in myocardial function [193], which is associated with adverse cardiac events over long-term follow-up [189, 190].

A recently-reported cluster analysis of echocardiographic variables in T2DM patients identified distinct clinical profiles associated with three different phenotypes [194]. The phenotype most associated with adverse outcome in this study (LVH with reduced GLS) corresponds with one of these groups, and differs from the other two – comprising patients with relatively mild dysfunction, and a group with diastolic dysfunction and hypertensive heart disease. In our experience, the negative prognostic effect of impaired GLS was most evident in patients with GLS<16% - the independent effect of which doubled the risk of HF, and provided a 2.4-fold increase in risk of the composite endpoint. As these patients had preserved EF at baseline, these results support the use of GLS as a criterion for SBHF in community-based patients with T2DM.

6.6.2 Functional and structural changes in T2DM as indicators of HF.

Patients with T2DM are at a 1.5-fold increment in risk of LV hypertrophy, independent of various confounders including obesity, age and gender [195]. This finding is independent of hypertension and has been associated with insulin resistance [195]. These results were confirmed in our study, which showed LVH in 68 patients (23%), and after adjustment for glycemic control, LVH by LVMi (indexed by BSA) was superior to biochemical variables in predicting incident HF. Although electrocardiography (ECG) is widely available and less expensive than echocardiography, it is also less sensitive in detecting LVH in T2DM [196, 197].

Global longitudinal strain derived from speckle tracking measures the extent of tissue deformation as a percentage of the baseline at a longitudinal direction, and it could be used to identify sub-clinical LVD in cardiomyopathies. Diabetic cardiomyopathy is defined as LVD that is independent of coronary artery disease and hypertension [161, 178]. Impaired GLS is reported to be highly prevalent even in normotensive asymptomatic T2DM [189, 198]. This longitudinal dysfunction is due to the complex interaction between metabolic, hemodynamic and endocrine abnormalities [190]. Limited studies have evaluated its predictive value for adverse cardiac events in T2DM.

E/e' is an important predictor of cardiovascular events in patients with systolic HF or acute coronary syndrome [199, 200]. However, the role of LVDD as a manifestation of diabetic heart disease is controversial. Ernande et al reported that GLS was the primary disturbance of T2DM, and that LVDD was primarily a consequence of hypertension [186, 189, 194]. In a study of 247 T2DM patients (mean age 60 years) with no history of cardiovascular complications, Liu et al showed that the presence of either impaired GLS (<17.9%) or high E/e' (>13.6) had a predictive value of cardiovascular events beyond clinical data [190]. However, in a prospective study of 406 middle-aged patients with DM, diastolic dysfunction (E/e' ratio >15) was a stronger

independent predictor of cardiac death than GLS [201]. In contrast, our results showed that GLS to be stronger predictor of incident HF than E/e' ratio. These differences in the reported literature are likely to reflect the different contribution of comorbid diseases in different populations.

6.6.3 Limitation.

The population of the present study has been selected from the community, based on the presence of at least one known non-ischemic cardiovascular risk factor and excluding patients with a known history of HF or established asymptomatic LV systolic dysfunction. Therefore, T2DM patients with established asymptomatic LV systolic dysfunction were excluded. Another limitation of the study is that we did not record circumferential and radial strain. Although these provide additional information regarding myocardial mechanics, longitudinal strain is the most robust and reproducible parameter. Additionally, we did not gather data on biomarkers – such as natriuretic peptides - which are potential predictors of HF and adverse outcome in T2DM. Finally, recruitment was partly through newspaper advertising, which may have resulted in population selection bias.

6.7 Conclusion.

Asymptomatic LV systolic dysfunction as an expression of SBHF is highly prevalent in elderly asymptomatic patients with T2DM. Impaired GLS (<16%) and LVH (by LVM/BSA) were independently associated with incident HF over 2-year follow-up. Importantly, impaired GLS adds incremental prognostic value to glycemic control and other conventional echocardiographic parameters. The detection of early myocardial dysfunction may allow identification of asymptomatic patients with T2DM who are at risk of developing symptomatic HF.

6.8 Postscript

Our study shows that in asymptomatic elderly community members with diabetes, GLS is a powerful predictor of incident HF, independent of other conventional echo parameters in patients with preserved EF. It highlights the importance of performing a comprehensive echocardiogram including strain images in asymptomatic patients even with preserved EF. The use of GLS to identify high-risk patients for incident HF may lead to changes in follow-up and treatment strategies. This study provides new information regarding the use of GLS to predict incident HF among T2DM patients. However, the recognition of HF and its progression requires more than the evaluation of LV dysfunction with clinical and echocardiographic parameters. The influence of depression on the progression of HF in T2DM patients will be explored in the next chapter.

6.9 Appendix

Appendix 6.1 Comparison of baseline characteristics between patients who completed follow-up study (n=290) and patients who loss to follow-up study (n=20).

	Completed n=290	**Loss to FU n=20**	**P value**
Demographic and clinical characteristics			
Age (years)	70.9±4.3	72±5.1	0.275
Male gender (n, %)	163(56.2)	8(40.0)	0.159
Weight (kg)	85.9±17.0	85.7±16.7	0.953
BMI (kg/m^2)	30.3±5.9	31.1±5.6	0.586
Waist circumference (cm)	103.4±13.0	107.3±15.3	0.213
HbA1c (mmol/mol)	53.7±10.3	53.9±8.7	0.915
Poor HbA1c (n, %)$^{\Diamond}$	38(13.1)	4(20)	0.364
Obesity (n, %)	142(49.0)	11(55.0)	0.602
Heart rate (n/min)	69±11	71±13	0.389
Systolic blood pressure (mmHg)	139±14	141±23	0.717
Diastolic blood pressure (mmHg)	81±10	80±10	0.652
Hypertension (n, %)	222(76.6)	14(70.0)	0.507
Family history of HF (n, %)	90(31.0)	7(35.0)	0.712
Past chemotherapy (n, %)	24(8.3)	3(15.0)	0.303
Past heart disease (n, %)	20(6.9)	2(10.0)	0.602
Aric risk (3 year) (%)	7.5±6.4	8.2±6.7	0.372
Medication			
Insulin (n, %)	69(23.8)	5(25.0)	0.127
Metformin (n, %)	196(67.6)	9(45.0)	0.386
ACEi / ARB (n, %)	201(69.3)	12(60.0)	0.251
Beta-blockers (n, %)	16(5.5)	0(0)	0.282
Calcium antagonists (n, %)	66(23.4)	2(10.0)	0.165
Diuretics (n, %)	33(11.4)	4(20.0)	0.251
Lipid lowering meds (n, %)	148(51.0)	10(50.0)	0.929
Echocardiography			
LV ejection fraction (%)	62.9±6.5	63.0±5.1	0.950
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.65±0.17	0.74±0.26	0.180
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.83±0.19	0.88±0.25	0.304
Transmitral diastolic flow velocity ratio (E/A)	0.80±0.21	0.79±0.28	0.939
Early diastolic mitral annular velocity (e') (m/s)	0.08±0.02	0.08±0.02	0.442
Average E/e' ratio (E/e')	9.2±2.7	9.8±3.1	0.313
E/e' ratio >13 (n, %)	30(10.3)	3(15.0)	0.515
Deceleration time(DT) (s)	246.4±52.4	244.6±50.7	0.886
LA volume (mL/m^2)	32.3±10.1	34.8±12.2	0.379
LA enlargement (n, %) $^{\Delta}$	102(35.2)	10(50)	0.187
LV mass index (g/m^2)	92.4±23.8	89.8±19.0	0.635
LV mass index (g/m$^{1.7}$)	74.7±21.4	73.3±17.2	0.772
LV mass index (g/m$^{2.7}$)	44.4±12.6	44.0±10.7	0.898
LV hypertrophy (n, %)*	68(23.4)	3(30.0)	0.513
GLS (%)	17.7±2.6	16.9±2.9	0.160
GLS<18% (n, %)	146(50.3)	12(60.0)	0.404
GLS<16% (n, %)	68(23.4)	7(35.0)	0.244
Presence of any SBHF features (n, %) †	169(58.3)	13(65.0)	0.555

Poor HbA1c, ICFFstd-HbA1c>64mmol/mol; LVH, left ventricular hypertrophy, cutoff >115 g/m^2 for males, >95 g/m^2 for females; LAE, left atrial enlargement, cutoff>34 mL/m^2; abnormal E/e', cutoff 13; GLS, global longitudinal strain, cutoff -16%.

Appendix 6.2 Cox regression analysis for primary composite endpoint in elderly asymptomatic patients with T2DM.All covariates were entered as continuous variables.

Variable	Unadjusted HR (95%CI) P value	Adjusted HR(95%CI)* P value
HbA1c	1.03(1.01, 1.05) 0.008	1.03(1.00,1.06) **0.039**
E/e' ratio	1.06(0.96,1.17) 0.251	1.00(0.91,1.10) 0.960
LA volume	1.06(1.03,1.08) <0.001	1.05(1.02,1.07) **0.001**
LVMi	1.02(1.01,1.03) <0.001	1.01(0.99,1.02) 0.165
GLS	1.27(1.15,1.41) <0.001	1.16(1.04,1.30) **0.008**

Chapter 7. Association of Depression with Heart Failure in T2DM

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7.1 Preface

The mechanisms of incident HF risk in T2DM are incompletely understood. While diabetic cardiomyopathy is an important potential substrate, the development of HF in T2DM is likely to be influenced by a number of other processes, including endothelial dysfunction, hyperglycemia, insulin resistance, dyslipidemia and inflammation. One potential risk factor that influences these processes is depression. Depression is highly prevalent in both HF and T2DM [202]. Depression not only triggers endothelial dysfunction through impaired cellular adhesion, migration and proliferation, but also promotes dyslipidemia [203]. In this study, we explored the association of depression and incident HF in elderly T2DM without any baseline cardiovascular symptoms.

7.2 Abstract

Background. Depression is a prevalent, independent predictor of mortality in patients with heart failure (HF).Depression is also common in type 2 diabetes mellitus (T2DM), which is itself an important risk factor for HF. However, association of depression with incident HF in T2DM is undefined. The aim of the present study was to evaluate the predictive value of depression in predicting incident HF in a community-based cohort of asymptomatic patients with T2DM.

Methods. We prospectively recruited 274 asymptomatic T2DM patients ≥65 years (age 71±4 y, 56% men) with preserved EF and no ischemic heart disease from a community-based population. The patient Health Questionnaire 9 (PHQ-9) was used to detect depression, and LV dysfunction was sought with a comprehensive echocardiogram, including LV hypertrophy (LVH) and subclinical diastolic function (E/e'). Over a median follow-up of 1.5 years (range 0.5-3), 20 patients were lost to follow-up and 254 individuals were followed for outcomes.

Results. At baseline, depression was present in 9.5%, LVH was identified in 26% and reduced E/e' in 11%. Over a median follow-up of 1.5 years, 37 of 245 patients developed new-onset HF and 3 died, giving an event rate of 107/1000 person-years. In a competing-risks regression analysis, depression (adjusted HR=2.54, 95%CI 1.18-5.46; p=0.017) was associated with incident HF and had incremental predictive power to clinical, biochemical and echocardiographic variables.

Conclusion. Depression is prevalent in asymptomatic elderly patients with T2DM, and depression independently and incrementally predicts incident HF.

7.3 Background

Heart failure (HF) is a common clinical syndrome in which the heart is unable to pump blood at an adequate rate or in adequate volume which is associated with high morbidity and mortality, which has been recognized as one of the most common and malignant complications of type 2 diabetes mellitus (T2DM).[36] HF has been reported in >22% elderly patients with diabetes, and the HF incidence rate was 12.6 per 100 person-years.[7] Among elderly patients with DM, the 5-year mortality rate was approximately 9-fold higher in those who developed HF than in those who did not.[7] Depressive symptoms are common in the community, but the 19% prevalence of depression in patients with T2DM is about double that of those without DM.[204]Depression is a serious mood disorder that negatively affects people's feeling, thinking and behaviour that affects both physical and mental health. In patients with existing HF, comorbid depression and diabetes are associated with a higher mortality and rehospitalisation rate.[205] The presence of depression more than doubled the risk of all-cause of mortality in HF (Hazard Ratio [HR] =2.29; 95% CI 0.94 - 5.40; p=0.05), and both DM and depression led to a nearly fourfold increment in all-cause mortality (HR=3.71; 95% CI 1.49-9.25; p=0.005).[205]

Depression is an independent predictor of HF onset in elderly patients with isolated systolic hypertension, which is independent of demographic characteristics, medical history and myocardial infarction risks.[206] Although prior studies have found the association of depression and adverse outcomes with diabetes alone or heart failure alone, the association of depression with incident HF in patients with diabetes has not been determined. The extent to which level of depression is able to predict incident HF in asymptomatic T2DM is uncertain. The current study was undertaken to evaluate the ability to predict incident HF in a community-based cohort of asymptomatic patients with T2DM.

7.4 Methods

7.4.1 Study population.

We prospectively recruited 274 asymptomatic T2DM patients aged ≥65 with preserved LVEF from a community-based population in Australia. Patients with existing HF or known ischemic heart disease (reported with coronary artery disease including CABG and/or myocardial infarction with regional scar) were excluded, as were patients with more than moderate valve disease, history of HF, LVEF <40%, or inability to acquire adequate echocardiographic images for baseline analysis.

7.4.2 Ethics, consent and permissions.

All participants provided written, informed consent, and the study protocol was approved by the Tasmanian Human Research Ethics Committee.

7.4.3 Clinical features.

T2DM was based on self-report of this diagnosis including the use of relevant medication. Obesity was defined as body mass index (BMI) ≥30 kg/m^2. Demographics, disease and family history and medication use were obtained using a standardized questionnaire. BMI was calculated as weight in kilograms divided by height in meters squared. In addition to

standardized weight and height measurements, waist circumference (WC) at the midpoint between the lower costal margin and the iliac crest was measured to the nearest millimeter by a trained examiner. After at least 10 minutes rest in a quiet room, supine resting blood pressure (BP) was measured twice and averaged in each patient. Active hypertension was defined by a mean systolic blood pressure (BP) ≥140 mmHg or a diastolic BP≥90 mmHg.[162] International Federation of Clinical Chemistry [IFCC] standardized hemoglobin A1c (cutoff 64 mmol/mol), fasting glucose, creatinine and estimated glomerular filtration rate (eGFR) were extracted from pathology records. To estimate missing values for HbA1c, we carried out imputation using linear regression equation.

7.4.4 Depression assessment.

All participants completed the Patient Health Questionnaire 9 (PHQ-9) at baseline assessment. Each item in the PHQ-9 questionnaire corresponds to one of the nine DSM-IV criteria for diagnosis of major depression. Respondents indicated their level of agreement with each of the items (0 = not at all, 1 = several days, 2 = more than half of the days, 3 = nearly every day).The validated cutoff PHQ-9 score ⩾10 was used as diagnosis for the presence of depression,[140] and further stratified respondents into four categories of depressive symptomatology based on the total PHQ-9 score: minimal (0~4), mild (5~9), moderate (10~20), and severe (⩾20).

7.4.5 Echocardiography.

A comprehensive echocardiogram including standard transthoracic 2D and Doppler echocardiography was performed using the same ultrasound machine (Siemens ACUSON SC2000, 4V1c and 4Z1c probes, Siemens Healthcare, Mountain View, CA) in accordance with the American Society of Echocardiography guidelines.[144, 207] Images were saved in raw data format and analyzed offline. LV internal dimensions and wall thickness, chamber volumes and valvular morphology were assessed. LV mass index (LVMi) was obtained from LV mass

measurement using standard criteria and normalized for body size [body surface area or height to the power of 1.7]. LV hypertrophy (LVH) was defined as LVMi (normalized for body surface area) >115 g/m^2 for males and >95 g/m^2 for females. LVEF was measured using the modified Simpson's biplane method. LV inflow was obtained using pulsed wave Doppler in the apical 4-chamber view; peak early (E) and late (A) diastolic velocities, deceleration time and E/A ratio were assessed. Peak early diastolic medial and lateral mitral annular velocity (e') and the ratio of mitral inflow early diastolic velocity to average e' velocity were obtained from pulsed tissue Doppler; E/e'>13 was used as an indicator of diastolic dysfunction.[154]

7.4.6 Outcomes.

Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires, clinical visits and repeated echocardiography. Symptoms and signs that were suspicious for HF were reviewed by three independent cardiologists, and the diagnosis of HF was established according to Framingham heart failure criteria.[4] Records of all-cause hospitalization and mortality were obtained from administrative data. The primary endpoint was new-onset of HF, and all-cause mortality was considered as a competing risk.

7.4.7 Statistical Analysis.

Descriptive data are presented as mean±standard deviation (SD) and dichotomous data as subject number and percentage. Comparisons between the groups were performed by independent samples t-test; the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Univariate and multivariate stepwise forward linear regression was performed in order to identify the variables with significant association with PHQ-9 score.

Univariable Cox regression was used to identify the predictors of incident HF among clinical, demographic and echocardiographic variables. We fitted a competing-risk model to compute

hazard ratio (HR) and 95% confidence interval (95%CI) for the associations between each risk factor and incident HF.[191] A multivariable model was constructed to determine the independent predictors, guided by univariable analyses and the clinical relevance of the variables. Competing risk methods were used to account for the competing risk of death when analyzing the endpoint of time to HF. The cumulative incidences of HF were calculated and graphically displayed separately for patients with and without depression. Gray's K-sample test was to compare the cumulative incidence estimates of HF between patients with/without depression,[192] which accounts for all-cause of death as a competing risk of HF. All data were analyzed using standard statistical computer software (SPSS 22, IBM, Chicago, IL and Stata, V.12.0, Stata Corp, College Station, Texas, USA); $p<0.05$ was deemed to be statistically significant.

7.5 Results

7.5.1 Patient characteristics.

Table 7.1 describes the clinical, echocardiographic and biochemical features of 274 asymptomatic T2DM patients ≥65 years old with preserved EF from the community who were prospectively recruited and underwent baseline tests. **Table 7.1** also includes the 254 T2DM participants who were included in the final analysis (see below). In the total recruited group of 274 subjects, the prevalence of LV dysfunction was 26% (by LVH) and 11% (by abnormal E/e' cutoff 13). In the 254 subjects included in the final analysis, baseline HbA1c was available in 196 individuals (age 71±4yrs, 55% men). In this subgroup, the baseline HbA1c was 53.2±11.4 mmol/mol. After imputation of missing values, the baseline HbA1c was 53.5±10.1 mmol/mol (**Table 7.1**).

7.5.2 Depression.

Based on PHQ-9 score, 37 (14%) patients had minimal-to-mild depressive symptoms (PHQ-9 score 5 to 9), and 25 (9%) patients were identified as having moderate-to-severe depressive symptoms (PHQ-9 score 10 to 20), and 2 (0.7%) patients were identified as having severe depressive symptoms (PHQ-9 score ⩾20), and were diagnosed as having depression using the cutoff of PHQ-9 score ≥10. **Table 7.2** shows the features associated with depression; these patients had higher BMI and more central obesity, more insulin use and higher HbA1c level. However, there was no difference in age, gender, blood pressure, heart rate and other risk factors of HF and echocardiographic parameters among patients with and without depression. The significant determinant of PHQ-9 score detected by linear regression was BMI.

7.5.3 Follow-up.

After a median follow-up time of 1.5 years (range 0.5-3 years), 2 of 274 T2DM participants (0.7%) were lost to follow-up and 18 of 274 participants (6.6%) were alive but unable to attend for clinic review (**Figure 7.1**). This group was no different from the remaining 254 individuals who completed follow-up (**Appendix 7.1**). The primary composite endpoint was reached by 40 patients; 37 patients developed new-onset HF and 3 died, giving an event rate of 107/1000 person-years.

Cox regression analysis was performed to analyze the association between clinical and biochemical variables and echocardiographic parameters of interest and the time to the primary composite endpoint (**Table 7.3).**Patients with events were characterized by obesity, worse glycemic control, baseline LVEF, LV mass (but not diastolic function parameters), beta blockade and depression. For PHQ-9 scores, it was significantly associated with events either as continuous covariate or binomial covariate. When categorized PHQ-9 score into three levels (0~4, 5~9 and ⩾10), PHQ-9⩾10 was independently associated with events. The cumulative

survival of the included 254 elderly asymptomatic T2DM stratified by the severity of depression was listed in **Appendix 7.3**. A multivariable Cox regression model (informed by significant univariable clinical associations and echocardiographic parameters of interest) was constructed to determine the independent predictors of the composite endpoint (**Table 7.4**). Obesity, LVH and depression were associated with increased risks of the composite endpoint.

7.5.4 Prediction of HF in T2DM.

A competing risk analysis that controlled for age, obesity and poor glycemic control was performed to assess whether depression and other echocardiographic parameters of interest were associated with incident HF in elderly asymptomatic patients with T2DM (**Figure 7.2**). The baseline clinical model, showing an independent effect of obesity ($p<0.001$), and poor glycemic control ($p=0.02$) on incident events, was improved by addition of echocardiographic features (LVH, $p=0.001$). However, the addition of depression ($p=0.017$) had incremental predictive power to clinical, biochemical and echocardiographic variables for the prediction of incident HF (**Figure 7.2**).

The cumulative incidence of HF with time among elderly asymptomatic T2DM stratified by depression status is shown in **Figure 7.3**. By the end of the follow-up, considering the competing risk, the cumulative incidence of HF was 0.36 in patients with depression and was 0.15 in patients without depression. Gray's test also showed that the cumulative incidence of HF was significantly lower in patients with depression than those patients without depression ($P<0.001$).

Table 7.1. Baseline characteristics (demographic, clinical, echocardiographic, physiologic) of 274 elderly asymptomatic patients with T2DM.

Demographic and clinical characteristics	Age (years)	71±4.4
	Male gender (n, %)	150(54.7)
	Weight (kg)	85.8±17.2
	Height (cm)	168.4±10.0
	BMI (kg/m^2)	30.3±5.9
	Waist circumference (cm)	103.2±13.3
	Obesity (n, %)	135(49.3)
	Heart rate (n/min)	69±11
	Systolic blood pressure (mmHg)	139±15
	Diastolic blood pressure (mmHg)	81±10
	Hypertension (n, %)	204(74.4)
	Family history of HF (n, %)	80(29.2)
	Past chemotherapy (n, %)	25(9.1)
	Past heart disease (n, %)	16(5.8)
Medication	Insulin (n, %)	65(23.7)
	Metformin (n, %)	184(67.2)
	ACEi / ARB (n, %)	183(66.8)
	Beta-blockers (n, %)	15(5.5)
	Calcium antagonists (n, %)	64(23.4)
	Diuretics (n, %)	31(11.3)
	Lipid lowering meds (n, %)	133(48.5)
Questionnaire	PHQ-9 score	3.2±4.3
	PHQ-9 score≥10 (yes/no)	26(9.5)
Echocardiography	LV ejection fraction (%)	63.1±6.4
	Mitral early-diastolic inflow velocity (E wave) (m/s)	0.65±0.17
	Mitral late-diastolic inflow velocity (A wave) (m/s)	0.83±0.19
	Transmitral diastolic flow velocity ratio (E/A)	0.79±0.22
	Early diastolic mitral annular velocity (e') (m/s)	0.08±0.02
	Average E/e’ ratio (E/e’)	9.2±2.8
	E/e’ ratio >13 (n, %)	29(10.6)
	Deceleration time(DT) (s)	246.8±52.4
	LV mass index (g/m^2)	85.7±19.0
	LV mass index (g/m$^{1.7}$)	74.4±20.8
	LV hypertrophy (n, %)*	36(13.2)
Biochemical characteristics	HbA1c (mmol/mol) (n=274)	53.5±10.1
	Fasting glucose (µmol/L) (n=109)	8.3±3.5
	Creatinine (µmol/L) (n=186)	81.3±24.0
	eGFR (mL/min/1.73m^2) (n=187)	
	≥90	37(19.8)
	60 to 89	115(61.5)
	45 to 59	25(13.4)
	30 to 44	9(4.8)
	15 to 29	1(0.5)

**LV hypertrophy was defined as LVMi>115 g/m^2 for males, >95 g/m^2 for female.*

Table 7.2 Baseline demographic, clinical and echocardiographic variable comparisons among T2DM patients categorized by the presence of depression (n=254).

	Depression (n=25)	**No depression (n=229)**	**p**
Demographic and clinical characteristics			
Age (years)	70.6±3.8	70.9±4.4	0.418
Male gender (n, %)	11(44.0)	131(57.2)	0.208
Weight (kg)	92.6±22.8	85.1±16.5	0.122
BMI (kg/m^2)	34.1±7.8	29.8±5.6	**0.012**
Waist circumference (cm)	109.0±14.2	102.4±13.1	**0.032**
Obesity (n, %)	18(72.0)	106(46.3)	**0.015**
Heart rate (n/min)	70±11	68±11	0.280
Systolic blood pressure (mmHg)	138±17	139±14	0.936
Diastolic blood pressure (mmHg)	80±12	81±9	0.748
Hypertension (n, %)	19(76.0)	171(74.7)	0.985
Family history of HF (n, %)	10(40.0)	63(27.5)	0.191
Past chemotherapy (n, %)	4(16.0)	18(7.9)	0.170
Past heart disease (n, %)	3(12.0)	11(4.8)	0.135
HbA1c (mmol/mol)	57.6±10.6	53.0±10.0	**0.049**
HbA1c >64 mmol/mol (n, %)	8(32)	24(10.5)	**0.002**
Medication			
Insulin (n, %)	11(44.0)	49(21.4)	**0.012**
Metformin (n, %)	18(72.0)	157(68.6)	0.725
ACEi / ARB (n, %)	19(76.0)	152(66.4)	0.331
Beta-blockers (n, %)	1(4.0)	14(6.1)	0.571
Calcium antagonists (n, %)	7(28.0)	54(23.6)	0.524
Diuretics (n, %)	4(16.0)	23(10.0)	0.360
Lipid lowering meds (n, %)	14(56.0)	109(47.5)	0.426
Echocardiography			
LV ejection fraction (%)	61.5±8.7	63.2±6.2	0.222
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.62±0.18	0.65±0.16	0.530
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.81±0.16	0.83±0.19	0.525
Transmitral diastolic flow velocity ratio (E/A)	0.79±0.21	0.77±0.25	0.693
Early diastolic mitral annular velocity (e') (m/s)	0.07±0.01	0.08±0.02	0.852
Average E/e' ratio (E/e')	8.6±1.9	9.2±2.8	0.336
E/e' ratio >13 (n, %)	1(4.0)	25(10.9)	0.280
Deceleration time(DT) (s)	231.6±50.4	248.6±52.9	0.129
LV mass index (g/m^2)	87.3±16.1	85.4±19.6	0.602
LV mass index (g/m$^{1.7}$)	82.3±27.0	73.6±20.2	0.130
LV hypertrophy (n, %)*	2(8.0)	33(14.4)	0.998

**LV hypertrophy was defined as LVMi>115 g/m^2 for males, >95 g/m^2 for females.*

Table 7.3 Baseline clinical and echocardiographic characteristics of patients with T2DM who met primary composite outcome (n=254).

	Event (n=40)	**No Event (n=214)**	**p**
Demographic and clinical characteristics			
Age (years)	72.1±5.1	70.6±4.2	0.054
Male gender (n, %)	28(70.0)	114(53.3)	0.085
Weight (kg)	96.5±20.4	83.8±16.0	**<0.001**
Height (cm)	169.4±10.5	168.4±9.8	0.561
BMI (kg/m^2)	33.8±7.6	29.6±5.3	**<0.001**
Waist circumference (cm)	111.2±14.4	101.5±12.5	**<0.001**
Obesity (n, %)	30(75.0)	94(43.9)	**0.002**
Heart rate (n/min)	68±13	69±10	0.618
Systolic blood pressure (mmHg)	137±13	139±14	0.303
Diastolic blood pressure (mmHg)	81±9	81±10	0.772
Hypertension (n, %)	30(75.0)	160(74.8)	0.582
Family history of HF (n, %)	9(22.5)	64(29.9)	0.155
Past chemotherapy (n, %)	5(12.5)	17(7.9)	0.592
Past heart disease (n, %)	3(7.5)	11(5.1)	0.106
HbA1c (mmol/mol)	57.6±11.2	52.7±9.8	**0.005**
HbA1c >64 mmol/mol (n, %)	12(30.0)	20(9.3)	**<0.001**
Medication			
Insulin (n, %)	14(35.0)	46(21.5)	0.155
Metformin (n, %)	24(60.0)	151(70.6)	0.432
ACEi / ARB (n, %)	28(70.0)	143(66.8)	0.303
Beta-blockers (n, %)	6(15.0)	9(4.2)	**0.024**
Calcium antagonists (n, %)	6(15.0)	55(25.7)	0.097
Diuretics (n, %)	4(10.0)	23(10.7)	0.834
Lipid lowering meds (n, %)	23(57.5)	100(46.7)	0.061
Questionnaire			
PHQ-9 score	4.8±0.8	3.6±0.3	0.086
PHQ-9 score≥10 (yes/no)	7(17.5)	18(8.4)	0.077
Echocardiography			
LV ejection fraction (%)	61.2±7.9	63.2±6.1	0.096
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.67±0.20	0.64±0.16	0.347
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.85±0.23	0.83±0.18	0.483
Transmitral diastolic flow velocity ratio (E/A)	0.79±0.24	0.80±0.20	0.705
Early diastolic mitral annular velocity (e') (cm/s)	7.59±1.75	7.52±1.50	0.798
Average E/e’ ratio (E/e’)	9.4±3.1	9.1±2.6	0.511
E/e’ ratio >13 (n, %)	4(10.0)	22(10.3)	0.632
Deceleration time(DT) (s)	243.3±57.8	247.7±52.0	0.662
LV mass index (g/m^2)	96.3±21.0	83.6±18.3	**0.001**
LV mass index (g/m$^{1.7}$)	88.0±26.5	72.0±18.9	**<0.001**
LV hypertrophy (n, %)*	14(35.0)	21(9.8)	**<0.001**

Table7.4 Cox regression analysis for primary composite endpoint in 254 elderly asymptomatic patients with T2DM.

Variable	No. of patients	No. of HF	No. of Death	Unadjusted HR (95%CI) p value	LVH-adjusted HR (95% CI)† p value	E/e'-adjusted HR (95%CI)†† p value	Adjusted HR (95% CI)††† p value
Age	254	37	3	1.06(0.99,1.13) 0.064	-	-	1.06(0.99,1.14) 0.055
Male gender	142	25	3	1.81(0.92,3.56) 0.086	-	-	1.36(0.61,2.92) 0.466
Obesity	124	29	1	3.61(1.76,7.39) **<0.001**	2.87(1.38,5.98) **0.005**	3.27(1.58,5.75) **0.001**	2.97(1.44,6.30) **0.004**
HbA1c	32	10	2	3.27(1.66,6.43) **0.001**	2.04(0.99,4.22) 0.054	2.47(1.22,5.00) **0.012**	2.01(0.93,4.10) 0.077
LVH	35	13	1	3.92(2.04,7.52) **<0.001**	3.24(1.65,6.38) **0.001**	-	2.67(1.25,,5.99) **0.011**
E/e'	26	4	0	1.04(0.37,2.94) 0.934	-	1.11(0.39,3.18) 0.845	0.82(0.26,2.52) 0.724
Depression	25	7	0	3.21(1.41,7.30) **0.005**	2.80(1.16,6.76) **0.022**	2.39(1.01,5.67) **0.048**	3.14(1.27,7.74) **0.013**

Abbreviations: HR=hazard ratio; CI=confidence interval;
Obesity, BMI≥30kg/m^2; Poor HbA1c, ICFFstd-HbA1c>64mmol/mol; LVH, left ventricular hypertrophy, cutoff >115 g/m^2 for males, >95 g/m^2 for females; E/e' ratio, cutoff >13; Depression, the score of PHQ-9 questionnaire ≥10.

†In the multivariate cox model, obesity, poor HbA1c, LVH and depression were entered into the model.

††In the multivariate cox model, obesity, poor HbA1c, E/e' and depression were entered into the model.

†††In the multivariate cox model, age, male gender, obesity, poor HbA1c, LVH, E/e' and depression were entered into the model.

Figure 7.1. Flow chart of study inclusion (n=254).

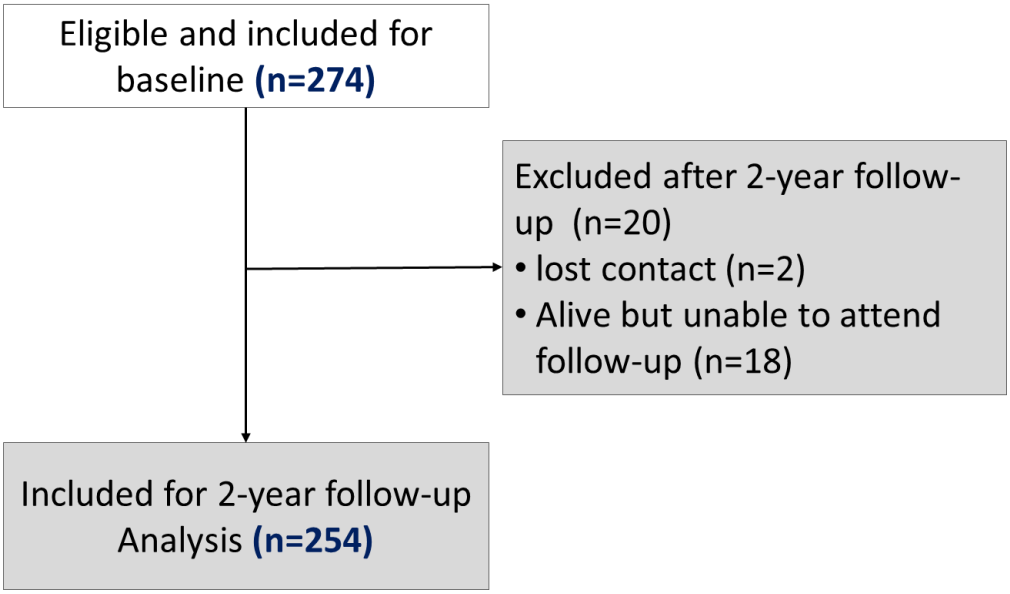
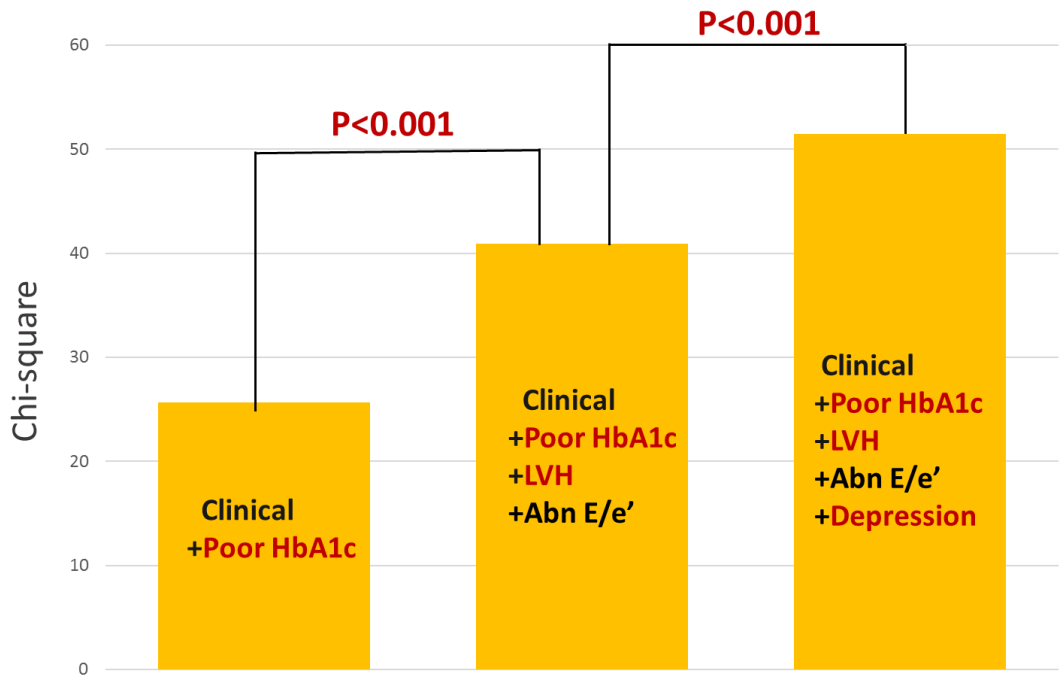


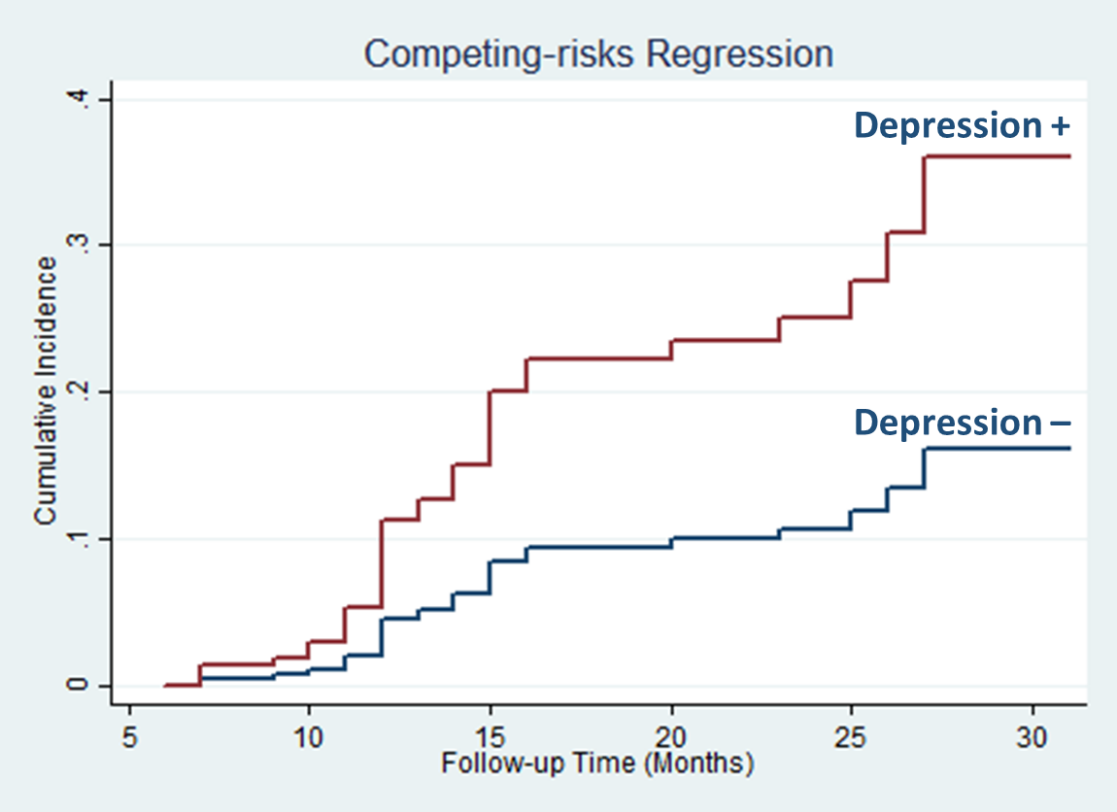
Figure 7.2 Prediction of incident HF in elderly asymptomatic patients with T2DM (competing risk analysis). LVH and depression showed incremental value over clinical parameters for incident HF.



	Model 1	Model 2	Model 3
Chi-square **P for chi-square change**	25.63	40.92 P<0.001	51.44 P<0.001
	HR (95% CI) **P value**	**HR (95% CI)** **P value**	**HR (95% CI)** **P value**
Age	1.05(0.98,1.12) 0.131	1.02(0.99,1.11) 0.124	1.07(1.01,1.14) **0.034**
Male gender	1.54(0.78,3.06) 0.212	1.10(0.52,2.32) 0.798	1.14(0.53,2.44) 0.738
Obesity	4.49(2.12,9.52) **<0.001**	3.85(1.83,8.12) **<0.001**	3.55(1.64,7.66) **0.001**
Poor HbA1c	2.06(1.11,3.83) **0.022**	2.41(1.27,4.58) **0.007**	2.29(1.18,4.45) **0.014**
LVH		3.51(1.67,7.37) **0.001**	3.48(1.60,7.58) **0.002**
Abnormal E/e'		0.90(0.31,2.63) 0.850	0.99(0.32,3.02) 0.980
Depression			2.54(1.18,5.46) **0.017**

Abbreviations: HR=hazard ratio; CI=confidence interval;
Obesity, BMI≥30kg/m^2; Poor HbA1c, ICFFstd-HbA1c>64mmol/mol; LVH, left ventricular hypertrophy, cutoff >115 g/m^2 for males, >95 g/m^2 for females; Abnormal E/e' ratio, cutoff >13; Depression, the score of PHQ-9 questionnaire ≥10.

Figure 7.3 Cumulative incidence estimates of HF in elderly asymptomatic T2DM stratified by patients with and without depression



7.6 Discussion

The results of this study show that depression (defined as PHQ-9 score ≥10) was significantly associated with increased risk of incident HF during follow-up of asymptomatic elderly patients with T2DM and preserved EF. This association was independent of clinical factors (including age, gender and BMI) and echocardiographic features such as LV hypertrophy and diastolic function. The presence of depression increased the likelihood of incident HF by 2.5-fold, and increased the composite endpoint 3.1-fold, compared with those without depression. Although depression has been linked with adverse outcomes in HF patients, to our knowledge, this is the first study to show an independent association between depression and incident HF in DM.

7.6.1 Depression and HF.

Depression is a common co-morbidity of HF, with variable reports of its prevalence. A meta-analysis of 25 studies showed depression to be present in 11% HF in NYHA (New York Heart Association) functional class I, 20% with class II, and approximately 40% of class III and IV HF. Depression is more widely diagnosed when this diagnosis is made by questionnaire (34%), and less with clinical interview (19%).[208] From 2008, American Heart Association recommended (AHA) recommended Patient Health Questionnaire (PHQ-9) for depression screening in cardiovascular patients. Given that there is always a tradeoff between sensitivity and specificity for questionnaire testing, PHQ-9 has a high specificity but a low sensitivity[209]. That means this screening method may can not capture all patients with the diagnosis of depression, however, it can identify highest risk patients for adverse cardiovascular events.

Depression is an independent predictor of adverse clinical outcomes in HF, and increases the risk of mortality by 40-50%.[210]In elderly patients with newly diagnosed HF, the presence of depression increased 1.2-fold risk of hospital admission and was suggested to routinely assessed at the time of HF diagnosis.[211]Even mild depression (defined as PHQ-9 score $\geq$5)has been associated with mortality and re-hospitalization in HF.[212] Depression is associated with a 2.4-fold increment of mortality, independent of age, gender, etiology, NYHA class, EF and LV systolic dysfunction.[213]

Few previous studies have sought whether psychosocial factors could independently predict incident HF. [206, 214, 215] Abramson et al[206] first found that depression, as defined by Center for Epidemiological Studies Depression Scale (CES-D) $\geq$16, was independently associated with a substantial increase in the risk of HF among elderly patients with isolated systolic hypertension. Williams et al[215] found an independent association between depression (CES-D $\geq$20, and incident HF among elderly women but not elderly men. The results from prospective cohort

studies are contradictory – the Nord-Trøndelag Health (HUNT) Study demonstrated the prospective association of self-reported depression at baseline with future HF in a dose-response manner, independent of a large number of baseline cardiovascular risk factors, acute myocardial infarction (AMI) and several chronic disorders.[214] However, the Multi-Ethnic Study of Atherosclerosis (MESA) found no significant association between depression (CES-D scale ≥16), and subsequent HF in an older population. However, in participants reporting fair/poor health status at baseline, this association was significant.[216] It is certainly plausible that sympathetic over activity might be associated with both HF mortality and HF incidence, but this remains unproven.

7.6.2 Depression and diabetes.

About 20-30% of elderly patients with diabetes suffer from clinical depression, and around 10% of them have major depression.[217] Even though the relationship between depression and diabetes is incompletely understood, it is clear that depression has an adverse impact on the course of diabetes, and diabetes complications may result in both the risk of depression and worsening the course of depression. Their association is primarily driven by somatic-affective symptoms of depression.[202] Additionally, the duration of depression lasts longer (usually ≥2 years) in most diabetic patients and the relapse rate is relatively high.[218] A previous study with 10-year follow-up also showed that all-cause of mortality increased with the severity of depression in diabetic subjects.[219]

7.6.3 HF in diabetes.

The underlying mechanisms between diabetes and the development of HF are multiple, but there is a growing recognition of a primary myocardial disease process - "diabetic cardiomyopathy" - that may lead to LV dysfunction, and subsequently HF. Hyperinsulinemia, inflammation and oxidative stress result in increased fatty acid metabolism and fetal gene

expression.[178] The resulting pathophysiological changes include impaired myocardial relaxation and cardiomyocyte resting tension, activation of the renin-angiotensin system (leading to vasoconstriction, salt and water retention, and fibrosis) and diabetic autonomic neuropathy. These changes lead to impaired diastolic and systolic function.[168]Furthermore, overweight has been proved to have a greater effect on LV structure in diabetes than in non-diabetes.[220] In our study, obesity has emerged as an important predictor of incident HF, further suggesting overweight/obesity are independently associated with LV dysfunction and increased risk of incident HF in diabetes. Moreover, NT pro Brain natriuretic peptide (NT-pro BNP), an objective measure of cardiac function, was higher but inadequately increased in overweight diabetic patients compared with normal weight diabetic patients, regardless of the presence/absence of cardiovascular disease, underlying the natriuretic handicap in diabetes.[221]

Several shared pathophysiological mechanisms may link T2DM, depressive symptoms and incident HF. Pro-inflammatory cytokines and platelet activation, rhythm disturbances, neuro hormonal activation, endothelial dysfunction and hypercoagulability are present in patients with depression.[222] These pathophysiological changes adversely influence the cardiovascular system and have been postulated to play an important role in the development and progression of HF.[222] Endothelial dysfunction plays an important role in cardiovascular homeostasis by producing various vascular regulators that mediate fibrinolysis, hypercoagulability, platelet activation and vascular tone, disturbances of which constitute the step linking diabetes to cardiovascular events.[203] Hyperglycemia and insulin resistance are associated with endothelial dysfunction[223] and cardiac damage.[203] Impaired nitric oxide production and oxidative stress may also lead to endothelial dysfunction, impaired vasodilation and large vessel impairment.[203] Hyperglycemia and hyperinsulinemia have also been significant contributors to cardiovascular complications through their role in stimulating coagulation and impairing fibrinolysis.[224] Pro-inflammatory cytokines are common in diabetes and significantly increase the risk of

progression of cardiovascular complications at all stages.[225] Additionally, patients with depression are more likely to take up risky lifestyles and behaviors and more likely to show non-adherence to medical regimens and behavior recommendations that affects the prognosis of HF.[226] Depression may be also involved with the lower social support that is implicated in the development of HF.

7.6.4 Limitation.

In the present study, the population were selected from the community with preserved EF, so diabetes patients with established asymptomatic LV systolic dysfunction were excluded. We used self-reported measures of symptoms of depression rather than diagnostic interviews. However, the use of the PHQ-9 survey for screening depression has been validated and has been recommended by the American Heart Association for the diagnosis of depression in coronary heart disease. [227]In addition, the blood examination in the cohort such as BNP or NT-pro BNP were not part of this study. Lastly, despite the longitudinal study design and high-risk nature of this population, the number of events was relatively small.

7.7 Conclusion

In this community cohort of asymptomatic patients with T2DM, depression was prevalent, and significantly associated with incident HF over 2-years of observation. This association is not explained by baseline demographic characteristics, glycemic control and LV dysfunction [including LV hypotrophy and subclinical diastolic dysfunction (evidenced by E/e')]. The mechanism of this association requires further investigation, and although it remains unclear as to whether a depression intervention in T2DM may prevent HF, depressed patients may warrant closer monitoring for the development of HF.

7.8 Postscript

This chapter showed how clinical outcomes were worse in T2DM patients with depression compared with those without during a 2-year observation. With adjustment for demographic, clinical, biochemical and echo parameters, the risk for incident HF was greater in those with depression. While our results also highlight the high prevalence of depression in elderly asymptomatic T2DM patients, further management or intervention for depression should be based on further research in other populations and age groups to determine if the effect of depression is similar to that observed in this study.

7.9 Appendix

Appendix 7.1 Comparison of baseline characteristics between patients who completed follow-up study (n=254) and patients who loss to follow-up study (n=20).

	Completed n=254	**Loss to FU n=20**	**P value**
Demographic and clinical characteristics			
Age (years)	70.9±4.3	72±5.1	0.341
Male gender (n, %)	142(55.9)	8(40.0)	0.389
Weight (kg)	85.8±17.3	85.7±16.7	0.820
BMI (kg/m^2)	30.2±5.9	31.1±5.6	0.536
Waist circumference (cm)	103.1±13.3	107.3±15.3	0.255
Obesity (n, %)	124(48.8)	11(55.0)	0.811
Heart rate (n/min)	69±11	71±13	0.445
Systolic blood pressure (mmHg)	139±14	141±23	0.550
Diastolic blood pressure (mmHg)	81±10	80±10	0.613
Hypertension (n, %)	190(74.8)	14(70.0)	0.195
Family history of HF (n, %)	73(28.7)	7(35.0)	0.518
Past chemotherapy (n, %)	22(8.7)	3(15.0)	0.403
Past heart disease (n, %)	14(5.5)	2(10.0)	0.103
HbA1c (mmol/mol)	53.4±10.2	54.2±9.5	0.733
HbA1c >64 mmol/mol (n, %)	32(12.6)	4(20)	0.245
Medication			
Insulin (n, %)	60(23.6)	5(25.0)	**0.037**
Metformin (n, %)	175(68.9)	9(45.0)	0.244
ACEi / ARB (n, %)	171(67.3)	12(60.0)	0.630
Beta-blockers (n, %)	15(5.9)	0(0)	**<0.001**
Calcium antagonists (n, %)	62(24.3)	2(10.0)	0.093
Diuretics (n, %)	27(10.6)	4(20.0)	0.445
Lipid lowering meds (n, %)	123(48.4)	10(50.0)	0.560
Questionnaire			
PHQ-9 score	3.2±4.3	2.8±5.1	0.787
PHQ-9 score≥10 (yes/no)	25(9.8)	1(5.0)	**0.009**
Echocardiography			
LVEF (%)	63.1±6.5	63.0±5.1	0.965
E wave (m/s)	0.65±0.16	0.74±0.26	**0.024**
A wave (m/s)	0.83±0.19	0.88±0.25	0.421
E/A ratio	0.79±0.21	0.79±0.28	0.974
e' (m/s)	0.08±0.02	0.08±0.02	0.512
E/e' ratio	9.2±2.7	9.8±3.1	0.347
E/e' ratio >13 (n, %)	26(10.2)	3(15.0)	0.086
DT (s)	247.0±52.8	244.6±50.7	0.844
LV mass index (g/m^2)	85.6±19.3	86.9±15.4	0.735
LV mass index (g/m$^{1.7}$)	74.5±21.1	73.3±17.2	0.775
LV hypertrophy (n, %)*	35(13.8)	1(5.9)	0.354

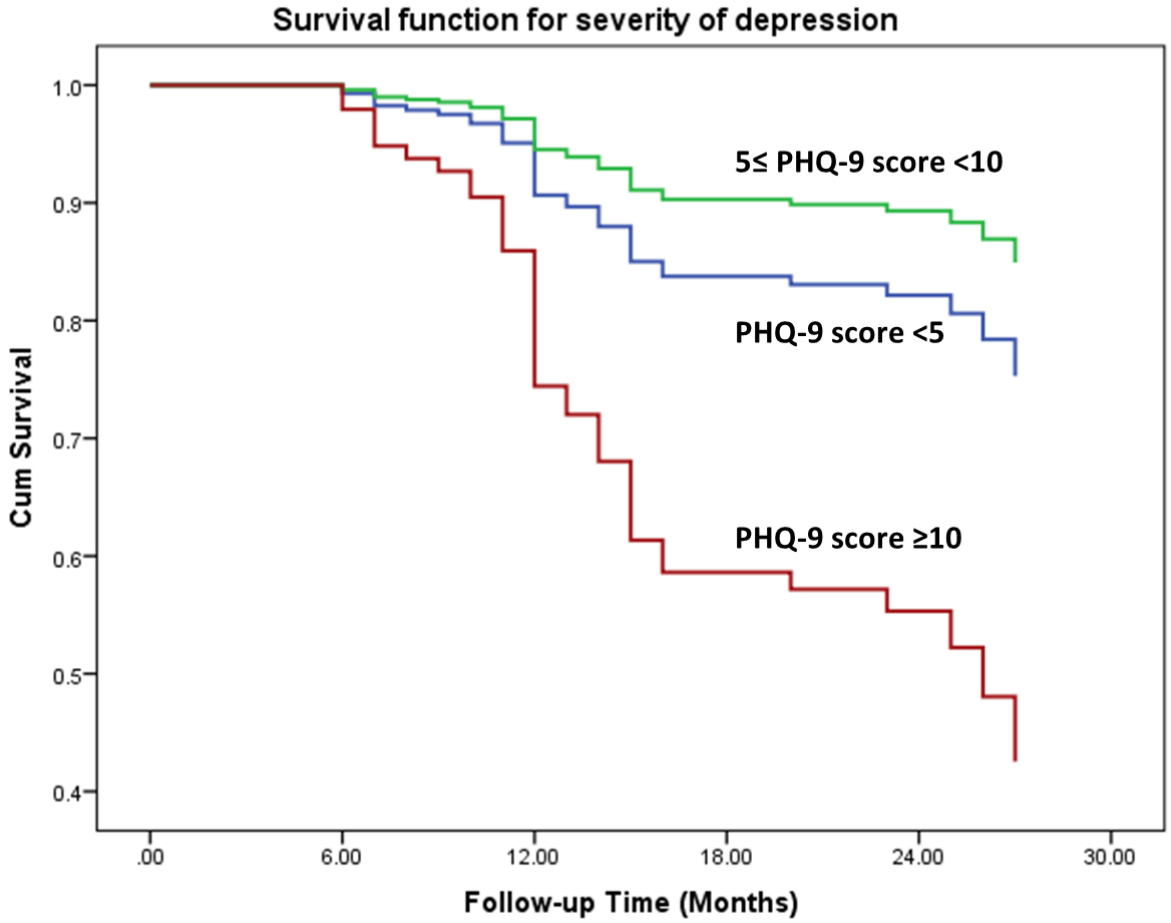
**LV hypertrophy was defined as LVMi>115 g/m^2 for males, >95 g/m^2 for females.*

Appendix 7.2 Univariable Cox regression analysis for primary composite endpoint in elderly asymptomatic patients with T2DM.

	HR (95% CI)	**P value**
Demographic and clinical characteristics		
Age	1.06(0.99,1.32)	0.064
Male gender (yes/no)	1.81(0.92,3.56)	0.086
Weight	1.04(1.02,1.05)	**<0.001**
BMI	1.10(1.06,1.15)	**<0.001**
Waist circumference	1.05(1.03,1.08)	**<0.001**
Obesity (yes/no)	3.61(1.76,7.39)	**<0.001**
Heart rate	0.99(0.97,1.03)	0.727
Systolic blood pressure	0.99(0.97,1.01)	0.314
Diastolic blood pressure	0.90(0.99,1.03)	0.895
Hypertension (yes/no)	1.07(0.52,2.19)	0.854
Family history of HF (yes/no)	0.70(0.33,1.47)	0.349
Past chemotherapy (yes/no)	1.54(0.60,3.93)	0.536
Past heart disease (yes/no)	1.46(0.45,4.74)	0.529
HbA1c (mmol/mol)	1.03(1.01,1.06)	**0.009**
HbA1c >64 mmol/mol (n, %)	3.27(1.66,6.43)	**0.001**
Medication		
Insulin (yes/no)	1.77(0.92,3.39)	0.086
Metformin (yes/no)	0.72(0.38,1.36)	0.310
ACEi / ARB (yes/no)	1.12(0.57,2.20)	0.749
Beta-blockers (yes/no)	3.25(1.36,7.77)	**0.008**
Calcium antagonists (yes/no)	0.50(0.21,1.18)	0.114
Diuretics (yes/no)	0.91(0.33,2.65)	0.909
Lipid lowering med (yes/no)	1.32(0.71,2.48)	0.382
Questionnaire		
PHQ-9 score	1.08(1.01,1.16)	**0.021**
PHQ-9 score≥10 (yes/no)	3.21(1.41,7.30)	**0.005**
Echocardiography		
LV ejection fraction	0.95(0.90,0.99)	**0.018**
Mitral early-diastolic inflow velocity (E wave)	3.46(0.54,22.39)	0.192
Mitral late-diastolic inflow velocity (A wave)	1.81(0.32,10.31)	0.503
Transmitral diastolic flow velocity ratio (E/A)	0.92(0.16,5.31)	0.929
Early diastolic mitral annular velocity (e')	1.05(0.86,1.28)	0.644
Average E/e' ratio (E/e')	1.05(0.94,1.17)	0.437
E/e' ratio >13 (yes/no)	1.04(0.37,2.94)	0.934
Deceleration time(DT)	0.99(0.99,1.00)	0.363
LV mass index (g/m^2)	1.03(1.02,1.04)	**<0.001**
LV mass index ($g/m^{1.7}$)	1.03(1.02,1.04)	**<0.001**
LV hypertrophy (yes/no)*	3.92(2.04,7.52)	**<0.001**

**LV hypertrophy was defined as LVMi>115 g/m^2 for males, >95 g/m^2 for females.*

Appendix 7.3 Cumulative survival of 254 elderly asymptomatic T2DM stratified by severity of depression**.**



Chapter 8. Evolution of Subclinical Left Ventricular Systolic Function during a 2-year Observation in T2DM

- *Paper under preparation for submission to JACC-Imaging*

8.1 Preface

As discussed in previous chapters, GLS is potentially a useful marker of patients at risk for the development of incident HF in diabetes. The role of GLS rather than ejection fraction in this setting is consistent with the predominance of HF with preserved EF in patients with diabetes – but little is known about the natural history of GLS over time. Whether the initiation of medical therapy in response to abnormal GLS can result in better outcome still needs to be tested. To address these gaps in knowledge, we investigated the longitudinal changes of GLS as well as other echo parameters in asymptomatic patients with preserved EF in the community. In addition, we sought to determine the predictors of deterioration of subtle myocardial dysfunction.

8.2 Abstract

Background. Left ventricular (LV) systolic function is an important predictor of incident heart failure (HF) in the community, including in patients with preserved ejection fraction. However, little is known about the natural history of subclinical LV function, measured by global longitudinal strain (GLS).

Methods. 246 asymptomatic elderly patients with T2DM (age 71±4yrs, 57.3% men) were recruited from a community-based population with preserved EF. All underwent a comprehensive clinical evaluation and echocardiography including GLS. All were followed for the development of HF symptoms over 2 years.

Results. Patients with T2DM and normal LVEF [mean age 71±4 years, 141 (57%) male] were evaluated. After 2-years follow-up, LVEF remained preserved and LVMi remained unchanged. In contrast, a significant worsening of GLS (17.8±2.6% to 17.3±2.9%, p=0.01) and increased of LAV index (24.3±5.2 to 29.6±7.9 g/m2, p<0.001). Diastolic function as assessed by E/e' ratio showed a mild decline during follow-up (9.1±2.6 to 9.7±2.9, p<0.001). During 2-year follow-up, 17% patients experienced worsening subclinical LV function and 8% experienced worsening diastolic function.

Conclusions. During a 2-year observation, elderly asymptomatic patients with T2DM and preserved EF showed mild deterioration of subclinical LV function by GLS and diastolic function by E/e', which warrant prospective evaluation.

8.3 Background

Diabetes mellitus (DM) can increase the risk of heart failure (HF) in the absence of coronary artery disease and hypertension, and some investigators have invoked the presence of a

"diabetic cardiomyopathy (DMC)". Previous studies have demonstrated that in patients with diabetes, subclinical left ventricular systolic dysfunction (LVSD) is frequent despite normal left ventricular ejection fraction (LVEF) and normal diastolic function. This subclinical LVSD may be the earliest marker of preclinical DMC [88].

LV global longitudinal strain (GLS) assessed by two-dimensional speckle tracking echocardiography (STE) has been proposed as an optimal marker of LVSD despite a normal LVEF. In the community, the prevalence of abnormal GLS but normal LVEF has as four times the prevalence of abnormal LVEF [228]. Echocardiographic changes consistent with LVSD, LV diastolic dysfunction (LVDD) and LV hypertrophy (LVH) in diabetic population have been described extensively and particularly when hypertension and obesity coexist [88, 194, 229]. Recently, the presence of impaired systolic strain in addition to demographic data and HbA1c level has been shown to help risk stratification for future cardiovascular events in patients with diabetes [190]. However, limited data are available on the time-course and determinants of impaired systolic strain in individuals with diabetes, and worsening of LV dysfunction may contribute significantly to an increasing risk of HF. In order to identify the predictors of deterioration of systolic strain over time, the present study aimed to analyze GLS on repeated echocardiograms over 2 years in patients with type 2 diabetes mellitus (T2DM) with preserved EF and without overt HF in the community.

8.4 Methods

8.4.1 Study population.

A total of 274 consecutive patients with T2DM self-referred between 2013 and 2015 were prospectively recruited from the Tasmanian community. The inclusion criteria were: age $\geqslant$ 65 years, no symptoms or history of heart failure and LVEF $\geqslant$ 40%. Exclusion criteria were: more than moderate valve disease, known coronary artery disease (CAD) including ischemia or

infarction, coronary artery bypass graft and coronary stenting, atrial fibrillation (AF) and inability to acquire adequate echocardiographic images for speckle tracking imaging analysis at baseline and follow-up. All participants provided written, informed consent, and the study protocol was approved by the Tasmanian Human Research Ethics Committee. After 2 years follow-up, 246 patients were included in the final analysis. There were 28 patients missing to attend for the follow-up echocardiogram due to 1) died, lost contact or moved to other States; 2) were alive but could not attend the clinic due to various reasons including time, traffic and temporary emergency.

8.4.2 Clinical data.

The diagnosis ofT2DM was based on self-report and diabetes treatment. Data on demographics, family history, medical history and use of medication were collected from an interviewer-administered questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and obesity was defined as BMI ≥30 kg/m^2. Waist circumference (WC) was measured to the nearest millimeter by a trained examiner using a tape measure at the midpoint between the lower costal margin and the iliac crest. Supine resting blood pressure (BP) was measured twice and averaged in each patient after at least 10 minutes' rest in a quiet room. Hypertension was defined by average systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥90 mmHg. International Federation of Clinical Chemistry (IFCC) standardized haemoglobin A1c (cut-off 64 mmol/mol) levels were obtained from local pathology records. Missing values for HbA1c were estimated by imputation using linear regression.

8.4.3 Echocardiography.

All patients were examined at baseline and after 2 years by a comprehensive echocardiogram including standard resting transthoracic 2D, Doppler echocardiographic studies and speckle

tracking echocardiography (STE). Calculations of morphometric parameters were done in accordance with the recommendations of American Society of Echocardiography (ASE) (Siemens ACUSON SC2000, 4V1c and 4Z1c probes, Siemens Healthcare, Mountain View, CA)[207]. LV internal dimensions and wall thickness, chamber volumes and valvular morphology were assessed. The biplane Simpson's method was used for calculation of LVEF. LA volumes were calculated using the Simpson biplane method and LA enlargement (LAE) was defined as LA volume index [LAVi, LA volume indexed to body surface area (BSA)] ≥34 mL/m2 (10). LV mass index (LVMi) was obtained from LV mass measurement using standard criteria and normalized for body size [BSA and height to the power of 1.7 or 2.7]. LV hypertrophy (LVH) was defined as LVMi (normalized for BSA) >115 g/m^2 for men and >95 g/m^2 for women.

LV inflow was obtained using pulsed wave Doppler in the apical 4-chamber view; peak early (E) and late (A) diastolic velocities, deceleration time (DT) and E/A ratio were obtained. Peak early diastolic medial and lateral mitral annular velocity (e') and the ratio of mitral inflow early diastolic velocity to average e' velocity were obtained from pulsed tissue Doppler; E/e'>13 was used as a cut-off of LVdiastolic dysfunction (LVDD). For deformation analysis, standard grayscale 2-dimensional images were acquired in conventional 4-chamber, 2-chamber, 3-chamber, parasternal short-axis views at the mid, basal, and apical level. Global longitudinal strain (GLS) was calculated by the average from three apical views using standard software.[73] Although shortening is described as a negative number, for computational simplicity (and because there were no positive GLS), we express GLS in this paper without this information. Our laboratory uses cutoffs of 16% to designate impaired GLS and 18% to designate normal GLS, and we evaluated both cutoffs. Significant deterioration of strain was defined as strain reduced by >20% of absolute value from baseline to follow-up assessment.

8.4.4 Outcomes.

The primary endpoint was deterioration of strain (as a continuous variable).

8.4.5 Statistical analysis.

All collected data were tabulated and analyzed using standard statistical computer software for windows (SPSS 22, IBM, Chicago, IL and Stata, V.12.0, Stata Corp, College Station, Texas, USA). Continuous variables are summarized as mean ± standard deviation (SD) and categorical data as frequencies and percentages. Paired Student's *t*-test and non-parametric tests were performed as appropriate, to assess changes between baseline and 2-year follow-up; $p<0.05$ was deemed to be statistically significant. Linear regression analyses were performed to identify factors associated with LV function evolution. Cox regression analyses were performed to identify predictors associated with composite endpoint during follow-up.

8.5 Results

8.5.1 Characteristics of Participants.

A total of 246 T2DM patients with preserved EF [mean age 71±4 years, 141 (57%) male gender] attended the follow-up study with echocardiographic data including GLS measurement. **Table 8.1** lists the baseline clinical, demographic and biochemical characteristics of the 246 T2DM patients. Mean haemoglobin A1c was 53.7±9.4 mmol/mol and 32(13%) had poor control (defined by haemoglobin A1c level cut-off 64 mmol/mol). In addition, 78(32%) patients had hypertension, 56(23%) patients had insulin injection and 163(66%) patients were taking metformin.

Echocardiographic parameters are summarized in **Table 8.2.** Systolic function based on the measurement of LV ejection fraction remained preserved from baseline to follow-up study. Likewise, mean E/e' ratio, LVMi and LA volume (24.3±5.2 vs 29.6±7.9 mL/m^2, $p<0.001$) were within the normal range. In contrast, the mean GLS decreased from 17.8±2.6% at baseline to 17.3±2.9% at follow-up ($p=0.01$).

Table 8.1 Characteristics of study population at baseline (n=246).

	Overall (n=246)
Demographic and clinical characteristics	
Age (years)	70.7±4.2
Male gender (n, %)	141(57.3)
Weight (kg)	86.6±17.5
Height (cm)	168.6±9.8
BMI (kg/m^2)	30.5±6.0
Waist circumference (cm)	103.7±13.3
Obesity (n, %)	124(50.4)
Heart rate (n/min)	68±11
Systolic blood pressure (mmHg)	139±15
Diastolic blood pressure (mmHg)	81±10
Hypertension (n, %)	189(76.8)
Family history of HF (n, %)	78(31.7)
Past chemotherapy (n, %)	20(8.1)
Past heart disease (n, %)	18(7.3)
Biomarkers	
HbA1c (mmol/mol)	53.7±9.4
Poor HbA1c (n, %)$^{\lozenge}$	32(13.0)
Medication	
Insulin (n, %)	56(22.8)
Metformin (n, %)	163(66.3)
ACEi / ARB (n, %)	173(70.3)
Beta-blockers (n, %)	16(6.5)
Calcium antagonists (n, %)	54(22.0)
Diuretics (n, %)	32(13.0)
Lipid lowering meds (n, %)	124(50.4)
Antiplatelet meds (n, %)	85(34.6)

Family history of HF was defined as a history of HF in first degree family member;
$^{\lozenge}$Poor HbA1c, ICFFstd-HbA1c>64mmol/mol.

Table 8.2 Evolution of echocardiographic parameters over time: between baseline and follow-up. (n=246).

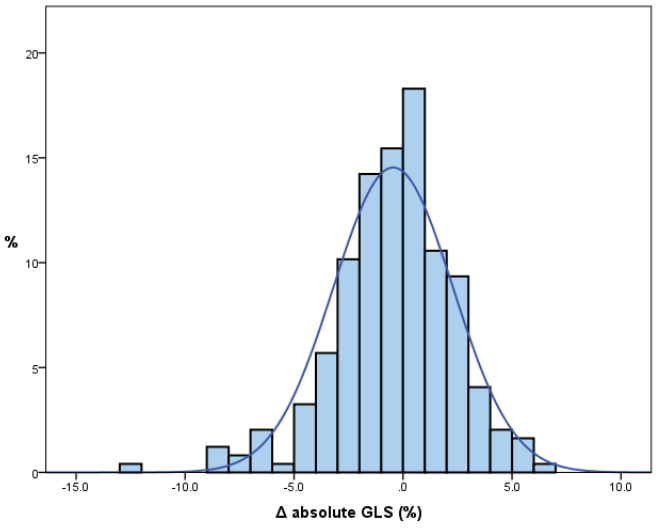
	Baseline	**2-year follow-up**	**p**
LV ejection fraction (%)	62.7±6.5	59.1±6.5	**<0.001**
Mitral early-diastolic inflow velocity (E wave) (m/s)	0.65±0.17	0.66±0.18	0.198
Mitral late-diastolic inflow velocity (A wave) (m/s)	0.83±0.20	0.81±0.19	0.701
Transmitral diastolic flow velocity ratio (E/A)	0.79±0.20	0.83±0.32	0.786
Early diastolic mitral annular velocity (e') (cm/s)	7.55±1.58	7.26±1.66	**<0.001**
Average E/e' ratio (E/e')	9.1±2.6	9.7±2.9	**<0.001**
Deceleration time(DT) (s)	248.7±53.2	232.3±59.8	**<0.001**
LV mass index (LVMi)(g/m^2)	85.8±19.3	87.2±24.0	0.255
LA volume index(mL/m^2)	24.3±5.2	29.6±7.9	**<0.001**
GLS (%)	17.8±2.6	17.3±2.9	**0.010**
Echocardiography categorical variables			
LA enlargement (n, %)	89(36.2)	114(46.3)	**0.004**
LV hypertrophy (n, %)	33(13.4)	39(15.9)	0.405
E/e' ratio >13 (n, %)	23(9.3)	34(13.8)	**0.028**
GLS<18% (n, %)	121(49.2)	103(41.9)	0.170
GLS<16% (n, %)	56(22.8)	55(22.4)	**<0.001**

8.5.2 Change in function

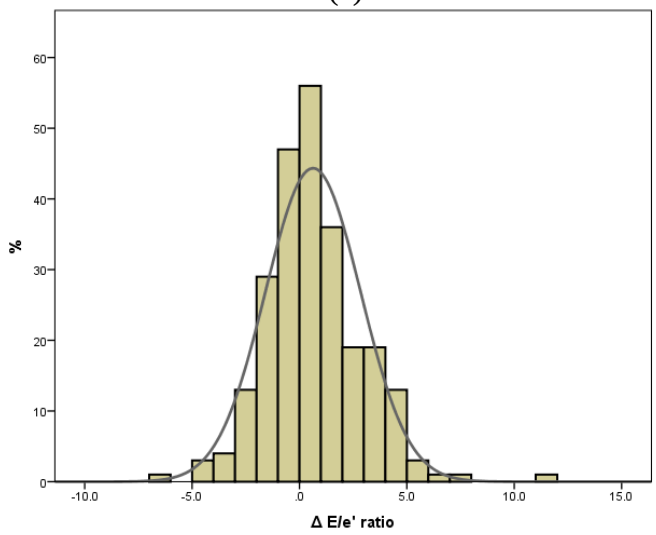
Over a median follow-up of 1.5 years (range 0.6~2.6), conventional echocardiography demonstrated no worsening in LV systolic function (**Table 8.2**). LVEF (62.7±6.5 vs 59.1±6.5, p<0.001) remained preserved and LVMi (85.8±19.3to 87.2±24.0 g/m^2, p=0.255) remained unchanged. LAV index was significantly increased from baseline assessment to follow-up (24.3±5.2to 29.6±7.9 g/m^2, p<0.001). For LV diastolic function, E/e' ratio was significantly increased during 2-year time (9.1±2.6 to 9.7±2.9, p<0.001) but still within normal range, indicating a mild decline in subclinical diastolic function. Despite subclinical LV systolic function as assessed by GLS at baseline (17.8±2.6%), there was a significant decline to 17.3±2.9% at follow-up (p=0.010). According to the value of GLS at baseline and follow-up, patients were divided into four groups: 78 (32%) patients were persistently normal, 27 (11%) patients became normal, 44 (18%) patients became abnormal and 97 (39%) patients were persistently abnormal (**Figure 8.2**). Among other echocardiographic parameters, e' and DT

were significantly worse compared with baseline examination (**Table 8.2**). **Figure 8.1** shows the histograms of changes over time in absolute number of GLS, E/e' ratio and LAV index and their percentage. The changes of these parameters followed a unimodal distribution with a predominance of deterioration (negative change) in GLS and worsening (increase) in E/e' and LAV index. The mean within-subjects percentage change of GLS was -1.61±15.8%, compared with change in EF of -4.8±14%, change in LAV index of 21.2±46.3% and change in E/e' ratio of 9.4±26.6% (**Figure 8.3**).

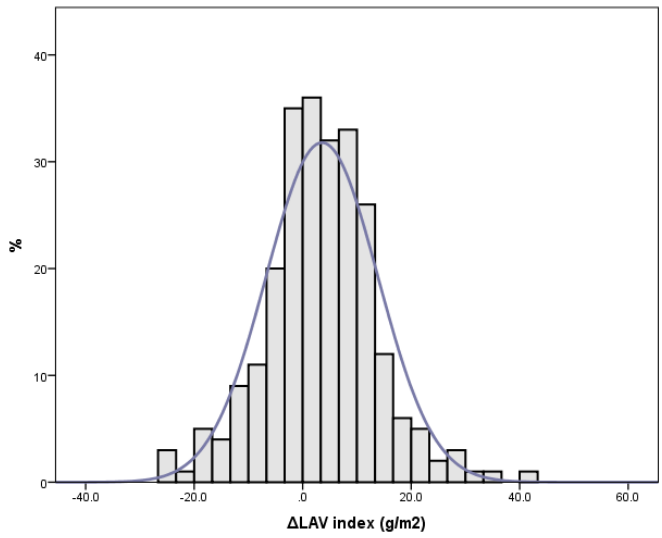
Figure 8.1 The histograms of change in (a) absolute GLS; (b) E/e' ratio; (c) LAV index in 246 T2DM patients. The curves represent the fitted normal density plots.



(a)

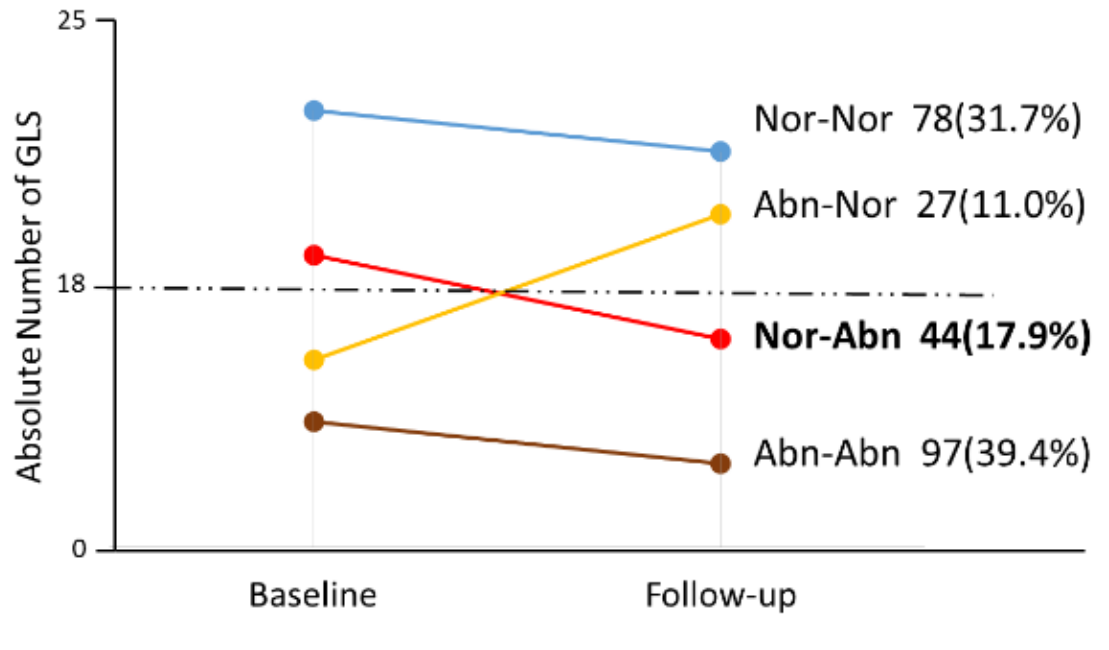


(b)

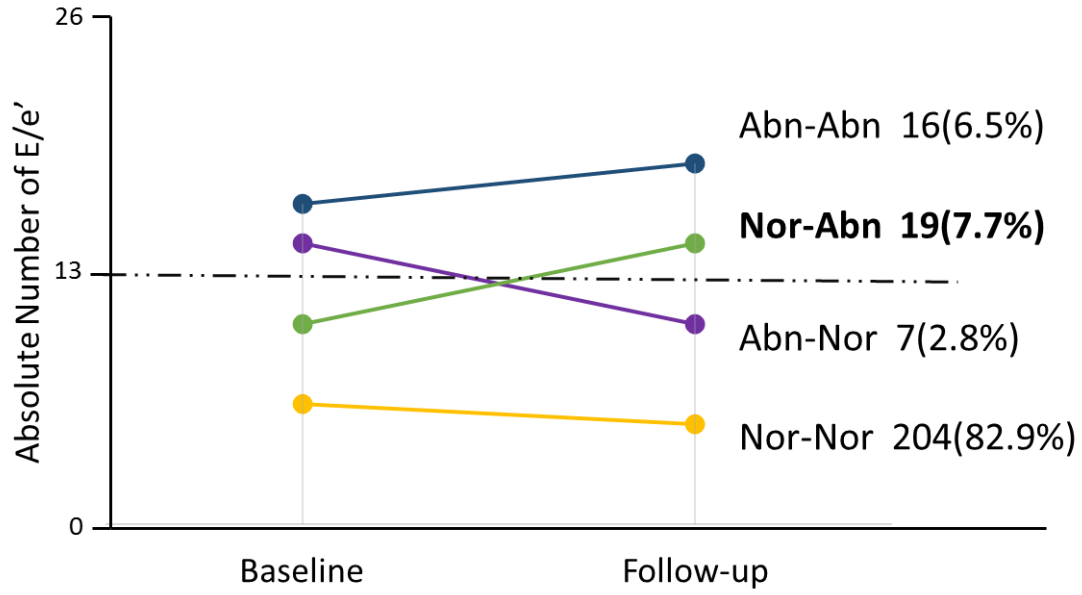


(c)

Figure 8.2 Within-individual change in systolic and diastolic function from baseline to 2-year follow-up. The number of patients (right) are presented for the four groups of changes, from baseline to 2 years. (a)The absolute value of GLS in asymptomatic T2DM with preserved EF grouped according to changes of GLS over time. (b) Progression of E/e' in asymptomatic T2DM with preserved EF grouped according to changes of E/e' over time.

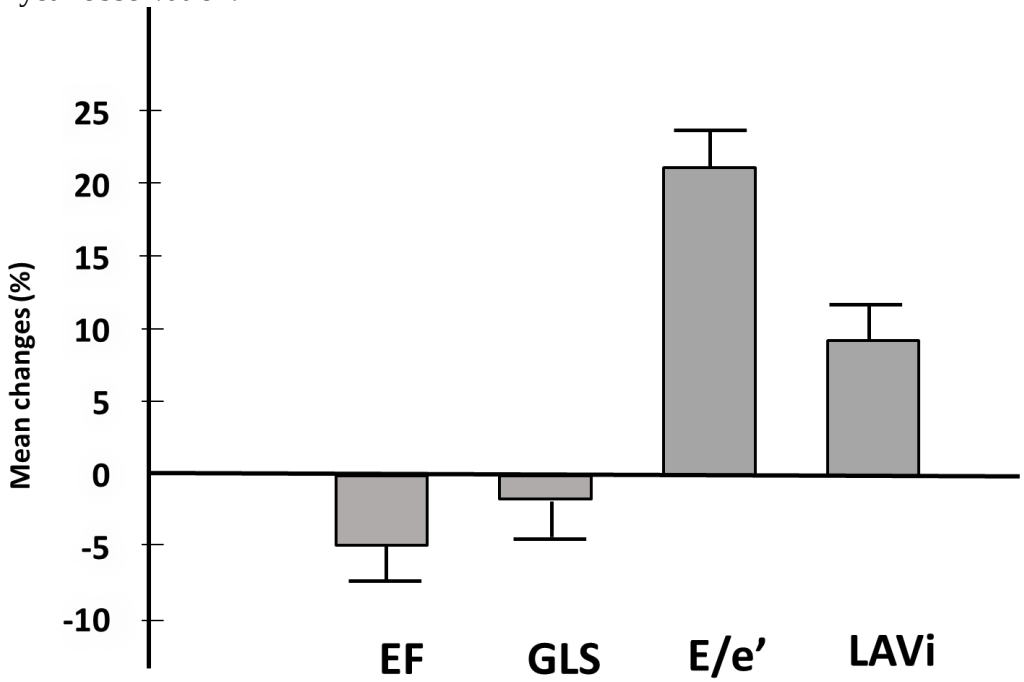


(a)



(b)

Figure 8.3 Mean within-subjects changes (%) in EF, GLS, E/e' ratio and LVA index during 2-year observation.



8.5.3 Factors predictive of worsening systolic and diastolic function.

In multivariate linear regression models (**Table 8.3**), baseline GLS (β -0.44 [-0.68 to -0.21]; p<0.001) was independently associated with worsening of GLS after adjustment for age, gender, obesity, follow-up duration, changes of heart rate and systolic BP. Age (β 0.10, [0.01 to 0.19]; p=0.027), gender (β -0.82, [-1.61 to -0.02]; p=0.04) and baseline E/e' (β -0.33, [-0.51 to -0.16]; p<0.001) were independent predictors of change in E/e'. For changes of LVA index, gender (β -2.87, [-5.66 to -0.07]; p=0.04), baseline E/e' ratio (β 0.92, [0.36 to 1.47]; p=0.001), LVMi (β 0.09, [0.03 to 0.16]; p=0.0070, LAV index (β -0.67, [-0.80 to -0.54]; p<0.001) and impaired GLS (cutoff 16%) (β 6.40, [3.03 to 9.77; p<0.001) were significant and independent predictors.

Table 8.3. Multivariate correlation of evolution of different subclinical LV function parameters (ΔGLS, ΔE/e' and ΔLVA index) in patients with T2DM.

	ΔGLS β(95%CI) P value	**ΔE/e' β(95%CI) P value**	**ΔLVA index β(95%CI) P value**
Chi-square	0.132	0.160	**0.544**
Age	0.037(-0.078,0.940) 0.528	**0.102(0.012,0.192) 0.027**	-0.149(-0.439,0.141) 0.312
Male gender	0.555(-0.525,1.636) 0.311	**-0.817(-1.611,-0.024) 0.044**	**-2.868(-5.664,-0.073) 0.044**
Obesity	-0.346(-1.402,0.709) 0.517	0.185(-0.616,0.100) 0.648	0.573(-1.981,3.128) 0.657
Follow-up duration	-0.086(-0.212,0.039) 0.175	0.001(-0.098,0.100) 0.982	-
ΔHeart rate	-0.002(-0.049,0.044) 0.931	-0.014(-0.049,0.021) 0.436	-
Δ Systolic BP	0.005(-0.017,0.028) 0.644	-0.010(-0.028,0.007) 0.229	-
Past heart disease	-	-	5.970(-0.202,12.142) 0.058
Poor HbA1c[◊]	-	0.470(-0.887,1.827) 0.494	-
E/e' ratio	-	**-0.334(-0.509,-0.159) <0.001**	**0.917(0.363,1.471) 0.001**
LVMi	-	-	**0.094(0.026,0.162) 0.007**
LAVi	-	-	**-0.673(-0.802,-0.543) <0.001**
GLS	**-0.444(-0.682,-0.205) <0.001**	-	-
GLS<16%	-	-	**6.402(3.032,9.772) <0.001**

Abbreviations: CI=confidence interval; [◊]Poor HbA1c, ICFFstd-HbA1c>64mmol/mol.

8.6 Discussion

In addition to cross-sectional estimates of the prevalence of subclinical LV dysfunction in 246 elderly asymptomatic T2DM with preserved EF. in the community, this study shows a longitudinal change in left ventricular systolic (GLS), and diastolic function measurements (E/e' and LVA). Each marker showed a meaningful change - for GLS, 11% patients improved, 18% became abnormal and 71% patients were unchanged, while for E/e', 8% patients experienced worsening, 3% improved and 89% were unchanged.

8.6.1 Assessment of subclinical LVD.

GLS has shown to be a better parameter than the conventional systolic marker LVEF for prognostic stratification in patients with HF and T2DM [189, 230]. It is well supported by previous research of the role of GLS in detecting LV function in patients with preserved EF and deterioration of GLS despite no change of EF[73]. Isolated diastolic dysfunction is commonly seen in patients with DM, however preclinical LV dysfunction defined by strain imaging may precede diastolic dysfunction. Holland et al[189] have highlighted the high prevalence of LV systolic dysfunction in elderly asymptomatic diabetes subjects with a normal EF and the role of abnormal GLS in predicting longitudinal adverse outcomes over a 10-year course.

8.6.2 Changes in GLS.

Previous work has demonstrated that GLS was more impaired in diabetic patients, 6-months after ST-segment elevation myocardial infarction, compared with nondiabetic patients (-15.8±0.3% vs -17.3±0.2%, $p<0.001$), despite having similar EF at baseline and follow-up.[231] However, the natural history of GLS in asymptomatic diabetic individuals with preserved EF had not been systematically evaluated. Roos *et al*[232], showed progression of multidirectional LV strain in 112 asymptomatic patients with type 2 diabetes mellitus during a 2-year observation, and mild progression of subclinical LV dysfunction assessed by 2D speckle

tracking imaging was observed in patients with stable clinical status. The difference is that we followed for change in strain and other echo parameters for LV and LA function and structure in a community-based population with aged ⩾65years regardless of the clinical status of the patients at follow-up. In our study, elderly asymptomatic patients with DM demonstrated subclinical LV systolic dysfunction, and nearly 20% developed abnormal GLS over 2-year follow-up. Baseline GLS was associated with this process, independent of clinical and other echocardiographic characteristics. These results highlight this as being in a high-risk patient group that warrants consideration of further therapeutic strategies to prevent HF progression and to improve prognosis. Additionally, this reflects a contribution to this increased risk from diabetic cardiomyopathy (DCM), independent of coronary artery disease and hypertension.

8.6.3 Changes in diastolic function.

In our study, as expected, advancing age and male gender were independently associated with the deterioration of diastolic function. However, blood pressure as well as changes of blood pressure were not determinants of diastolic function changes in our study, which has been indicated in both diabetes and non-diabetes cohort in previous research [88, 233, 234]. Bergerot et al.[235] also reported a negative association between blood pressure and diastolic function in diabetes, similar to the results of our study. This may be due to the relatively well-controlled blood pressure at baseline in his and our study. Our results serve as a reference for the natural history of the diastolic function assessed by E/e' ratio in elderly asymptomatic patients with T2DM, which emphasizes the need of a prospective population-based study for a more accurate range and trend of diastolic function changes in this population group for better understanding the mechanism and progression of diabetic cardiomyopathy.

8.6.4 Changes in left atrial volume

LA enlargement (LAE) and dysfunction is of particular importance in patients with diabetes and LV dysfunction as evaluation of patients with diabetes using LA function may reflect underlying diastolic dysfunction and estimating atrial contractile function that contribute to cardiac workload[236]. Previous research has demonstrated that T2DM patients were found to have increased LA volume and impaired atrial compliance and contractility[237]. In addition, LAE in diabetes was independent of hypertension and diastolic function[236]. In our study, it is likely that impaired global strain and diastolic dysfunction both contributed to the increased LA volume. It suggested that subclinical systolic dysfunction in T2DM may independently influence the LA structure with the additive impact of LV diastolic dysfunction.

8.6.3 Limitation.

First, T1DM were excluded from our study as the mechanism affecting the heart may be different from that in T2DM. Second, circumferential and radial strain were not recorded, which would have provided additional details about myocardial mechanics, although longitudinal strain is the most robust of these myocardial deformation parameters. Additionally, for biomarkers, in the present study only HbA1c was collected. Other biomarkers were lacking which may potentially be related to the changes of LV function in T2DM. Furthermore, LV mass did not significantly increase and it may due to the short duration of follow-up. Lastly, as the present cohort was more than 95% white, inferences to other ethnic or racial populations is not valid.

8.7 Conclusion

During a 2-year observation, elderly asymptomatic patients with T2DM and preserved EF showed mild deterioration of subclinical LV function by GLS and diastolic function. The implications of these findings for screening and repeat testing warrant further evaluation.

8.8 Postscript

Among 246 community-based T2DM patients followed longitudinally, we found that changes in subclinical LV function by GLS and diastolic function over time was only mild, and subclinical systolic dysfunction in T2DM may independently influence the LA structure with the additive impact of LV diastolic dysfunction. These findings for screening and repeat testing warrant further evaluation. The clinical implications of these findings are two-fold. First, in evaluating the evolution of subtle cardiac dysfunction, a contribution to the increased risk from diabetic cardiomyopathy DCM should be paid more attention to. Second, more studies are required in this area to the need of more accurate range and trend of subclinical LV function changes in this population group for better understanding the mechanism and progression of diabetic cardiomyopathy.

8.9 Appendix

Appendix 8.1. Univariate correlation of evolution of different subclinical LV function parameters (ΔGLS, ΔE/e' and ΔLVA index) in patients with T2DM.

	ΔGLS β(95%CI) P value	**ΔE/e' β(95%CI) P value**	**ΔLVA index β(95%CI) P value**
Demographic and clinical characteristics			
Age	0.016(-0.066,0.098) 0.702	0.059(-0.007,0.125) 0.079	0.002(-0.306,0.310) 0.991
Male gender	-0.203(-0.901,0.494) 0.566	-0.262(-0.824,0.300) 0.359	0.430(-2.187,3.047) 0.747
Weight	-0.013(-0.033,0.007) 0.191	0.000(-0.016,0.016) 0.988	0.059(-0.015,0.133) 0.118
Height	-0.005(-0.040,0.030) 0.766	-0.009(-0.037,0.020) 0.547	-0.032(-0.163,0.100) 0.634
BMI	-0.035(-0.093,0.022) 0.225	0.014(-0.032,0.060) 0.544	0.195(-0.019,0.409) 0.073
ΔBMI	0.035(-0.022,0.093) 0.228	-0.014(-0.061,0.032) 0.547	-0.194(-0.406,0.018) 0.073
Waist circumference	-0.016(-0.043,0.010) 0.215	-0.003(-0.024,0.018) 0.780	0.091(-0.005,0.187) 0.062
Obesity	-0.338(-1.027,0.352) 0.336	0.083(-0.474,0.640) 0.769	**3.494(0.942,6.046) 0.007**
Heart rate	0.005(-0.027,0.038) 0.748	0.002(-0.024,0.029) 0.858	0.002(-0.120,0.124) 0.972
ΔHeart rate	0.020(-0.026,0.065) 0.389	-0.011（-0.046,0.024） 0.540	-0.074(-0.227,0.079) 0.338
Systolic blood pressure	0.007(-0.016,0.030) 0.525	0.012(-0.007,0.030) 0.204	0.005(-0.081,0.092) 0.904
Δ Systolic blood pressure	0.011(-0.007,0.028) 0.232	-0.014(-0.028,0.000) 0.053	0.051(-0.014,0.117) 0.125
Diastolic blood pressure	-0.012(-0.047,0.024) 0.526	-0.002(-0.031,0.027) 0.877	0.030(-0.104,0.164) 0.660
Δ Diastolic blood pressure	0.020(-0.009,0.050) 0.169	-0.014(-0.037,0.010) 0.257	0.008(-0.102,0.118) 0.884
Hypertension	-0.135(-0.953,0.683) 0.745	-0.303(-0.961,0.356) 0.367	1.077(-1.989,4.142) 0.490
Family history of HF	-0.563(-1.302,0.176) 0.135	**-0.689(-1.281,-0.097) 0.023**	-0.346(-3.128,2.436) 0.807
Past chemotherapy	-0.570(-1.831,0.692) 0.375	-0.119(-1.138,0.900) 0.818	2.516(-2.211,7.243) 0.296
Past heart disease	-0.263(-1.589,1.063) 0.969	0.403(-0.665,1.471) 0.459	**6.982(2.088,11.876) 0.005**
Biomarkers			
HbA1c	-0.016(-0.053,0.020) 0.382	0.016(-0.013,0.046) 0.277	0.087(-0.049,0.223) 0.207
Poor HbA1c	-0.618(-1.642,0.405) 0.235	**1.005(0.187,1.823) 0.016**	1.082(-2.765,4.928) 0.580

Medication			
Insulin	-0.188(-1.017,0.641) 0.656	0.359(-0.308,1.025) 0.290	0.795(-2.266,3.857) 0.609
Metformin	-0.089(-0.832,0.654) 0.813	-0.524(-1.119,0.071) 0.084	0.746(-1.997,3.489) 0.593
ACEi	-0.196(-0.915,0.523) 0.592	-0.0244(0.0824,0.335) 0.407	1.661(-0.990,4.312) 0.218
ARB	0.278(-0.444,1.000) 0.448	0.163(-0.419,0.745) 0.582	-0.015(-2.686,2.656) 0.991
Beta-blockers	0.759(-0.0789,2.308) 0.335	-0.694(-1.942,0.553) 0.274	2.237(-3.488,7.962) 0.442
Calcium antagonists	0.018(-0.744,0.779) 0.964	0.142(-0.472,0.755) 0.650	0.798(-2.014,3.609) 0.577
Diuretics	0.691(-0.399,1.781) 0.213	-0.384(-1.264,0.496) 0.391	-2.313(-6.341,1.716) 0.259
Lipid lowering meds	-0.098(-0.903,0.707) 0.811	-0.576（-1.220,0.069） 0.080	1.461(-1.508,4.430) 0.333
Baseline Echocardiography			
LV ejection fraction	0.034(-0.019,0.087) 0.203	-0.040（-0.082,0.003） 0.066	-0.149(-0.050,0.347) 0.141
ΔLV ejection fraction	**-0.068(-0.108,-0.028) 0.001**	0.007(-0.026,0.040) 0.667	0.006(-0.147,0.158) 0.940
E/A	0.155(-1.634,1.943) 0.865	**-2.529(-3.935,-1.123) <0.001**	-2.258(-11.717,1.201) 0.110
E/e’	0.071(-0.060,0.203) 0.286	**-0.253(-0.354，-0.152) <0.001**	**0.527(0.037,1.017) 0.035**
LVMi	0.009(-0.006,0.023) 0.244	0.002(-0.010,0.014) 0.759	**0.057(0.002,0.112) 0.042**
ΔLVMi	0.005(-0.012,0.023) 0.536	0.014(0.000,0.027) 0.055	**0.145(0.083,0.208) <0.001**
LAVi	-0.005(-0.039,0.029) 0.780	0.006-0.022,0.034） 0.664	**-0.273(-0.397,-0.149) <0.001**
GLS	**-0.451(-0.573,-0.329) <0.001**	0.048(-0.060,0.1570 0.380	0.429(-0.072,0.9310 0.093
LA enlargement	0.048(-0.673,0.769) 0.896	0.211(-0.369,0.791) 0.474	**-5.694(-8.300,-3.088) <0.001**
LV hypertrophy	0.599(-0.213,1.411) 0.148	0.005(-0.652,0.661) 0.989	2.641(-0.399,5.682) 0.088
E/e’ ratio >13	0.031(-1.155,1.217) 0.959	**-1.420(-2.359,-0.480) 0.003**	**4.501(0.090,8.913) 0.046**
GLS<18%	**-1.627(-2.286,-0.967) <0.001**	-0.011(-0.568,0.546) 0.970	2.207(-0.368,4.4782) 0.093
GLS<16%	**-1.843(-2.633,-1.053) <0.001**	0.167(-0.496,0.831) 0.620	**3.219(0.158,6.280) 0.039**

Chapter 9. Cost-effectiveness Implications of a HF Screening Program in Diabetes

9.1 Preface

The cost of HF as well as diabetes are a huge burden to the health care system. The incidence of HF appears to be stable, but will likely increase as the population ages and the proportion with T2DM increases. Early diagnosis and intervention may have a role in the avoidance of an epidemic of diabetic HF. Nonetheless, the establishment of a screening process is dependent on a number of steps. Evidence of an effective prevention strategy in non-ischemic HF is limited. Such a prevention strategy for early HF might be based on beta blockers and/or ACE inhibitors, The recent TOPCAT study demonstrated that the mineralocorticoid antagonist spironolactone, could reduce HF mortality in subgroups of patients with preserved EF [238]. The assumption that early recognition of LV dysfunction could improve outcome is based on defining the efficacy of such a treatment strategy. However, the process of screening by echocardiogram) and/or treatment of LV dysfunction involves additional costs. These costs may be partially or fully offset by reductions in longer-term complications and mortality and their associated costs.

According, we developed a Markov model to assess the cost-effectiveness among three strategies from a healthcare payer perspective. These three strategies are 1) usual care, 2) primary prevention and 3) screening of LVD and GLS guided prevention.

9.2 Abstract

Background. The derivation of global longitudinal strain (GLS) from 2D echocardiography can identify asymptomatic left ventricular dysfunction (LVD), a precursor of heart failure (HF) in type 2 diabetes mellitus (T2DM). Screening and early intervention for LVD might reduce the frequency of HF. We assessed the cost-effectiveness of GLS screening and early intervention for LVD, primary prevention with aldosterone antagonist (AA) for cardioprotection, and usual care in T2DM.

Methods. A Markov model, based on a US healthcare payer perspective, an annual cycle and ten-year horizon was developed to compare the costs and quality-adjusted life years (QALYs) in T2DM >65 years of 1) usual care, 2) primary prevention and 3) screening of LVD and GLS guided prevention. Transition probabilities, costs and utilities were based on an observational study of 290 subjects and the literature. QALYs, costs and incremental costs/QALY gained were calculated. Univariable and probabilistic sensitivity analyses assessed robustness of results and accounted for uncertainty.

Results. Usual care was dominated by all other strategies. GLS-guided prevention resulted in higher QALYs than primary prevention (6.43 vs 6.26) and lower costs ($55,588 vs 58,598), with acceptable incremental cost-effectiveness in 81.5% of simulations. The projected 10-year survival was 82% with normal GLS, 70% for treated abnormal GLS and primary prevention, 67% for untreated abnormal GLS and 67% for usual care. HF and mortality incidence, and the relative risk of incident HF and death in diabetes taking AA had the greatest impacts on results.

Conclusion. GLS-based guidance of HF prevention in elderly asymptomatic T2DM patients appears to be cost-saving.

9.3 Background

Type 2 diabetes mellitus (T2DM) is a well-recognized independent risk factor for incident heart failure (HF), with an incidence rate 2-5 times greater than in the general population [5]. HF remains a leading cause of hospitalization among people >65 years of age and imposes an immense economic burden, estimated to be $108 billion annually [239, 240]. The incidence of HF appears to be stable [241], but will likely increase as the population ages and the proportion with T2DM increases.

Myocardial fibrosis is thought to be a contributor to LV dysfunction in T2DM, and studies of mineralocorticoid antagonists in patients with asymptomatic diastolic dysfunction or HF patients with preserved ejection fraction (HFpEF) have shown significant improvement in diastolic function and markers of cardiac fibrosis [242]. In a recent trial of patients with symptomatic HFpEF, aldosterone blockade led to better functional capacity [243] – a result concordant with most (American rather than European) patients recruited to the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT), in whom spironolactone preserved myocardial function and reduced HF admissions [238, 244]. The recognition of early LV dysfunction may limit treatment to those who would benefit the most, thereby minimizing the number of patients at risk of side-effects from spironolactone [88, 245]. Reduced LV global longitudinal strain (GLS) to ≥-18% – which may be detected despite normal diastolic function [88, 240] - has been identified in 32-37% of asymptomatic patients with T2DM and preserved ejection fraction, and is a powerful independent predictor of adverse cardiac events [88, 240, 245]. A recent cost-effectiveness study showed screening for unrecognized clinical HF in elderly community-dwelling T2DM patients by checking the electronic record is cost-effective, at a willingness-to-pay threshold of €20,000/QLAYs [246]. However, recognition of HF in the preclinical phase (LVD) may be more effective in preventing the progression of the condition. Although strain imaging has now provided a robust means of

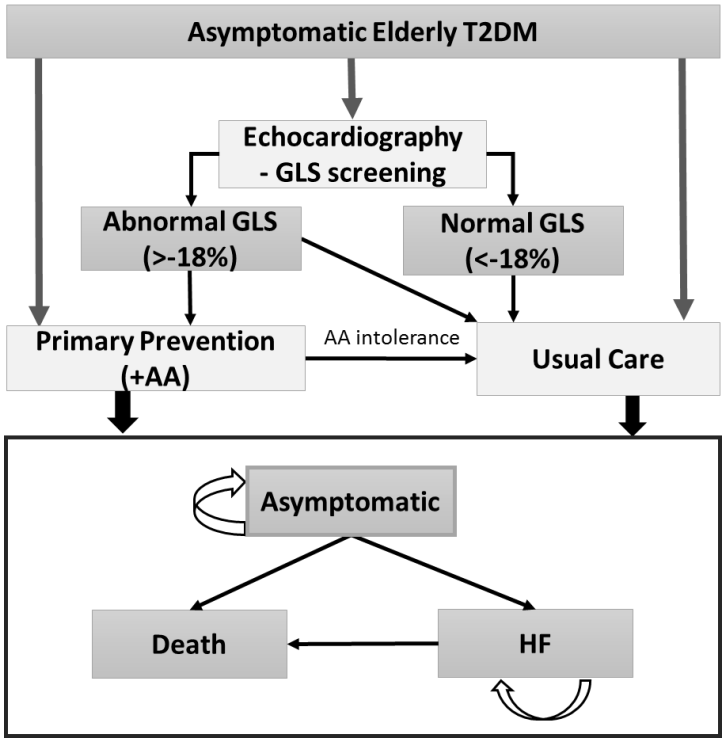
detecting LVD, screening for and/or treatment initiation of LVD may involve additional costs. It has not been shown whether these may be partially or fully offset by reductions in longer-term complications and mortality and their associated costs. Accordingly, we sought to assess the cost-effectiveness of two potential strategies versus usual care to address LVD in elderly subjects (>65 years) with T2DM, from a healthcare payer perspective.

9.4 Methods

9.4.1 Model development.

We developed a Markov model to evaluate the outcomes and costs associated with three strategies for the early detection and prevention in asymptomatic elderly people with T2DM (**Figure 9.1**). 1) Usual care – no cardioprotection, 2) Primary prevention - taking spironolactone without GLS measurement, 3) GLS guided therapy – selective use of spironolactone based on GLS.

Figure 9.1 Markov process for comparing primary prevention, GLS-guided prevention and usual care.



The time horizon of the model was ten years, with a cycle length of one year. Outcomes and costs of 10,000 patients were generated using a Markov model with Monte Carlo simulation developed with standard software (TreeAge Pro 2017, TreeAge, and Williamstown, MA). The reference case involved men and women of initial age 65 years. Half-cycle correction was used as recommended by current modelling guidelines [247]. The model estimated 10-year costs and quality-adjusted life years (QALY). Discounting at 3% annually was performed for both costs and QALYs [248]. Costs were reported in 2015 US dollars.

9.4.2Health states, transitions and assumptions.

A simplified presentation of the model is depicted in **Figure 9.1**. In the usual care arm, patients could remain asymptomatic or progress to cardiac events (i.e. cerebrovascular disease and HF) or death. As a consequence of receiving spironolactone, the primary prevention cohort could develop an adverse drug reaction (e.g. allergy, side-effect and intolerance) and then discontinue medication and jump to the usual care state, or remain adherent to spironolactone (then remain asymptomatic or progress to cardiac events or death). The GLS-guided prevention cohort started with echocardiographic screening, and based on normal or abnormal GLS diagnosis, patients would be prescribed spironolactone or not. Asymptomatic patients with abnormal GLS who were unable to tolerate taking medication for prevention, also jumped to the usual care state.

Transition probabilities data were weighted based on evidence from the literature and our experience in a prospective study of 290 asymptomatic T2DM patients, with definition of the following health states and transitions (**Table 9.1**):

1) Subclinical LV dysfunction. The reported prevalence of abnormal GLS (≥-18%) in asymptomatic subjects with T2DM ranges from 32-54% with a weighted average of 39% [88, 189, 245]. The relative risks (RR) of all-cause mortality and hospitalization in elderly subjects with

T2DM for abnormal and normal GLS are 1.24 (95%CI 0.90-1.70) and 0.81 (95%CI 0.56, 1.17), respectively [189]. Based on our experience, the RR of incident HF in elderly subjects with T2DM for abnormal and normal GLS are 1.29 (95%CI 0.85-1.96) and 0.71 (95%CI 0.42-1.21), respectively [249]. These RRs were used to estimate the annual incidence rate of HF in abnormal and normal GLS subjects with T2DM. Spironolactone significantly reduced the mortality and incident heart failure rate in symptomatic patients (RR 0.83, 95%CI 0.69, 0.99) [238]. This RR was used to estimate the annual incident rate of cardiac events in T2DM patients taking spironolactone. As this effect size is extrapolated from symptomatic patients, it was thoroughly tested in sensitivity analysis. The adherence rate of taking cardio-protective medication after abnormal GLS diagnosis was assumed to be 26.5%, based on our experience [250]. Discontinuation rates for spironolactone were taken from the TOPCAT cohort and were 24.7% in the first year and varied annually from 7.1-10.5% (average 7.5%) [238]. Sensitivity analyses were conducted using a range from minimum to maximum (0~90%) proportions of these and other rates.

2) Heart Failure (HF).The incidence rate of HF in asymptomatic T2DM is 0.7-3%, reaching 13% in sicker patients of more advanced age [7, 22, 251, 252]. We used a weighted average incidence rate of 1.4% per year, and the highest reported rate in the sensitivity analysis. The estimated annual HF event rates in T2DM with and without subclinical dysfunction were 1.8% and 1.0% respectively [249]. Based on the effect size of spironolactone, the estimated HF incident rate reduced to 1.2% per year for all asymptomatic T2DM patients and 1.5% for abnormal GLS T2DM patients. For a scenario analysis of T2DM with comorbidities, we anticipated a HF incidence of 10.3% based on our experience [249], providing an incident HF rate of 13.3% in those with impaired GLS and 7.4% with preserved GLS.

3) Mortality. The reported all-cause mortality for T2DM in the base case varied from 1.7% to 3.7% between studies; the weighted average was 3.3% per year [7, 251-253]. Diabetes patients with screening-detected HF had a higher annual mortality rate than those without (3.1% vs 1.5%) [254]. Spironolactone was expected to reduce the risk of mortality in T2DM to 2.8% per year for treated elderly asymptomatic T2DM [238]. The mortality rates for T2DM patients with abnormal and normal GLS were estimated at 4.1% and 2.7% respectively [189]. The estimated mortality rate for abnormal GLS diabetes patients with cardio-protection was 3.4% [189, 238].

Table 9.1 Transition probabilities and mortality rates

Parameters	Mortality	refs	HF	refs	HF - Death	refs
Distribution	Beta		Beta			
Usual care	0.033	7, 251-253	0.014	7, 22, 251, 252	0.176	7, 89
Primary prevention group (+spironolactone)	0.028	7, 238, 251-253	0.012	7, 22, 238, 251, 252	0.138	7, 89, 255
Echo group (Abnormal GLS + spironolactone)	0.034	7, 189, 238, 251-253	0.015	7, 22, 238, 251, 252, 256		
Echo group (Abnormal GLS - spironolactone)	0.041	7, 189, 251-253	0.018	7, 22, 251, 252, 256		
Echo group (Normal GLS)	0.027	7, 189, 251-253	0.010	7, 22, 251, 252, 256		

9.4.4 Utilities.

Utility parameters are summarized in **Table 9.2**, and were obtained from literature by searching the words "utility'" and "quality of life" in conjunction with the relevant health states. Utility weights were multiplied by the duration in each health state to calculate quality adjusted life years (QALYs). The utility weight for elderly T2DM was obtained from the Translating

Research into Action for Diabetes (TRIAD) study [257]. Elderly HF patients' utility varied according to functional class and hospitalization [258, 259].

Table 9.2 Utility values and costs for each health state.

	Utility	Cost ($/yr; ±SD)
Echocardiography		$466±320[260]
Cardio-protective medication		$105±53[261]
T2DM	0.80±0.17[257]	$4,500±353[262]
HF	0.51±0.19[258, 259]	$14,400±3,327[263, 264] Annual follow-up costs $5,800±3,054
Death	0	$14,740±410[265]

9.4.5 Cost information.

The cost analysis was taken from the perspective of the healthcare provider and consequently used the amount reimbursed to the provider as the cost of care. The costs incorporated direct costs related to ultrasound screening, diagnosis and each health state. Costs were converted to 2015 US dollars using the healthcare inflation index. A willingness to pay threshold of $50,000/QALY gained was applied [266]. The annual costs of medications and echocardiography costs were obtained from published sources [260, 261]. The health care costs of the last year of life of elderly people differed according to hospitalization, long-term care and age [265]. The first year and annual follow-up costs of HF and annual costs of T2DM all have been stated in literature (**Table 9.2**).

9.4.6 Sensitivity analysis.

One-way sensitivity analyses were conducted to identify the critical sources of variation in the input data - such as cardiac event rate and mortality in the primary prevention group, and the balance of heart failure risk in each group. A threshold analysis was conducted on the variables with the greatest influence to determine the point when additional cost per QALY exceeded $50,000 for the dominant strategy. Second order Monte Carlo simulations were performed as probabilistic sensitivity analyses on a hypothetical 10,000 patient cohort. Beta distributions

were assigned to utilities and probability weights, gamma distributions were assigned to costs and triangular distributions were assigned to RRs. Each input factor was varied by its standard error derived from the associated literature. Means and 95% credible intervals (95% confidence intervals) were computed for each of the posterior distributions. Cost-effectiveness acceptability curves (CEACs) were generated from the probabilistic sensitivity analysis and quantified and graphically represented uncertainty [247]. We estimated the probabilities that interventions would be considered "good value for money" as the willingness to pay threshold was incrementally increased from zero to $100,000/QALY gained [266].

9.4.7 Scenario analysis.

A scenario analysis was conducted based on our study reporting relatively high annual rates of HF and death in diabetes with impaired GLS, which would give the high mortality and HF incidence in cardioprotective medication management of the asymptomatic diabetes patients.

9.5 Results

9.5.1 Health outcomes and costs of primary prevention, GLS-guided prevention and usual care.

The costs and QALYs from 10,000 simulations are listed in **Table 9.3**. The outcomes of both GLS-guided prevention and primary prevention were superior to usual care. QALYs post GLS-guided prevention were slightly greater than those obtained from primary prevention (6.43 vs 6.26) and the costs were lower for GLS-guided prevention than primary prevention ($55,588 vs $58,598). GLS-guided prevention was cost-saving compared with primary prevention.

The survival curves from 10,000 simulations showed that normal GLS group had the highest survival rate (82%), followed by the treated abnormal GLS group, primary prevention group and then usual care group. The treated abnormal GLS group suggested an early survival advantage with eventual equalization with the primary prevention group (70%). The highest

mortality rate was in the untreated abnormal GLS group (67%) and usual care group (67%) (**Figure 9.2**).

Figure 9.2 Comparison of survival with GLS-guided prevention, primary prevention and usual care.

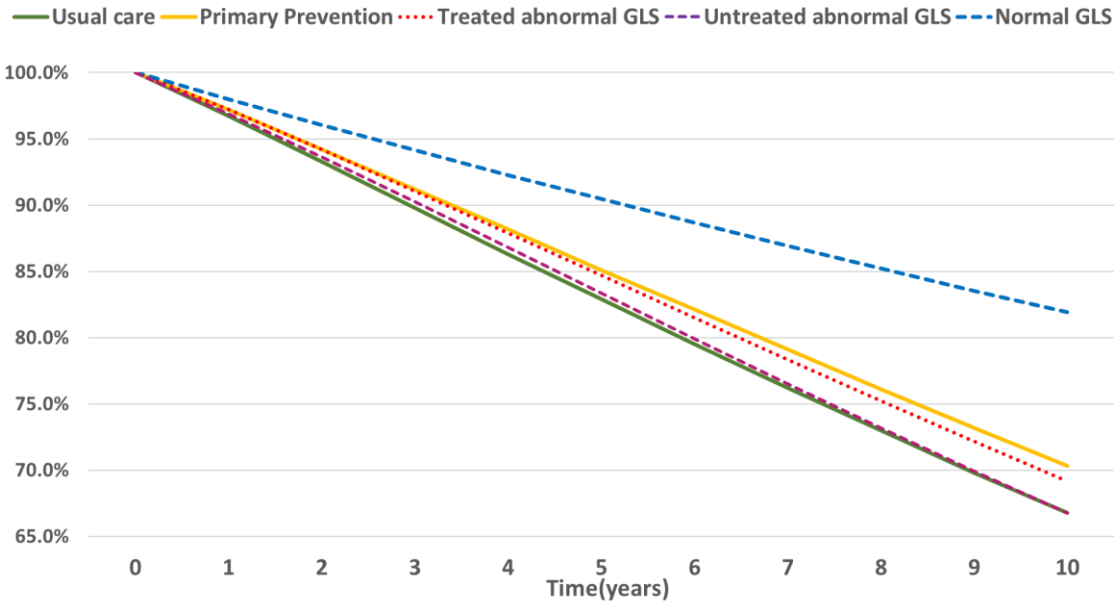


Figure 9.3 Tornado diagram (willingness to pay [WTP] =$50,000) identifying the main sources of variance in the input parameters that determine net health benefit in the model. The variables that have the greatest impact on the balance among the three strategies are the annual event rate of HF and death and the relative risk of incident HF and mortality with spironolactone in asymptomatic elderly T2DM patients.

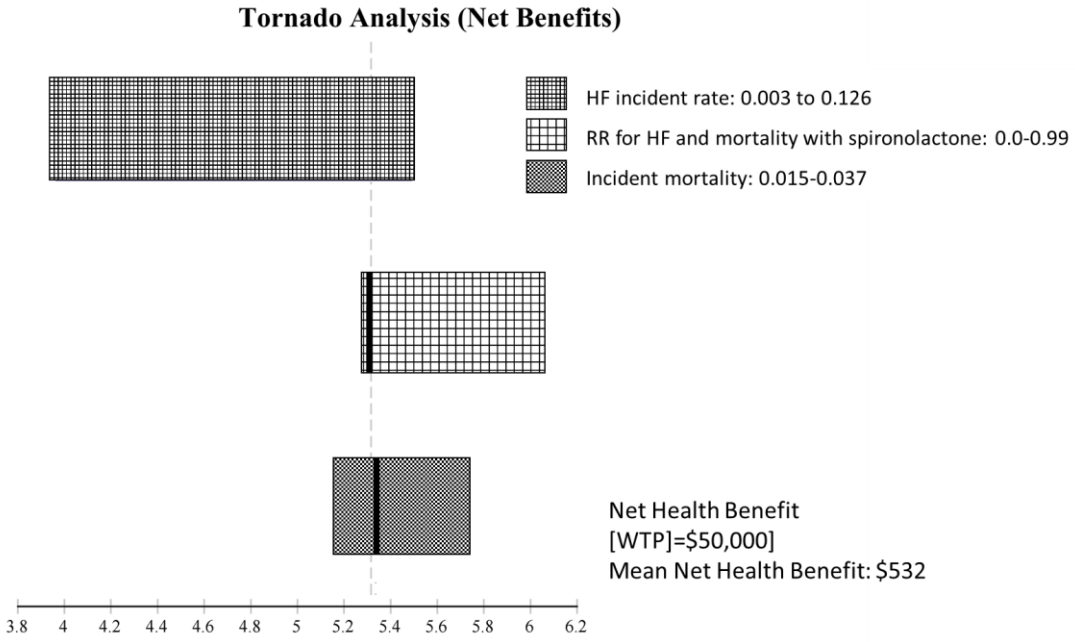


Table 9.3 Costs (USA$), effectiveness (QALYs), and incremental cost-effectiveness ratio ($/QALYs) of usual care, primary prevention and GLS-guided prevention in elderly asymptomatic T2DM.

	Costs and QALYs for each strategy		**Incremental analysis**			
Base case	QALYs	Cost ($)	Incremental QALYs	Incremental Cost($)	ICER compared to next best option	Implication
Usual care	6.12	60,109	--	--	--	--
Primary prevention	6.26	58,598	0.14	-1,511	Dominant to usual care	Primary prevention is a better option than usual care
GLS-guided prevention	6.43	55,588	0.17	-3,010	Dominant to primary prevention	GLS-guided prevention is a better option than primary prevention
Scenario analysis						
Usual care	5.20	82,313	--	--	--	--
Primary prevention	5.48	78,333	0.28	-3,980	Dominant to usual care	Primary prevention is a better option than usual care
GLS-guided prevention	5.73	73,513	0.25	-4,820	Dominant to primary prevention	GLS-guided prevention is a better option than primary prevention

9.5.2 Sensitivity analyses.

The effect of variation of parameter values was explored in sensitivity analyses. Threshold analyses were used to investigate the limits of transition probabilities, mortalities, costs and utilities which could have an impact on the outcome of the model. The main impacts on outcomes are illustrated in a "tornado diagram" (**Figure 9.3**), which identified that the parameters with the greatest impact were: the annual incidence of HF and death in asymptomatic T2DM as well as the RR for cardiac events with spironolactone. Each factor was analyzed across a clinically plausible range as shown in the one-way sensitivity analyses in **Figure 9.4**. GLS-guided therapy had a superior net monetary benefit from lower HF incident rate to higher rate (0.3%~12.6%) in asymptomatic T2DM (**Figure 9.4a**). GLS-guided therapy had a superior net monetary benefit when the RR for incident HF and death in diabetes taking spironolactone exceeded 0.60 (**Figure 9.4b**) and the annual mortality rate exceeded 2.6% (**Figure 9.4c**).

9.5.3 Monte Carlo Simulation.

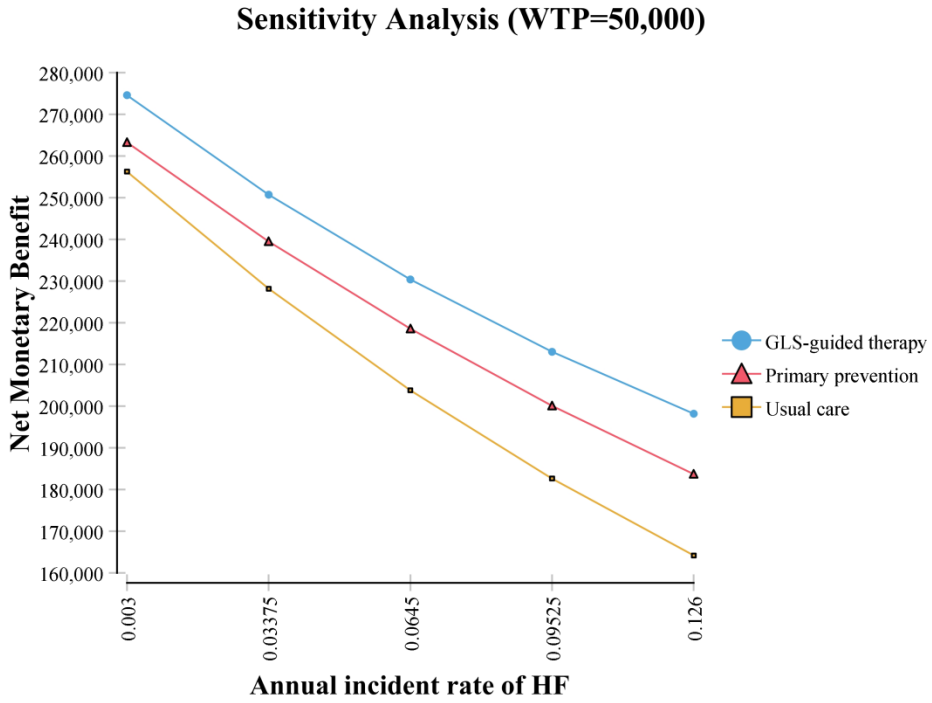
A probabilistic sensitivity analysis (second order Monte Carlo simulation) with 10,000 random samples simultaneously drawn from all distributions was used to assess uncertainty due to the distributions of transition probabilities, utilities and costs (**Figure 9.5**). The cost-effective points for GLS-guided prevention lying to the right of WTP line comprise 81.5% of patients, including 81% of simulations where this strategy was dominant (better outcomes and less cost) and 0.5% with incremental cost-effectiveness relative to primary prevention. The points lying to the left of WTP line included 0.1% where GLS-guided prevention had better outcome but at excessive cost and 12.6% where primary prevention was a better choice. The left quadrant includes 5.8% of subjects where GLS-guided prevention was dominated by primary prevention. A cost-effectiveness acceptability curve (**Figure 9.6**) illustrates the results of costs and QALYs from 10,000 samples. In the base case, at a WTP threshold of $50,000/QALY, 82% of GLS-

guided simulations were considered cost-effective, versus only 18% for primary prevention and 0% for usual care. When the willingness to pay was $100,000, the results were the same as at the WTP of $50,000. For a WTP in the range of $50,000/QALY to $100,000/QALY, GLS-guided prevention had a higher rate of simulations considered cost-effective compared with the other two strategies.

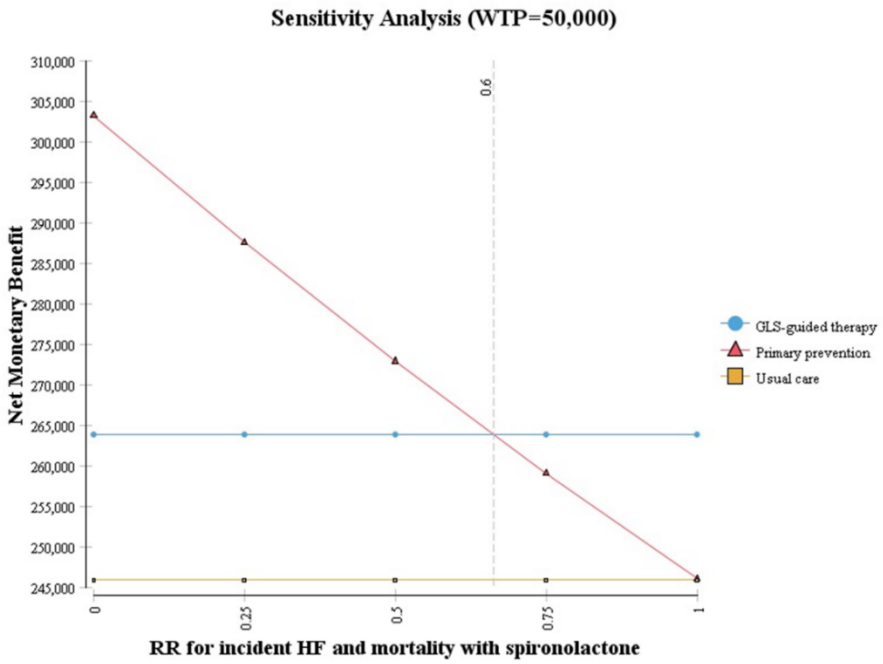
9.5.4 Scenario analyses.

The costs and QALYs from 10,000 simulations for the scenario analyses are listed in **Table 9.3**. Because of the high incidence rate of HF, GLS-guided prevention was still cost-saving compared with primary prevention. In this circumstance, usual care was dominated by the other two strategies. At a WTP threshold of $50,000, 77% percentage simulations were considered cost-effective with primary prevention and this increased modestly to 78% at a WTP threshold of $100,000.

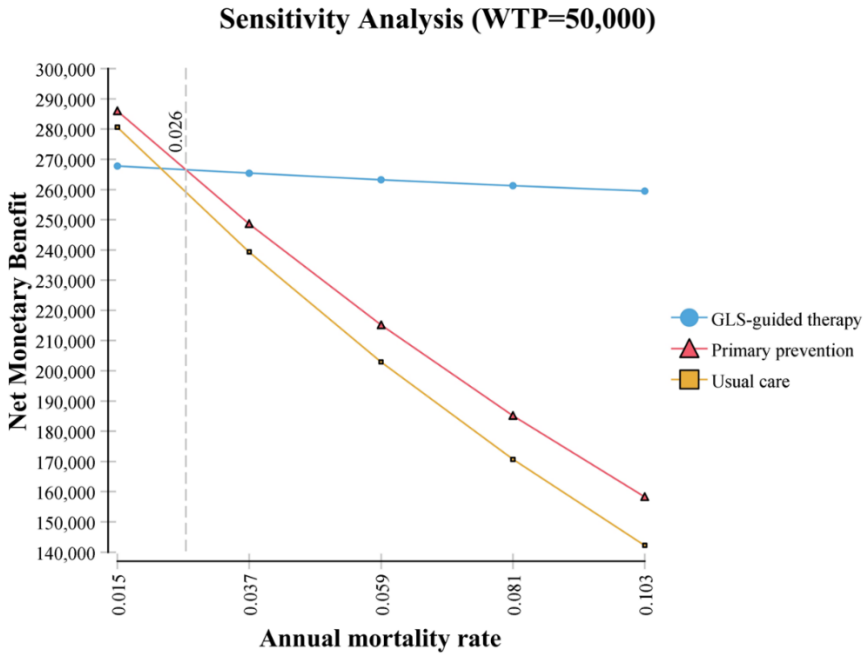
Figure 9.4 One-way sensitivity analyses to assess the impact of variations in (a) annual HF incidence rate in elderly asymptomatic T2DM, (b) RR for incident HF and mortality with spironolactone, and (c) annual mortality in elderly asymptomatic T2DM on net monetary benefits of three strategies, given willingness-to-pay (WTP) of $50,000.



(a)


Sensitivity Analysis (WTP=50,000)
Net Monetary Benefit
310,000
305,000
300,000
295,000
290,000
285,000
280,000
275,000
270,000
265,000
260,000
255,000
250,000
245,000
0.6
0
0.25
0.5
0.75
1
RR for incident HF and mortality with spironolactone
GLS-guided therapy
Primary prevention
Usual care

(b)


Sensitivity Analysis (WTP=50,000)
Net Monetary Benefit
300,000
290,000
280,000
270,000
260,000
250,000
240,000
230,000
220,000
210,000
200,000
190,000
180,000
170,000
160,000
150,000
140,000
0.026
0.015
0.037
0.059
0.081
0.103
Annual mortality rate
GLS-guided therapy
Primary prevention
Usual care

(c)

Figure 9.5 Scatter plot of cost-effectiveness in the Monte Carlo simulation of 10,000 elderly asymptomatic patients undertaking GLS-guided prevention and primary prevention. In this figure, the cost-effective points for "GLS-guided prevention" lying to the right of WTP line comprise 81% of patients where this strategy was dominant (better outcomes and less cost) and 0.5% of patients where this strategy is incrementally cost-effective relative to primary prevention.

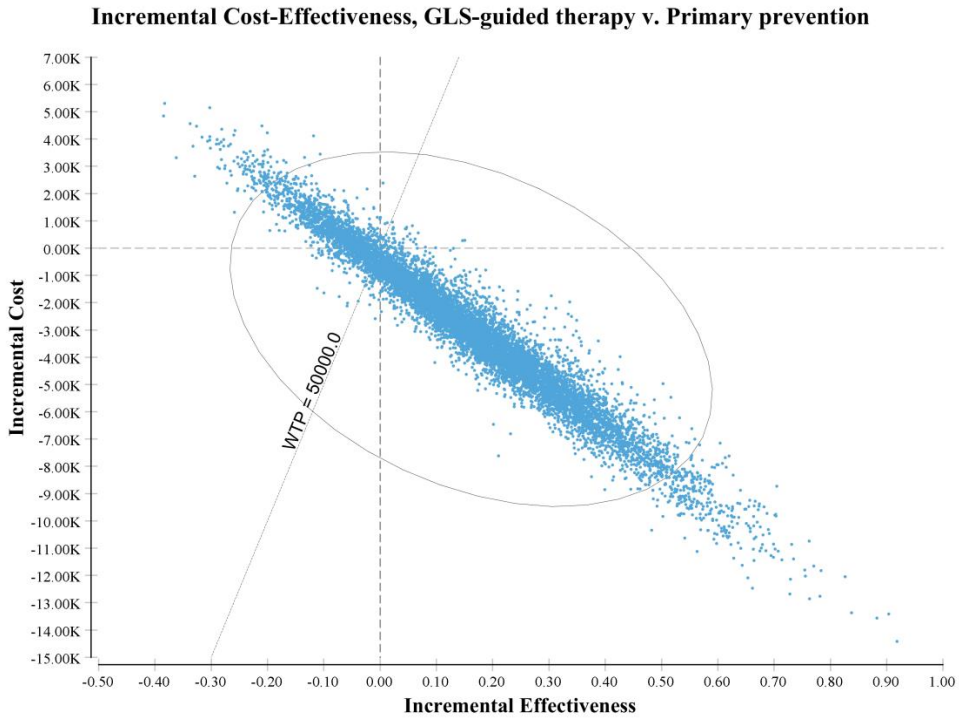
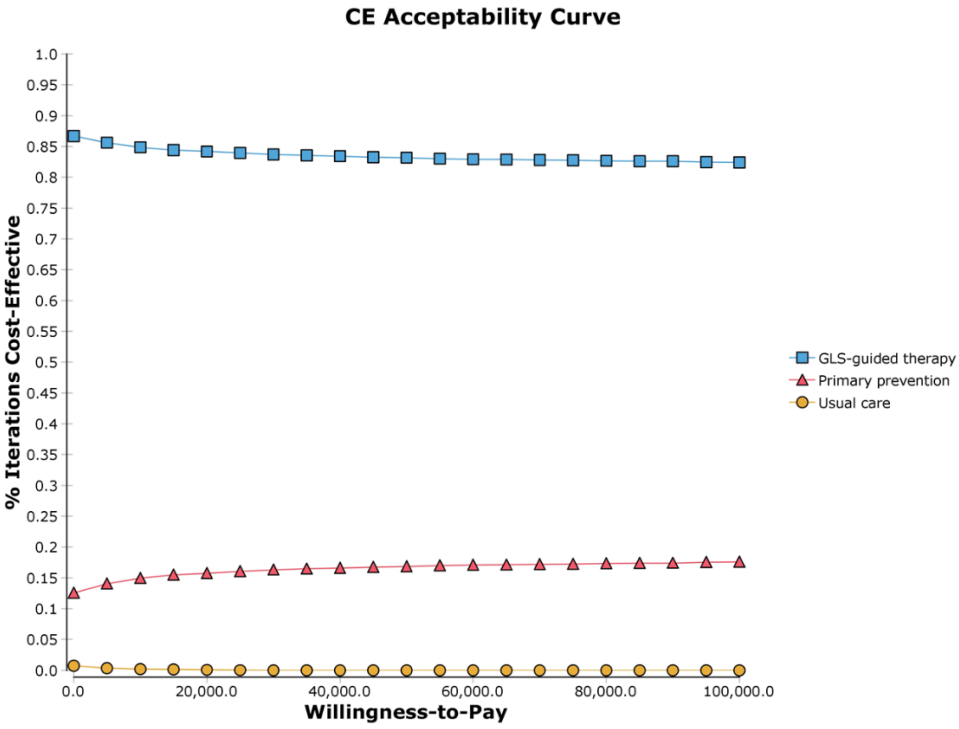


Figure 9.6 Cost-effectiveness acceptability curves.



9.6 Discussion

In this decision analysis exploring alternative strategies for HF prevention in asymptomatic T2DM, the model accounted for adverse cardiac events: heart failure, changes in length and quality of life and 10-year total costs. The two most important findings of this decision analysis relate to the difference between quality of life results and costs. Despite similar survival of three strategies (except the normal GLS sub-group), differences in QALYs and costs were observed between each protective strategy, but both protective strategies dominated usual care. The analysis demonstrated that more selective treatment - based on the identification of preclinical LVD using GLS (QALYs 6.43, Cost $55,588) - was cost-saving compared with primary prevention (QALYs 6.26, Cost $58,598). This suggests that treating diabetes with reduced GLS or preserved EF can improve survival and is cost-effective.

9.6.1 Scenario Analysis

In the scenario analysis, relatively high annual rates of HF and death in diabetes with impaired GLS from our study (Tas-ELF study) were applied. The result is consistent with the result in base case model as GLS-guided therapy is always dominant and cost-saving. As GLS is of higher prognostic value, the model outcome is more favorable to GLS-guided therapy when event rates are higher – as in T2DM patients with abnormal GLS.

9.6.2 Model Assumptions

In our model, assumptions including transition probabilities, utilities, and costs were subject to sensitivity analysis with a broad range to determine the impact of the assumptions. Use of a sensitivity analysis provides the opportunity of reassessment using different assumptions. The main impacts on the outcomes are the efficacy of the cardio-protective medication, annual incidence of HF and death in asymptomatic patients with T2DM. When spironolactone is used as the cardio-protective medication, GLS-guided therapy dominates the other strategies.

However, when annual mortality rate decreases to below 2.6%, both primary prevention and usual care derive superior net monetary benefit to GLS-guided therapy. In other words, in a low death rate population, either primary prevention or usual care are a better option than GLS-guided prevention.

9.6.3 Age and T2DM as contributors to subclinical LV dysfunction.

The sustained growth of HF burden has been driven by increased survival following acute events, combined with population aging [267]. The prevalence of HF increases with advancing age, accounting for 2-3% in the general population, and ≥10% among people ≥75 years of age [268]. The prognosis of HF in elderly people is worse than in younger patients, reflecting the impact of age-related structural and functional abnormalities as well as co-existing co-morbidities and worse health status [269]. However HFpEF in elderly patients may be underdiagnosed, because the initial symptoms of HF (e.g. exercise intolerance, decreased functional capacity) are often attributed to aging. Hence, the recognition of preclinical HF using sensitive diagnostic methods such echocardiography may be of value in trying to delay or prevent HF [267]. GLS is superior to LVEF as a predictor of prognosis [270].

The detection of preclinical DCM may be important for preventing progression to HFpEF [245]. Although subclinical dysfunction has been recorded by both systolic (e.g. GLS) or diastolic markers (e.g. tissue Doppler imaging), in the presence of preserved EF [189, 270], recent reports have proposed that abnormal GLS is a more specific marker of DCM [88]. While GLS is not specific for pathology, being abnormal in myocardial fibrosis [271] and myocardial dysfunction [189] from other causes, it may be sufficiently sensitive to follow therapeutic interventions.

The appropriate preventive therapy in patients with subclinical LVD is undefined. Angiotensin converting enzyme inhibitors are widely used for renal protection in T2DM, but their cardioprotective effects do not seem to have reduced the problem of HF in this group.

Mineralocorticoid receptor antagonists are beneficial in treating diabetic nephropathy independent of their effect on blood pressure [272]. The recent post hoc analysis from TOPCAT showed that despite failing to achieve a reduction in the primary composite outcome in the overall study, spironolactone was associated with 26% cardiovascular mortality reduction and 25% total HF hospitalized events in Western communities [238]. Perhaps more importantly, mineralocorticoid antagonists improve LV function and hemodynamics in LV dysfunction and HFpEF [242].

9.6.4 Limitations.

Whenever possible, we chose transition probabilities from our own experience, but the utilities and costs in this model are drawn from various independent sources, which may cause inconsistencies. Transition probabilities were estimated using relative risk. Inevitably, although these values were considered to be the most realistic estimates, they are not firm values, hence the need for sensitivity analysis and distribution sampling. Although some parameters were based on assumptions, the most influential parameters (HF and mortality in various health states) were derived from published data and our own observations. It should be noted that the results of sensitivity analyses showed that variations of these transition probabilities had limited impact on outcomes.

9.7 Conclusion

Based on this Markov model, screening for asymptomatic LV dysfunction (evidenced by abnormal longitudinal myocardial deformation) in elderly patients with T2DM appears cost-saving. These results could be used to inform clinical trials aimed at the early detection and treatment of LV dysfunction, with the intent of preventing the development of HF in T2DM.

Chapter 10. Summary and Conclusions

The aim of this thesis was to determine the role of strain imaging (GLS) in early detection of LV dysfunction for HF prevention in elderly asymptomatic patients with T2DM. From this thesis, I am able to make a number of conclusions:

1. Prediction on HF in T2DM.

- Five common clinical variables (coronary artery disease, impaired HbA1c, insulin use, increased fasting glucose and advanced age) are identified which are significantly associated with increased risk of incident HF in patients with T2DM. Diabetic patients with these risk factors are at high risk for development of HF and should undergo screening.

2. Prevalence and functional implications.

- Simple measurement of waist circumference which is linked to insulin resistance is a predictor of function capacity in elderly asymptomatic T2DM, independently and incrementally to clinical, biochemical, therapeutic and echo variables.
- SBHF defined as subclinical LV dysfunction detected by GLS is highly prevalent in elderly asymptomatic patients with T2DM in the community. GLS is associated with incident HF in elderly asymptomatic T2DM- importantly, this is independent and incremental to clinical and echo parameters and glycemic control.
- Compared with SAHF due to other causes, SAHF due to T2DM have more impaired LV function (both systolic and diastolic), less well-being and worse functional capacity. Not all types of SAHF are the same.

3. Outcomes.
    - The incidence rate of new-onset of HF in elderly asymptomatic T2DM was high in TasELF study cohort ~ 15.5% per year (112/1000 person-years). T2DM-SAHF showed a worse prognosis compared with other-SAHF. T2DM with impaired GLS and exercise capacity, AF and obesity is associated with a worse outcome.
    - In T2DM-SAHF, depression is prevalent and independently and incrementally predicts incident HF.

4. Development of a community screening program.
    - There is a mild deterioration of subclinical LV function by GLS and diastolic function in elderly asymptomatic patients with T2DM and preserved EF.
    - GLS is a feasible and reliable marker in the community and provides incremental predictive value of incident HF in elderly asymptomatic T2DM.

5. Cost-effectiveness of screening LV dysfunction.
    - The preventive treatment guided by screening for asymptomatic LV dysfunction (evidenced by abnormal GLS) for HF in elderly patients T2DM is cost-saving. This result could be used to inform clinical trials aimed at the early detection and treatment of LVD, with the intent of preventing the development of HF in T2DM.

As the growing needs of early diagnosis of incident HF for early intervention in diabetes, we have found that GLS with its strong predictive value of incident HF is potentially a useful

marker for early screening strategy, while current literature do not offer strong evidence of its usefulness in clinical decision-making. In addition, I have done a systematic review and meta-analysis study to identify the highest risk T2DM patients for most effective screening and intervention approach. Furthermore, I have built up a decision tree cost effectiveness model to determine the cost-effectiveness of screening LV dysfunction program in T2DM in the community and the results showed that the preventive treatment guided by GLS for HF prevention in elderly patients T2DM is cost-saving.

In conclusion, early detection by strain imaging followed by preventive treatment for LV dysfunction can prevent the development of HF in elderly asymptomatic patients with T2DM. The measurement of GLS should be integrated into the early diagnosis of LVD and following decision-making in elderly T2DM.

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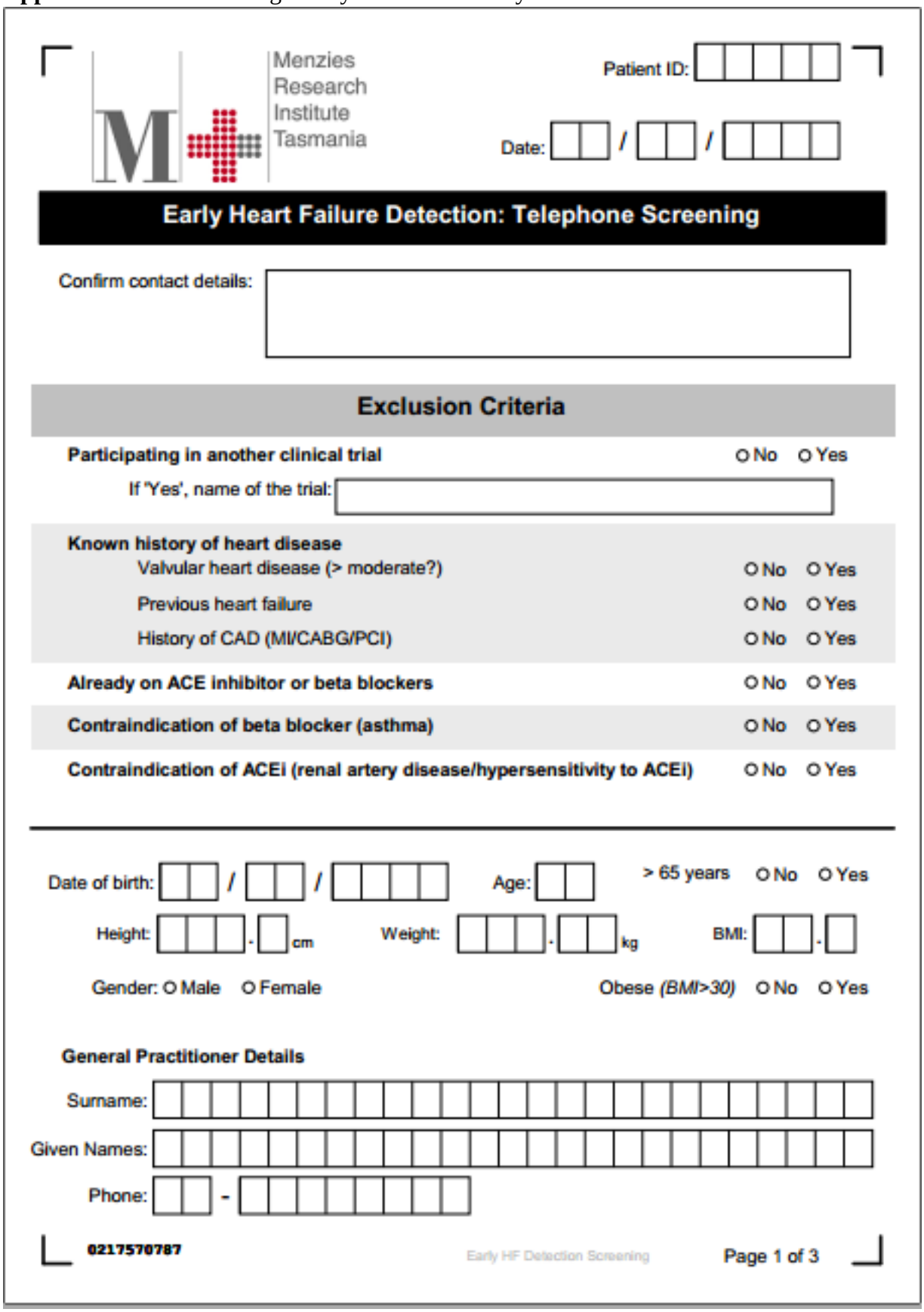
Appendix

Appendix 11.1HF screening survey in Tas-ELF study.



Menzies Research Institute Tasmania

Patient ID: ☐☐☐☐☐

Date: ☐☐ / ☐☐ / ☐☐☐☐

Early Heart Failure Detection: Telephone Screening

Confirm contact details:

Exclusion Criteria

Participating in another clinical trial ○ No ○ Yes

If 'Yes', name of the trial:

Known history of heart disease

Valvular heart disease (> moderate?) ○ No ○ Yes

Previous heart failure ○ No ○ Yes

History of CAD (MI/CABG/PCI) ○ No ○ Yes

Already on ACE inhibitor or beta blockers ○ No ○ Yes

Contraindication of beta blocker (asthma) ○ No ○ Yes

Contraindication of ACEi (renal artery disease/hypersensitivity to ACEi) ○ No ○ Yes

Date of birth: ☐☐ / ☐☐ / ☐☐☐☐ Age: ☐☐ > 65 years ○ No ○ Yes

Height: ☐☐☐.☐ cm Weight: ☐☐☐.☐☐ kg BMI: ☐☐.☐

Gender: ○ Male ○ Female Obese *(BMI>30)* ○ No ○ Yes

General Practitioner Details

Surname:

Given Names:

Phone: ☐☐ - ☐☐☐☐☐☐☐☐

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Medical History

Known history of allergy to medication: ☐

Diabetes (T2DM): ○ No ○ Yes

If Yes, year of diagnosis and medication: ☐

High blood pressure ○ No ○ Yes

If Yes, year of diagnosis and medication: ☐

If first contact, BP reading: SBP: ☐☐☐ DBP: ☐☐☐

Past chemotherapy (self-reported history) ○ No ○ Yes

If Yes, when: ☐

F/H of Heart Failure (F/H of CM) ○ No ○ Yes

If Yes, details of F/H: ☐

Age when diagnosed: ☐☐☐

Known cardiac disease but not existing heart failure *(medical record)* ○ No ○ Yes

History of > moderate valvular heart disease (baseline echo) ○ No ○ Yes

History of previous heart failure (self-reported history or medical record) ○ No ○ Yes

History of Ischemic heart disease ○ No ○ Yes

Details of Cardiac Disease if known: ☐

Existing medical therapy with beta blockers and ACE inhibitors (self-reported history) ○ No ○ Yes

Contraindications/Intolerance to beta blockers or ACE inhibitors (self-reported history) ○ No ○ Yes

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Medication details

Diabetes Medication:

Insulin:	O No	O Yes
Metformin (Glucophage/Riomet):	O No	O Yes
Miglitol (Glyset), Acarboss (Precose):	O No	O Yes
Nateglinide (Starlix):	O No	O Yes
Sitagliptin (Januvia):	O No	O Yes
Combination pills:	O No	O Yes

Hypertension Medication:

ACEi:	O No	O Yes
Beta Blocker:	O No	O Yes
Calcium antagonists:	O No	O Yes
ARB:	O No	O Yes
Diuretic (loop or thiazide):	O No	O Yes
Aldosterone antagonist therapy:	O No	O Yes

Hypertension Medication:

Anti-platlet:	O No	O Yes
Anticoagulant:	O No	O Yes
Lip lowering:	O No	O Yes
Antiarrhythmic drugs:	O No	O Yes

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Menzies Research Institute Tasmania

Patient ID: ☐☐☐☐☐

Date: ☐☐ / ☐☐ / ☐☐☐☐

Early Heart Failure Detection

Inclusion Criteria

Aged > 65 years	O No	O Yes
Diabetes (T2DM) *(self-reported history or use of meds)*	O No	O Yes
Obesity *(BMI>30)*	O No	O Yes
High blood pressure *(self-reported history of physician diagnosis or current use of meds)*	O No	O Yes
Past chemotherapy *(self-reported history)*	O No	O Yes
F/H of Heart Failure *(self-reported history)*	O No	O Yes
Known cardiac disease but not existing heart failure *(medical record)*	O No	O Yes

Exclusion Criteria

Unable to provide written informed consent to participate in this study	O No	O Yes
Participating in another clinical research trial where randomized treatment would be unacceptable	O No	O Yes
History of > moderate valvular heart disease *(baseline echo)*	O No	O Yes
History of previous heart failure *(self-reported history or medical record)*	O No	O Yes
Existing medical therapy with beta blockers and ACE inhibitors *(self-report history)*	O No	O Yes
Contraindications/Intolerance to beta blockers or ACE inhibitors *(self-reported history)*	O No	O Yes
Systolic BP <110mmHg	O No	O Yes
Pulse <60/minute	O No	O Yes
Baseline NYHA >2	O No	O Yes
Oncologic life expectancy < 12 months *(Medical record)*	O No	O Yes
Inability to acquire interpretable images *(baseline echo)*	O No	O Yes
Others	O No	O Yes

Charlson Comorbidity Index score

Myocardial infarction:	O No O Yes
Heart failure:	O No O Yes
PVD (intervention, surgery, AAA):	O No O Yes
Cerebrovascular disease or stroke:	O No O Yes
Hemiplegia:	O No O Yes
Cognitive impairment:	O No O Yes
Chronic lung disease or COPD:	O No O Yes
Connective tissue disease:	O No O Yes
Peptic ulcer:	O No O Yes
Diabetes mellitus:	O No O Uncomplicated O Endorgan damage
Diagnosis of renal disease:	O No O Yes
Leukemia:	O No O Yes
Lymphoma:	O No O Yes
Solid organ tumor:	O No O Yes
Cirrhosis:	O No O Mild O Mod-severe
HIV:	O No O Yes
Age:	O <40 O 41-50 O 51-60 O 61-70 O 71-80

Physical Measures

Height: ☐☐☐.☐ cm

Weight: ☐☐☐.☐☐ kg

Waist: ☐☐☐.☐ cm

Hip: ☐☐☐.☐ cm

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Clinical Risk Variables

Hypertension:	O No	O Yes
Dyslipidemia:	O No	O Yes
Angina:	O No	O Yes
Atrial fibrillation or flutter:	O No	O Yes
Cardiomyopathies:	O No	O Yes
Sleep-disorder breathing:	O No	O Yes
Alcohol abuse:	O No	O Yes
Depression:	O No	O Yes
Thyroid disease:	O No	O Yes

SOF Frailty Index

Weight loss: In the last two years, weight loss unintentionally >= 5%	O No	O Yes
Inability to rise from a chair 5 times without using his/her arms	O No	O Yes
Do you feel full of energy?	O No	O Yes

Brachial and Central Blood Pressure

Device number: ☐☐

At least 5 minutes supine rest: ○ No ○ Yes

	Echo Reading 1			Echo Reading 2		
	SBP (mmHg)	DBP (mmHg)	Pulse Rate (bpm)	SBP (mmHg)	DBP (mmHg)	Pulse Rate (bpm)
Brachial	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
Central	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐

Exclude if average SBP < 110mmHg, or > 180 mmHg or if average pulse < 60 bpm

Baseline NYHA: ☐ Exclude if > 2

	6' Walk Pre Reading 1		6' Walk Pre Reading 2	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Brachial	☐☐☐	☐☐☐	☐☐☐	☐☐☐
Central	☐☐☐	☐☐☐	☐☐☐	☐☐☐

	6' Walk Post Reading 1		6' Walk Post Reading 2	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Brachial	☐☐☐	☐☐☐	☐☐☐	☐☐☐
Central	☐☐☐	☐☐☐	☐☐☐	☐☐☐

ECG

Af:	O No O Yes
CLBBB:	O No O Yes
Left ventricular hypertrophy:	O No O Yes

Baseline Echo

EF: ☐☐ % Exclude if < 40%

> Moderate valve disease:	O No O Yes
Unable to acquire good images:	O No O Yes
Other findings for exclusion:	

Serum markers

Hematocrit:	☐☐.☐ %	Hemoglobin:	☐☐.☐ mmol/L
RDW:	☐☐.☐ %	Sodium:	☐☐☐ mmol/L
Blood urea nitrogen:	☐☐.☐ %	Creatinine:	☐.☐☐ mmol/L
Serum Albumin:	☐☐.☐ mg/L		
Troponin:	☐.☐☐ ug/L	eGFR:	☐.☐ ml/min
C-reactive protein:	☐☐.☐☐ mg/L	Glucose:	☐☐.☐ mmol/L
HbA1c:	☐☐.☐ mmol/mol	TSH:	☐☐.☐ mIU/L
Total cholesterol:	☐☐.☐ mmol/L		
NT-proBNP:	☐☐☐☐ pg/ml	B-type natriuretic peptide	☐☐☐☐ pg/mL

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Past therapies

Anthracyclines, herceptin, other chemo agents or chest radiotherapy:	O No	O Yes
Previous coronary artery bypass graft surgery:	O No	O Yes
Previous other cardiac surgery:	O No	O Yes
Previous percutaneous transluminal coronary angioplasty:	O No	O Yes

Medication

Beta blockers (including sotolol):	O No	O Yes
ACEi/ARB:	O No	O Yes
Diuretics (loop or thiazide):	O No	O Yes
Aldosterone antagonist therapy:	O No	O Yes
Calcium antagonists:	O No	O Yes
Antiarrythmic drugs:	O No	O Yes
Lipid lowering meds	O No	O Yes
Anti-platelet	O No	O Yes
Anti-coagulants	O No	O Yes
Nonsteroidal anti-inflammatory agents:	O No	O Yes

Appendix 11.2 Questionnaires used in TasELF study.

Menzies Research Institute Tasmania

Patient ID: TASELF ☐☐☐☐

Date: ☐☐ / ☐☐ / ☐☐☐☐

Tasmanian Study of Echocardiographic detection of Left ventricular dysfunction (TAS-ELF)

Instructions: Please read carefully

Please answer all questions to the best of your ability (leave blank if unknown).

Your answers will be completely confidential.

Indicate your response by filling in the circle next to the most appropriate answer

Example

Shade Circles Like This	●
Not Like This	⊗ or ⊘
Cross Out Mistakes Like This	✕●

Or by writing clearly using the boxes where provided.

Please use BLOCK LETTERS where required e.g H O B A R T ☐☐

Cross out any mistakes & write correct answer just below the relevant boxes

Please use a black or blue pen if possible

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Personal information

Surname:

Given Names:

Date of birth: / / Age:

Gender: O Male
O Female

Ethnicity O European
O Indigenous & Pacific Islander
O African
O East Asian
O South Asian
O Other

What is the highest level of education you have completed? (Select only one answer)

- O Primary School
- O Year 7, 8 or 9 or equivalent
- O Year 10 or equivalent
- O Year 11 or equivalent
- O Year 12 or equivalent
- O Trade/apprenticeship (e.g. hairdresser, chef)
- O Certificate/diploma (e.g. child care, technician)
- O University Degree
- O Higher University Degree (e.g. Grad Dip, Masters, PhD)
- O Other _____ (please specify)

What is your current marital status?

- O Single
- O Married
- O De facto
- O Separated/Divorced
- O Widowed
- O Other _____ (please specify)

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Do you have private health Insurance: O No O Yes

Do you live in a nursing home: O No O Yes

Smoking History

Over your lifetime, have you smoked at least 100 cigarettes, or a similar amount of tobacco?

O Yes O No

IF 'YES'

Have you ever been a daily smoker? O Yes O No

IF 'YES'

When did you start smoking daily?

☐☐ Years of Age

OR ☐☐☐☐ Year

How often do you now smoke cigarettes, cigars, pipes or any other tobacco products?

O Daily

O At least once a week (but not daily)

O Less often than weekly

O Not at all

If you no longer smoke each day, when did you finally stop smoking daily?

☐☐ Years of Age

OR ☐☐☐☐ Year

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Address

Address:

City/Suburb:

State: Postcode:

Telephone Numbers

Home: - Work: -

Mobile: -

email:

General Practitioner Details

Surname:

Given Names:

Practice:

Address:

City/Suburb:

State: Post Code:

Phone: - Fax: -

email:

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The DASI Patient Questionnaire

Can you: (please fill in the circle beside Yes or No)

1.	Take care of yourself, that is, eat, dress, bathe or use the toilet?	O Yes O No
2.	Walk indoors, such as around your house?	O Yes O No
3.	Walk a block or two on level ground?	O Yes O No
4.	Climb a flight of stairs or walk up a hill?	O Yes O No
5.	Run a short distance?	O Yes O No
6.	Do light work around the house like dusting or washing dishes?	O Yes O No
7.	Do moderate work around the house like vacuuming, sweeping floors or carrying groceries?	O Yes O No
8.	Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	O Yes O No
9.	Do garden work like raking leaves, weeding or pushing a lawn mower?	O Yes O No
10.	Have sexual relations?	O Yes O No
11.	Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis or throwing a ball?	O Yes O No
12.	Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?	O Yes O No

MINNESOTA LIVING WITH HEART FAILURE© QUESTIONNAIRE

The following questions ask how much any heart symptoms affected your life during the past month (4 weeks). After each question, fill in the circle, 0, 1, 2, 3, 4 or 5, to show how much your life was affected. If a question does not apply to you, fill in the 0 circle after that question.

Did these symptoms prevent you from living as you wanted during the past month (4 weeks) by -

	No					Very Much
	Very Little					
1. causing swelling in your ankles or legs?	O 0	O 1	O 2	O 3	O 4	O 5
2. making you sit or lie down to rest during the day?	O 0	O 1	O 2	O 3	O 4	O 5
3. making your walking about or climbing stairs difficult?	O 0	O 1	O 2	O 3	O 4	O 5
4 making your working around the house or yard difficult?	O 0	O 1	O 2	O 3	O 4	O 5
5. making your going places away from home difficult?	O 0	O 1	O 2	O 3	O 4	O 5
6. making your sleeping well at night difficult?	O 0	O 1	O 2	O 3	O 4	O 5
7. making your relating to or doing things with your friends or family difficult?	O 0	O 1	O 2	O 3	O 4	O 5
8. making your work to earn a living difficult?	O 0	O 1	O 2	O 3	O 4	O 5
9. making your recreational pastimes, sports or hobbies difficult?	O 0	O 1	O 2	O 3	O 4	O 5
10.making your sexual activities difficult?	O 0	O 1	O 2	O 3	O 4	O 5
11. making you eat less of the foods you like?	O 0	O 1	O 2	O 3	O 4	O 5
12. making you short of breath?	O 0	O 1	O 2	O 3	O 4	O 5
13. making you tired, fatigued, or low on energy?	O 0	O 1	O 2	O 3	O 4	O 5
14. making you stay in hospital?	O 0	O 1	O 2	O 3	O 4	O 5
15. costing you money for medical care?	O 0	O 1	O 2	O 3	O 4	O 5
16. giving you side effects from treatments?	O 0	O 1	O 2	O 3	O 4	O 5
17. making you feel you are a burden to your family or friends?	O 0	O 1	O 2	O 3	O 4	O 5
18. making you feel a loss of self-control in your life?	O 0	O 1	O 2	O 3	O 4	O 5
19. making you worry?	O 0	O 1	O 2	O 3	O 4	O 5
20. making it difficult for you to concentrate or remember things?	O 0	O 1	O 2	O 3	O 4	O 5
21. making you feel depressed?	O 0	O 1	O 2	O 3	O 4	O 5

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EQ-5D Health Questionnaire

By filling one circle in each group below, please indicate which statements best describe your own health state today.

1. **Mobility**
   - I have no problems in walking around O
   - I have slight problems in walking around O
   - I have some problems in walking around O
   - I have severe problems in walking around O
   - I am confined to bed O

2. **Personal Care**
   - I have no problems with personal care O
   - I have slight problems washing or dressing myself O
   - I have some problems washing or dressing myself O
   - I have severe problems washing or dressing myself O
   - I am unable to wash or dress myself O

3. **Usual Activities** (eg work, study, housework, family or leisure activities)
   - I have no problems with performing my usual activities O
   - I have slight problems with performing my usual activities O
   - I have some problems with performing my usual activities O
   - I have severe problems with performing my usual activities O
   - I am unable to perform my usual activities O

4. **Pain / Discomfort**
   - I have no pain or discomfort O
   - I have slight pain or discomfort O
   - I have moderate pain or discomfort O
   - I have severe pain or discomfort O
   - I have extreme pain or discomfort O

5. **Anxiety / Depression**
   - I am not anxious or depressed O
   - I am slightly anxious or depressed O
   - I am moderately anxious or depressed O
   - I am severly anxious or depressed O
   - I am extremely anxious or depressed O

We would like to know how good or bad your health is **TODAY**.

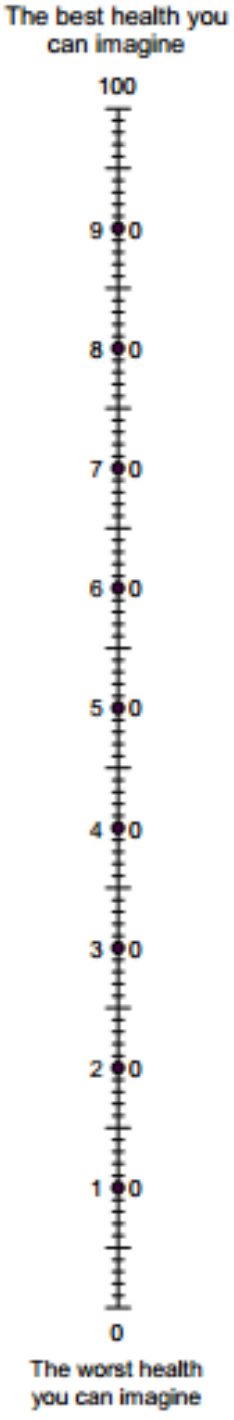
This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐☐☐



Patient Health Questionnaire (PHQ-9)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
For office coding:	0 +	_____ +	_____ +	_____
Total score:				

10. If you checked off **any** problems, how **difficult** have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all ○
- Somewhat difficult ○
- Very difficult ○
- Extremely difficult ○

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GAD-7

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

For office coding: 0 + _____ + _____ + _____

Total score: ☐☐

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Appendix 11.3 Information sheet of Tas-ELF study.

PARTICIPANT INFORMATION SHEET

CLINICAL TRIAL

TAsmanian Study of Echocardiographic detection of Left ventricular dysfunction (TAS-ELF)

Invitation

You are invited to participate in a research study to identify whether an additional investigation designed to identify the early stages of heart muscle damage can avoid heart failure or its consequences in people at risk of heart failure.

The study is being conducted by Prof Tom Marwick, Dr Kaz Negishi, Leah Wright and Hilda Yang of Menzies Research Institute Tasmania, Hobart. It will be performed at Menzies Research Institute and regional locations, based around the Menzies Biobus. Eight hundred subjects will be involved.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. 'What is the purpose of this study?'

Heart failure is a common and serious problem in our community. Early stages of heart failure can develop in apparently well people who have risk factors for heart failure. If this process is left unchecked, it can sometimes progress to heart failure. Some new cardiac imaging methods have allowed the early detection of cardiac problems before the patient develops heart failure. We are trying to establish whether this information could guide treatment to protect patients from developing heart failure. Sensitive measures of the heart and an exercise test will be taken in order to measure cardiac status.

2. 'Why have I been invited to participate in this study?'

You are eligible to participate in this study because you have risk factors that make you more likely than other people to develop heart failure.

3. 'What if I don't want to take part in this study, or if I want to withdraw later?'

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the GP or other clinicians caring for you.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason.

4. 'What does this study involve?'

If you agree to participate in this study, you will be asked to sign the Participant Consent Form.

This study is a randomised trial (see definition below) that will be conducted over at least two years. Cardiac measurements will be performed using a painless ultrasound test of the heart. You will be randomised to have either have a standard measurement (ejection fraction, EF) or a new measurement (global longitudinal strain, GLS) from these ultrasound pictures. The aim is to identify whether the information provided by the new test leads to better heart outcomes because your physician is more likely to start you on medications to protect the heart.

We will follow the response of your heart at the beginning and end of these treatment periods by taking ultrasound pictures, an exercise test and blood samples. You will need to attend the clinic on each of these occasions, as well as during regular follow-up.

Definition

'Randomised trial':

Sometimes doctors don't know the best way of treating patients with a particular condition so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different investigations or treatments, and the results are compared to see whether one approach is better. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the doctor nor the study participant can decide which investigation the participant receives.

If you agree to participate in this trial, you will then be asked to undergo the following procedures:

- A screening questionnaire to confirm eligibility, relevant medical history and quality of life.

- Ultrasound pictures of your heart , obtained by pressing an ultrasound probe against the skin. This machine transmits sound waves and collects the reflected waves to make a picture of the reflecting structures.
- We will measure the distance you are able to walk in 6 minutes.
- We will take up to 30 mls (about 2½ table spoons) of blood to test for biochemical markers.

In addition, the researchers would like to have access to your medical record to obtain information relevant to the study.

At the end of the follow-up period, you will then be asked to undergo:

- A repeat questionnaire regarding symptom status and quality of life.
- We will measure the distance you are able to walk in 6 minutes.

We wish to stay in touch with you (by phone or email) for at least 2 years, and have permission to contact you again in the future.

5. 'How is this study being paid for?'

The study is independently supported by the investigators. The Tasmanian Community Fund has partially funded the ultrasound equipment for this study, and the study is also supported by and equipment company (Siemens), who are supporting the application of new software and providing training. None of the investigators have any duality or conflict of interest. No money is paid directly to individual researchers.

6. 'Are there risks to me in taking part in this study?'

The treatments used to protect the heart will be at the discretion of your doctor, informed by the results from the investigator. The types of medications used to respond to an abnormal test are the same, whichever test is used. The classes of drugs we expect to use have been used extensively and are generally safe and well tolerated. Side-effects occur rarely but include low blood pressure (dizziness), gastrointestinal disturbances and skin reactions. If you have a significant symptoms that you think may be due to the agent, please call us and we will discuss stopping the drug.

It is important that women participating in this study are not pregnant and do not become pregnant during the study as the medication we might use may damage an unborn baby. If you are a woman of childbearing age and there is any possibility that you are pregnant, the researchers will need to perform a urine pregnancy test before you start in the study. If necessary, you should use reliable contraception (such as oral or implanted contraception, an IUD or have had a tubal ligation if you are female). If at any time you think you may be pregnant, it is important to let the researchers know immediately.

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study. In addition to the risks related to the medication, the other known risks of this study are possibly:

- Discomfort associated with having blood samples taken.
- Discomfort associated with the ultrasound test – which involved pressure against the chest wall.
- Inconvenience associated with visits for the study, or follow-up phone calls.

There may also be risks associated with this trial that are presently unknown or unforeseeable.

7. 'What happens if I suffer injury or complications as a result of the study?'

It is extremely unlikely that you will suffer any injuries or complications as a result of this study. However, if this occurs, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. You do not give up any legal rights to compensation by participating in this study.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

8. 'Will I benefit from the study?'

This study aims to further medical knowledge and may improve treatment of patients at risk of heart failure, however it may not directly benefit you.

9. 'Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything. However, you may be reimbursed for parking/travel expenses.

10.'What will happen to my blood and ultrasound images after the study?'

The images will be stored on a secure computer and blood samples you provide during the study will be stored in a freezer and tested for biochemical markers. The samples will be destroyed 7 years after completion of the study. They will not be used for other research projects, except with your written consent or, under some circumstances, with the approval of a Human Research Ethics Committee at that time.

11. 'How will my confidentiality be protected?'

Of the people treating you, only the investigators and nursing staff involved in the study will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your details and results that will be held securely at Menzies Research Institute Tasmania.

12. 'What happens with the results?'

If you give us your permission by signing the consent document, we plan to publish the results in peer-reviewed journals and present the findings at scientific conferences. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

13. 'What happens to my treatment when the study is finished?'

You may be able to continue with treatments following completion of this study if your doctor considers them to be of benefit to you. This decision will be made in consultation between you and your treating doctor about the most appropriate treatment for you at that time.

14. 'What should I do if I want to discuss this study further before I decide?'

When you have read this information, the researcher will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact Prof Tom Marwick on 03 6226 7703.

15. 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote [*HREC project number H0012445*].

Thank you for taking the time to consider this study.

This information sheet is for you to keep.

Appendix 11.4 Participant Consent Form

PARTICIPANT CONSENT FORM

Project Title: **Tasmanian Study of Echocardiographic detection of Left ventricular dysfunction (TAS-ELF)**

I have read and I understand the Participant Information Sheet version 1 dated 01/06/2013.

I freely agree to participate in this project according to the conditions in the Participant Information.

I will be given a copy of the Participant Information Sheet and Consent Form to keep

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

I am aware or I have been informed of the risk associated with the study.

Participant's Name (printed) ……

Signature Date

Name of Witness to Participant's Signature (printed) ……

Signature Date

Researcher's Name (printed) ……

Signature Date

Note: All parties signing the Consent Form must date their own signature.