AKERSHUS UNIVERSITY HOSPITAL

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Studies on Mechanical Dispersion by Strain Echocardiography in the General Population and among subjects with Stable Coronary Artery Disease

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«For hjertet er livet enkelt: det slår så lenge det kan. Så stopper det."

“For the heart, life is simple: it beats for as long as it can. Then it stops.”

K.O. Knausgård

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1 Preface

When I embarked upon this PhD fellowship in August 2014, I was planning the greatest expedition of my life: crossing Greenland on skies in the spring of 2015, a 600 km distance across the world's 2nd largest glacier, from the West coast to the East coast. I expected it to be both mentally and physically challenging and that I needed perseverance. The key to success for the great polar explorer Roald Amundsen, was his meticulous planning and preparation. Inspired by him, I tried to prepare in detail for every type of challenge along the way. Looking back, the real challenge and the biggest expedition of my life, turned out to be the work of this PhD. After all these years of the PhD expedition, I am probably left with a worse maximal oxygen uptake and an increase in cardiovascular risk factors than what the Greenland experience left me with. At the job interview for this fellowship, I remember that both my main supervisor, ***Helge Røsjø***, and co-supervisor, ***Kjetil Steine***, tried to warn me about the dedication and amount of work that a PhD demands. Ironically, I did not understand the meaning of their warnings, and contrary to the Greenland expedition, I started on this journey quite naive and unprepared. However, I would not have it any other way. I am happy I did not know in advance the amount of time it would take, and the challenges I encountered along the way. Especially the year spent in a dark room analyzing more than 800 echocardiography recordings, was mentally challenging and might have scared me off if I had known in advance. Upon finishing the last echocardiography analysis in July 2016, I felt like I had "reached the East coast of Greenland". However, now waited the real work. Cleaning and preparing the database. Finding out what to write about in the articles and in this thesis from the vast amount of information available from the ACE 1950 Study. And, towards the end of this expedition, trying to find time for the PhD between hectic full-time clinical work during the pandemic. I am now proud and happy to be standing by the "shore on the East coast of Greenland", and looking back, I have only good memories. I feel an enormous amount of gratitude to have been given the opportunity to pursue a PhD and to be a part of the ACE 1950 Study research team. The present work has been carried out at the Department of Cardiology, ***Akershus University Hospital*** and Institute of Clinical Medicine, ***University of Oslo***, and was supported by a grant from the ***South-Eastern Norway Regional Health Authority***.

2 Acknowledgements

My greatest role models, are my parents, ***Tone Nerdrum*** (the cardiologist) and ***Per Aagaard*** (the geologist). In many ways, this PhD has allowed me to combine their interests and expertise, with my mother's in-depth knowledge in cardiology and strain echocardiography and my father's extensive experience as a professor and a researcher. Growing up, I often heard happy stories about their time as newlyweds when they were doing their PhDs at the University of California (San Francisco and Berkley). I have been there with them on several occasions and it always gave me a thrill to take in the atmosphere of the university campus. They imprinted the idea that doing a PhD was doable and fun, which is probably what inspired me to follow in their footsteps.

I want to thank my main supervisor, Professor ***Helge Røsjø***, for eagerly welcoming me when I knocked on your office door in 2014 to inquire about the PhD fellowship you had announced. I am utmost thankful to you for giving me this opportunity, for letting me be part of the "echo group" of the ***Akershus Cardiac Examination (ACE) 1950 Study*** research team and the ***Cardiovascular Research Group***, and for the hours and effort spent to guide me through to the end of this project. I also want to express my enormous gratitude to Associate professor ***Kjetil Steine,*** for being my co-supervisor, but also for being my echocardiography mentor, both during the PhD fellowship and in the clinical work. I feel very proud and thankful to be part of your next generation of echocardiography "newbies". I would also like to thank Professor ***Torbjørn Omland***, the head of the Cardiovascular Research Group and a mentor to us all. I always listen carefully when you speak, trying to take in as much of your knowledge that I can.

The ACE 1950 Study is a major foundation of this thesis. A special thank you to the 3706 men and women who dedicated time and effort to participate in our study. To the late Professor ***Pål Smith***, you will be fondly remembered as a senior researcher and one of the founders of the study. To the research personnel keeping the "express train" of the ACE 1950 Study inclusion rolling at an incredible speed at the Akershus University Hospital: ***Marit Holmefjord Pedersen***, ***Vigdis Bakkelund***, ***Annika Lorentzen***, ***Hege Kristin Netmangen Larsen***, ***Zarina Aslam*** and all the rest, you rock! The ACE 1950 Study was a collaboration between two hospitals, and a similar nicely coordinated study inclusion was performed by the research group at ***Bærum Hospital***. I would like to thank the principal investigator Professor

Arnljot Tveit for welcoming me to the team and always being positive. Also, a special thank you to ***Trygve Berge*** who was an experienced PhD students in the "echo group" when I started. Thank you for always being helpful and kind, and for keeping the process of the echocardiography inclusion and analysis well-organized. I am also grateful to ***Steve Enger*** for your big contribution to the echocardiography process. ***Inger Ariansen*** at the Norwegian Institute of Public Health deserves a special thanks for being our connection to ***the Age 40 Program*** and for always being readily available to answer my questions.

I would also like to extend a special thank you to ***Jørgen Gravning*** for allowing me to be part of the work on the stable coronary artery patients, a study performed by excellent scientists (co-authors to Paper 3) at ***Oslo University Hospital, Rikshospitalet***.

These years would not be the same without the large group of amazing fellow students and researchers in the Cardiovascular Research Group and the ***Journal Club***. I have a special place in my heart for the ultrasound group and the time we spent together in the darkness, trying to obtain perfect images with the endless buzzing of the GE machines. **Osman Pervez**, thank you for teaching me the techniques of echocardiography, for all discussions and meaningful conversations, and for being such a great colleague and buddy. ***Brede Kvisvik***, we are yin and yang, balancing each other out both workwise and behaviour-wise. Thanks for all the years side-by-side, discussing nerdy echo issues. ***Thea Vigen***, you have brought in so much laughter, joy and meaning to my PhD life that it's hard to describe. Thanks for always welcoming me to your "psychology chair" and colloquium of life in your office. ***Eivind Bjørkan Orstad***, last but not least of the "echo group". I love working with you, both in research and clinical work. You have a special way of making patients and collegues feel calm and happy, like a combination of a beta blocker and a Cipralex.

There are many more in our research group to thank. ***Peder Myhre,*** for providing a special level of energy, knowledge and interest, ***Magnus N. Lyngbakken***, for always being available for questions, both small and more complex, especially when it comes to statistics, and ***Nina Caspersen*** for good friendship and providing music and singing into this period. ***Geeta Gulati***, we had a great time as roommates at the ESC Conference 2016 in Rome, and I appreciate the good advice and input you have given me on presentation skills. Thanks to the rest of my colleagues at "Hytta", our townhouse office: ***Julia Brox Skranes***, ***Fjola Dogg Sigurdarsdottir*** and ***Jon Brynhildsen***, you have made "Hytta" to an inspiring place to be.

Although not part of the office consortium, ***Sjur Hansen Tveit*** and ***Øyvind Johannessen,*** you have very much been part of my research family.

To my funny, intelligent, inspiring and loyal friends, you are always there for me and enrich my life: ***KK, BIC, Bodøfamilien, Therese***, ***Gunn Merete, Stine and Loreta***. Some of you have even helped me with this PhD: thank you ***Henriette Paus*** for helping me make some truly nice strain figures for my articles, thanks to ***Agathe Backer-Grøndahl*** for giving me a crash course in statistics, and to ***Yngvild Nuvin Blaker*** for guiding me through PhD life.

A special thanks to the rest of my dear family: My sister ***Ellisiv*** who is my best friend. My loyal brother ***Gunnar*** who always has my back. My brother-in-law ***Christoffer*** and sister-in-law ***Sandra***. Thanks to you all for letting me play such a big part in my nephews' and niece's life.

Roland, I saved the best for last. Thank you for engaging in the conversation at Krazy Kanguruh and for everything that has happened after. Your love and support means everything to me. This thesis is dedicated to you.

Erika Nerdrum Aagaard
Oslo, Norway, January 2023

3 Abbreviations

2CH	Two-chamber
2D	Two-dimensional
4CH	Four-chamber
A	mitral inflow peak late diastolic velocity
ACE	Akershus Cardiac Examination
APLAX	Apical long axis view
BMI	Body mass index
CAD	Coronary artery disease
cTn, hs-cTn	Cardiac troponin, high-sensitivity cardiac troponin
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
E	mitral inflow peak early diastolic velocity
e’	peak early diastolic velocity by tissue velocity imaging
ECG	Electrocardiogram
EF	Ejection fraction
GLS	Global longitudinal strain
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICC	Intraclass correlation coefficient
IQR	Interquartile range
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LV	Left ventricle/ventricular
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SCORE2	Systematic coronary risk estimation 2
SD	Standard deviation
SGLT2	Sodium glucose transporter 2
STEMI	ST-segment myocardial infarction
ULN	Upper limit of normal

4 Thesis summary

Mechanical dispersion by two-dimensional (2D) speckle tracking echocardiography is a novel method to measure left ventricular contraction heterogeneity. Increased mechanical dispersion has shown promising ability to predict outcome, specifically fatal arrhythmias and sudden cardiac death in patients with cardiomyopathies and after acute myocardial infarction (1-4). However, knowledge is still sparse on the promising echocardiography index in the general population and among patients with stable coronary artery disease (CAD), and no generally accepted reference limit has been established.

Accordingly, the overall aim of this thesis was to provide new knowledge on mechanical dispersion in subjects from the general population and among patients with stable CAD. By using data from a large Norwegian age-specific (age 62-65 years) population study, the Akershus Cardiac Examination (ACE) 1950 Study, we aimed to provide a reference value for mechanical dispersion and to investigate if mechanical dispersion associate with risk factors of cardiovascular disease (CVD). We also aimed to investigate if mechanical dispersion at age 62-65 years is associated with biomarkers reflective of subclinical myocardial injury and dysfunction. Furthermore, linking data from the ACE 1950 Study with a previous population study performed when the same subjects were 40 years old, the Age 40 Program, we aimed to examine if risk factors in early mid-life associate with increased mechanical dispersion measured two decades later. Lastly, this thesis aimed to investigate if mechanical dispersion is associated with long-term prognosis among patients with stable CAD, and how its predictive ability is compared to established biomarkers and echocardiographic indices of CVD.

We provide an upper reference limit of mechanical dispersion of 61 ms for individuals of 62-65 years old, calculated from a healthy reference population of 594 women and men. We also demonstrate in the general population that CAD and hypertension are independently associated with increased mechanical dispersion, and that the dyssynchrony index is associated with high-sensitivity cardiac troponin (hs-cTn) T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations, which are reflective of subclinical myocardial injury and dysfunction, respectively. In addition, increasing body mass index and triglyceride concentrations at age 40 were associated with increasing mechanical dispersion two decades later in analyses that adjusted for other clinical variables. Finally, among patients

with stable CAD, we also show that mechanical dispersion associate with long-term prognosis of all-cause mortality and composite endpoints, and that it has incremental prognostic value to ejection fraction, global longitudinal strain and hs-cTnI, but not to NT-proBNP.

We believe the findings of this thesis provide new and useful information on mechanical dispersion that warrants further investigation and may aid its implementation into clinical cardiology practise.

4.1 Norsk sammendrag

Mekanisk dispersjon, beregnet med ultralyd-metoden 2D speckle tracking strain, er en ny ekkokardiografisk metode for å måle eventuell heterogenitet i kontraksjonsmønsteret til hjertets venstre hovedkammer (ventrikkel). Økt mekanisk dispersjon har vist å være lovende til å forutsi utfall, særlig alvorlige ventrikulære rytmeforstyrrelser (arytmier) og plutselig hjertedød, hos selekterte pasientgrupper. Vi vet imidlertid lite om mekanisk dispersjon i den generelle befolkningen, samt hos pasienter med stabil (kronisk) koronarsykdom, og det eksisterer ingen etablert referanseverdi for den nye ekkokardiografiske markøren.

Hovedmålet for avhandlingen var å bidra til ny kunnskap om mekanisk dispersjon i den generelle befolkningen og hos pasienter med kronisk koronarsykdom. Med data fra den store norske aldersspesifikke (62-65 år) befolkningsstudien, Akershus hjerteundersøkelse 1950 (The ACE 1950 Study), var formålet å etablere en øvre referanseverdi for mekanisk dispersjon. I tillegg ønsket vi å undersøke om mekanisk dispersjon er assosiert med kjente risikofaktorer for kardiovaskulær sykdom. Vi søkte også å undersøke om mekanisk dispersjon er assosiert med biomarkører som reflekterer subklinisk myokardskade (høysensitiv troponin T) og myokard dysfunksjon (NT-proBNP). Videre brukte vi data fra 40-årsundersøkelsene, som majoriteten av deltakerne fra Akershus hjerteundersøkelse 1950 hadde deltatt på 20 år tidligere, til å se om risikofaktorer for kardiovaskulær sykdom ved 40 årsalder er assosiert med økt mekanisk dispersjon ved 62-65-årsalder. Siste arbeidet i avhandlingen undersøkte mekanisk dispersjon hos pasienter med kronisk koronarsykdom. Vi undersøkte om mekanisk dispersjon hos disse pasientene er assosiert med langtidsprognose, og hvordan markøren er som prediktor sammenliknet med etablerte biomarkører og ekkokardiografiske markører for kardiovaskulær sykdom.

Vi viser at øvre referanseverdi for mekanisk dispersjon er 61 ms for aldersgruppen 62-65 år, beregnet av en frisk referansepopulasjon på 594 kvinner og menn. Vi viser også at etablert koronarsykdom og hypertensjon er uavhengig assosiert med økt mekanisk dispersjon. I tillegg er markøren for dyssynkroni assosiert med høysensitiv troponin T- og NT-proBNP-konsentrasjon. Risikofaktorene økende kroppsmasse indeks og triglyserid-konsentrasjon ved 40 år er assosiert med økt mekanisk dispersjon mer enn 20 år senere, også etter statistisk justering for andre kliniske variabler. Hos pasienter med kronisk koronarsykdom er mekanisk dispersjon assosiert med langtidsprognose for død og kompositt endepunkt, og mekanisk dispersjon gir tilleggsverdi for risikovurdering til høysensitiv troponin I og de ekkokardiografiske markørene, ejeksjonsfraksjon og global longitudinell strain, men ikke til NT-proBNP-måling.

Funnene i avhandlingen gir ny og viktig kunnskap om mekanisk dispersjon, som kan føre til videre forskning på emnet, og implementering av mekanisk dispersjon som et klinisk verktøy innen kardiologi.

5 List of scientific papers

Paper 1

Left ventricular mechanical dispersion in a general population: Data from the Akershus Cardiac Examination 1950 Study.

Aagaard EN, Kvisvik B, Pervez MO, Lyngbakken MN, Berge T, Enger S, Orstad EB, Smith P, Omland T, Tveit A, Røsjø H, Steine K.

Eur Heart J Cardiovasc Imaging. 2020 Feb 1; 21(2):183-190.

Paper 2

Associations between cardiovascular risk factors, biomarkers and left ventricular mechanical dispersion: insights from the ACE 1950 Study.

Aagaard EN, Lyngbakken MN, Kvisvik B, Berge T, Pervez MO, Ariansen I, Tveit A, Steine K, Røsjø H, Omland T.

Eur Heart J Open. 2022 Feb 12; 12(2):oeac006.

Paper 3

Mechanical dispersion as a marker of left ventricular dysfunction and prognosis in stable coronary artery disease

Kvisvik B, Aagaard EN, Mørkrid L, Røsjø H, Lyngbakken MN, Smedsrud MK, Eek C, Bendz B, Haugaa KH, Edvardsen T, Gravning J.

Int J Cardiovasc Imaging. 2019 Jul; 35(7):1265-1275.

6 Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, and mortality rate has increased worldwide since 1990 (5). In 2015 one third of all deaths were caused by CVD. However, population aging and population growth account for most of the increase in CVD deaths globally, and the age-adjusted death-rates have declined (6). Since the 2nd World War, we have gained increasing knowledge of the development of CVD and its risk factors due to the Framingham Heart Study and other epidemiological studies (7-9). A public health focus on improved blood pressure and eating habits, smoking cessation and advances in medical and surgical treatment, have contributed to a drastic decline in CVD prevalence and deaths in high-income countries, including Norway, since the 1970s (5, 10) (Figure 1).

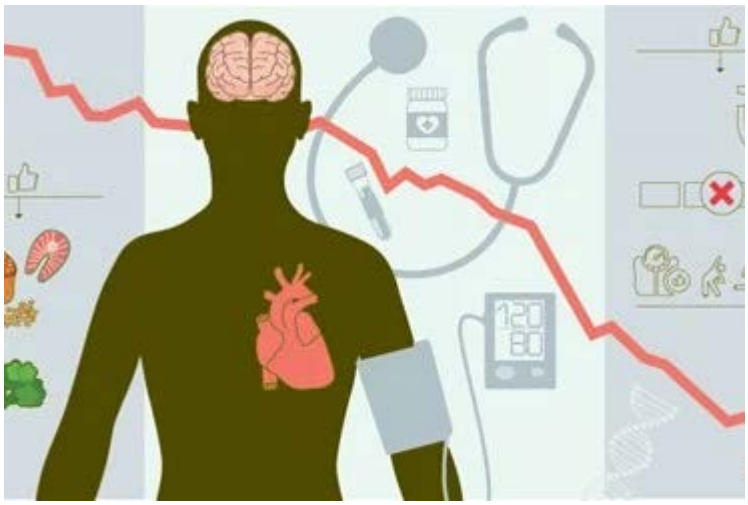

Figure 1. Since 1970 there has been a steady decrease in mortality from cardiovascular disease in Norway due to reduced smoking, improved eating habits and blood pressure control, and better treatment. Reprinted with permission from the Norwegian Public Health Institute (11).

Despite the good trends for high-income countries, there is concern because of a global increase in the prevalence of overweight and diabetes mellitus (DM), all known risk factors for CVD (12). There is also a concern that the decline in CVD and mortality seen in high-income countries is flattening out, which may be partly due to the same increase in CVD risk factors (5, 13). These trends are also found in Norway, and currently one fifth of the adult Norwegian population have established CVD or are classified as high-risk subjects for developing disease (11, 14, 15).

6.1 Framework for studies of the development of cardiovascular disease

Development and progression of disease can be considered as a continuum ranging from healthy subjects, to those with risk factors but no symptoms or physical signs of disease (subclinical disease), to overt disease (16). The American Heart Association used this framework for describing progression of heart failure (HF) in their guidelines from 2009 (17). In this model, healthy subjects with risk factors are categorized as stage A HF, while the most severely ill patients with end-stage HF refractory to conventional treatment are categorized as stage D HF (Figure 2). Subjects in stage A HF have known cardiovascular (CV) risk factors like smoking, hypertension, obesity, treatment with cardio-toxic chemotherapy, or physical inactivity, but have no evidence of CVD, also if assessed through detailed clinical phenotyping (i.e. imaging modalities like echocardiography, CT coronary angiography, etc.). Subjects with stage B HF have no symptoms, but they have objective alterations in myocardial structure or function that can be detected by detailed imaging. Hence, subjects with stage B HF are considered to suffer from subclinical disease, and it is expected that over time these subjects will develop symptoms and move to stage C HF (clinical HF) and later possibly stage D HF (refractory HF). This framework for disease development and progression can be a useful model to target prevention of HF and to guide research on improved diagnostic tools and therapy for all stages of HF. The framework is valid also for the development of other types of CVD, including coronary artery disease (CAD) and valvular heart disease. In this thesis, I have studied subjects in different disease stages, with participants from the general population, predominantly in stage A or B included in paper 1 and 2, and patients with established CAD (stage C) in paper 3.

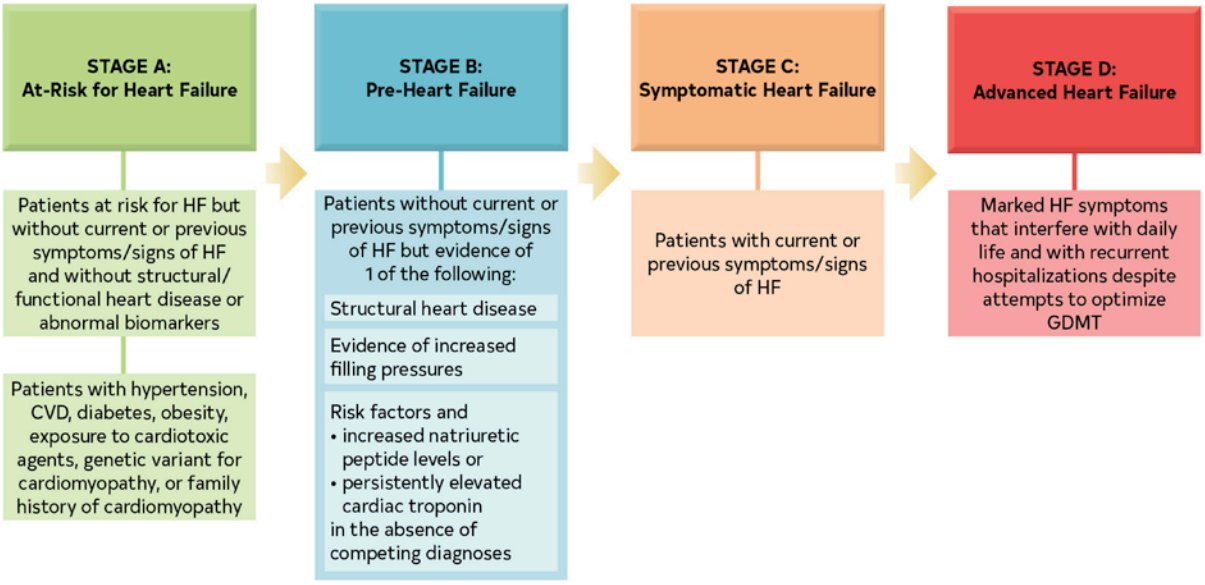

Figure 2. Stages of heart failure development by Heidenreich et al. (18). GDMT, guideline-directed medical therapy. Reprinted with permission from Elsevier. Copyright through Copyright Clearance Center's RightsLink.

6.2 Cardiovascular disease

The term CVD covers diseases of the heart and arteries, and the three main disease groups are cardiac disease, stroke and peripheral artery disease (19). Atherosclerosis is the major underlying pathophysiology in CVD, although other mechanisms such as disorders of microcirculation and myocardial fibrosis development also contribute to cardiac disease, especially to disease progression in HF (13, 20, 21). CAD is the predominate form of CVD and is often synonymous with CVD when discussing the risk of CVD in the general population. For this section, I will primarily discuss risk factors for CAD, although some risk factors overlap with other CVD, such as heart failure due to other cause than atherosclerotic disease.

6.2.1 Risk factors for cardiovascular disease

Several risk factors for the development of CVD have been established, both unmodifiable and modifiable (22, 23). Age, sex and genetic make-up are unmodifiable risk factors (22). There is an interplay among risk factors, and a subject with a positive family history for premature CAD, should be systematically examined at a young age for other risk factors for CVD. Still, regardless of assumed risk status, screening for CV risk in the general population is not recommended before the age of 40 years for men and 50 years for women (22). The

rationale for this strategy is that male and elderly subjects have higher CV risk and that prevalence of CVD in the age groups below the cutoff is very low.

The major modifiable risk factors for CVD are smoking, hypertension, obesity, DM, dyslipidemia, and sedentary lifestyle with lack of exercise (24, 25). As these risk factors are modifiable, interventions in the form of smoking cessation, dietary advice, exercise and weight loss, and pharmaceutical treatment will reduce the risk of developing CVD. It has been postulated that up to 80% of CVD are preventable by eliminating health risk behaviors (26). The 2021 European guidelines on CVD prevention in clinical practice uses the revised Systematic Coronary Risk Estimation algorithm, the SCORE2 system, which is based on a large European cohort, to estimate an individual's 10-year risk of fatal or non-fatal CVD event (myocardial infarction, stroke) (13, 27). The SCORE2 calculates risk based on age, sex, smoking status, systolic blood pressure, and non-high-density lipoprotein cholesterol (calculated as total cholesterol minus high-density lipoprotein cholesterol), and presents the risk estimates according to assumed 10-year risk for incident myocardial infarction, stroke or CVD death. The scoring system calculates different risk profiles depending on geographic differences and present scoring charts for high-, moderate- and low-risk countries. Figure 3 shows the SCORE2 chart for low-risk countries (like Norway) and the risk model illustrates the significant contribution by smoking and hypertension to CV risk. SCORE 2 is one of several risk assessment systems that have been developed and fits specifically the European population best, while a specific scoring system for Norwegian individuals (the NORRISK 2) have been developed based on data from Norway (28). It is important that the clinician assessing an individual's CVD risk uses the scoring system that best represents the individual's actual risk (29).

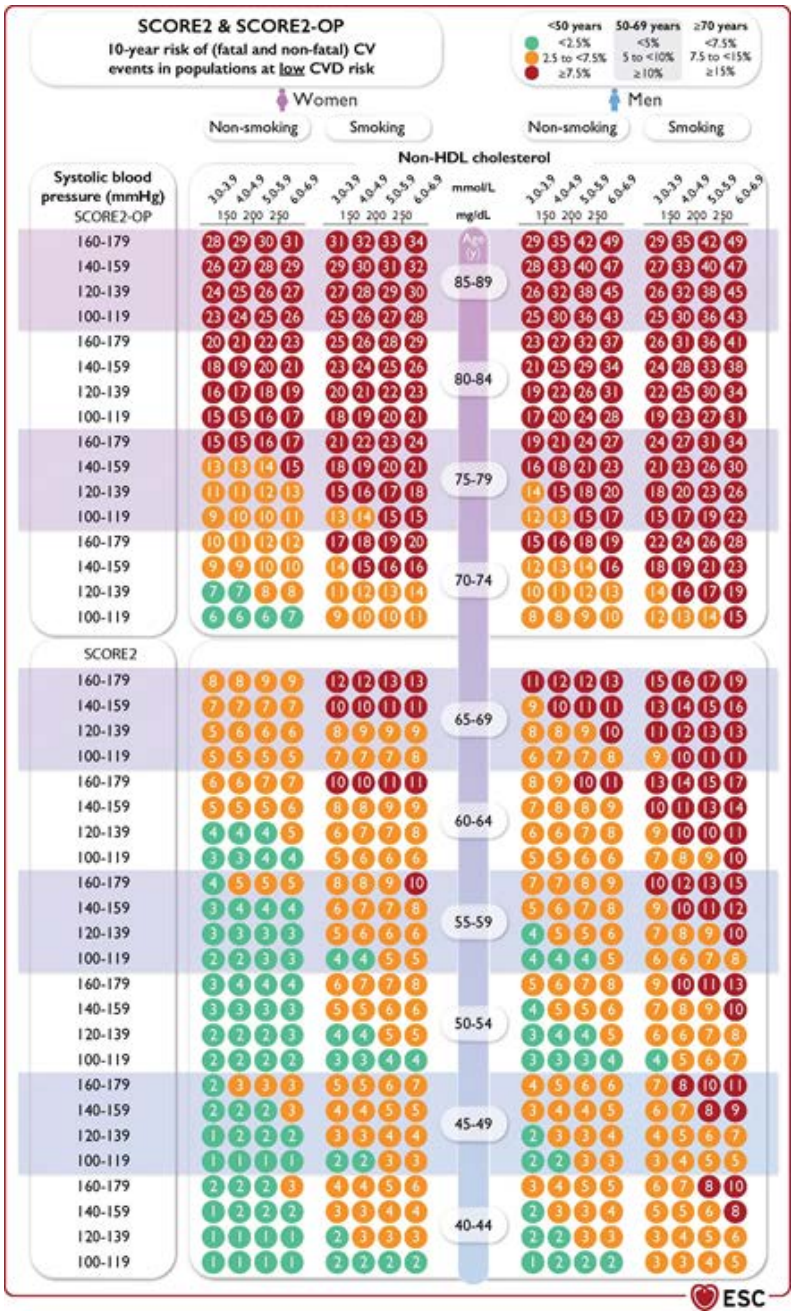

Figure 3. The SCORE2 chart: 10-year risk of fatal CVD in European low-risk countries based on: Age, sex, smoking, systolic blood pressure and total cholesterol. SCORE = Systematic Coronary Risk Estimation. Visseren et al Eur Heart J 2021 (13). Reprinted with permission from Oxford University Press and Copyright Clearance Center.

Smoking

Smoking is the risk factor contributing the most to CVD, and smoking also represents incremental risk to hypertension, dyslipidemia and DM for driving CVD progression (30). It is estimated that life-time smokers will have 10 year shorter life-span compared to non-smokers, and half of the deaths in smokers are caused by CVD (22). The mechanism whereby smoking drives CVD is mainly through atherosclerosis and the effect on destabilizing plaques

and the superimposed thrombotic phenomena (31). Due to the multitude of negative effects by smoking on CV health, smoking cessation is the most important preventive action after a myocardial infarction to prevent new myocardial infarctions or death (31, 32).

Hypertension

Systolic blood pressure is one of the variables included in the SCORE2 system, and hypertension is a principal risk factor for several types of CVDs, including CAD and HF (22). The overall prevalence of hypertension is dependent on the age group, gender, race of the cohort, and the blood pressure limits used to define hypertension (Europe mainly blood pressure >140/90 [systolic/diastolic] and the US >130/80) (33). Using current European blood pressure limits, the prevalence of hypertension globally is considered between 30-45% in the adult population (≥18 years) (34). Findings from the SPRINT trial, a hallmark randomized-controlled trial on hypertensive subjects where the treatment goal was systolic blood pressure <120 mmHg for the intensive-treatment group versus <140 mmHg in the standard-treatment group, the prevalence of acute coronary syndrome, HF, CV death and all-cause mortality were all lower in the intensive-treatment group (35). Based on this trial, US guidelines for hypertension now consider subjects with blood pressure >130/80 mmHg as suffering from hypertension, which increased the prevalence among adults in the US with hypertension from 32% to 46% (36). The European guidelines on hypertension from 2019 have maintained a higher blood pressure goal of <140/90 mmHg before hypertensive treatment should be initiated, due to higher numbers of serious adverse events like syncope, electrolyte disturbances, and kidney impairment in the intensive-treatment group of the SPRINT trial. However, in the newest European guidelines for preventive cardiology, the goal for systolic blood pressure was adjusted to <130 mmHg if tolerated (13). Accordingly, the correct blood pressure targets for starting pharmacological intervention is still debated, although the SPRINT trial provided important new knowledge of benefits also for treatment beyond the current European guidelines.

The degree of blood pressure elevation in relation to the individual's total CV risk, calculated by a validated risk model like SCORE2, should always be considered before starting drug treatment for hypertension (22). End-stage organ damage by hypertension, like left ventricular (LV) hypertrophy and renal impairment are independent risk factors for CVD, and assessment with echocardiography may be considered, although is currently not recommended routinely as it does not change risk evaluation. Whether the patient receives pharmacological intervention or not, the treating physician should motivate and monitor life-

style interventions with more physical activity and encourage weight loss and reduction in intake of salt and alcohol (if excessive) (37). Regular monitoring of blood pressure status is mandatory, and physicians should target additional CV risk factors, including assessing smoking status and encouraging and supporting smoking cessation.

Dyslipidemia

The role of hypercholesterolemia as a CVD risk factor is well-documented, and increased levels of plasma low-density lipoprotein cholesterol are causally linked to the development of fatty streaks and atherosclerotic plaques in the vessel wall, which is the first manifestations of atherosclerosis (38). It is also well-known that reducing lipid concentrations, and especially low-density lipoprotein cholesterol concentrations, is associated with favorable clinical outcomes for CVD. Pertinent to this point, the overall reduction of cholesterol concentrations on the population level, together with smoking cessation and more intensive blood pressure treatment, are the most important factors that over the last decades have reduced CV morbidity and mortality in high-income countries (39, 40). As for hypertension, the decision to start pharmacological therapy in subjects without known CAD, depends on the total CV risk, which should be calculated by risk models like SCORE2.

Potential causes for secondary hyperlipidemia like hypothyroidism, alcohol abuse, and Cushing's disease should always be considered. It is imperative to start early high-dose treatment with statins (primary prevention) in subjects with clear evidence or suspicion of genetic causes for lipid elevation, like familial hypercholesterolemia, as these subjects have especially increased risk of CAD, also at a young age. Familial hypercholesterolemia should be suspected in subjects with extremely abnormal lipid levels or a high number of family members with premature atherosclerotic heart disease (39).

Obesity and diabetes mellitus

Both obesity and DM are important modifiable risk factors for CVD. The most commonly used measure to define obesity is body mass index (BMI), calculated as (mass [kg])/(height [m])^2. Using BMI as the index, overweight is defined as BMI $\geq$25 kg/m^2 and obesity as BMI $\geq$30 kg/m^2 (22). Obesity is becoming a large health issue worldwide, and the increasing prevalence of obesity could counter-act the positive effects seen from smoking cessation and the reduction in blood pressure and cholesterol levels on CV risk (12, 41). Increasing BMI also has direct negative effects on blood pressure, lipids and glucose tolerance, and obesity is closely linked to type 2 DM (42). Obesity causes insulin resistance due to excess circulating glucose, which then leads to type 2 DM (43, 44). The risk of CVD is doubled in subjects with

DM, and both the prevalence and severity of CAD and HF are increased in subjects with DM compared to non-diabetic, age- and gender-matched subjects, which subsequently increases mortality for subjects with DM compared to subjects without DM (45, 46). Weight control and regular physical activity should be part of the treatment of DM to improve glycemic control and reduce CVD morbidity and mortality (22). Recent findings from large randomized-controlled trials on a new type of antidiabetic medication, sodium-glucose transporter 2 (SGLT2) inhibitor, revealed a reduction in CVD, and especially HF hospitalizations, in patients with DM who were treated with SGLT2 inhibitors (47-49). This led to the hypothesis that SGLT2 inhibitors could be beneficial as a pure HF medication, also in patients without DM. Several randomized-controlled trials were initiated where HF patients without DM were treated with either SGLT2 inhibitor or placebo in addition to optimal medical treatment. The results showed a 26 % reduction in CV death or worsening of HF for dapagliflozin versus placebo, and a 25% reduction in CV death or HF hospitalization for empagliflozin versus placebo (50, 51). Due to these findings, SGLT2 inhibitors were added to the standard HF treatment in the latest international HF guidelines (52). The prevalence of both obesity and type 2 DM is increasing, and recent estimates in Europe indicate that 53% and 6.9% are considered to suffer from obesity and type 2 DM, respectively (53).

6.2.2 Coronary artery disease

Atherosclerosis is a disease of the arteries caused by several factors, the main modifiable risk factors being smoking, hypertension, and hyperlipidemia. Over time these risk factors leads to deposition of lipids in the vessel wall that may progress to atheromas, calcification and obstructive plaque formation in the wall of the arteries (Figure 4) (54). Progressive atherosclerosis in the coronary arteries, which supply the myocardium with oxygen and nutrients, can over time lead to symptoms and the patient will then receive a diagnosis of CAD. In patients with chronic coronary syndrome, previously referred to as stable CAD, there are relatively stable obstructive plaques that lead to chest discomfort in situations of increased myocardial oxygen consumption (i.e. during physical activity) due to mismatch between myocardial oxygen availability and myocardial oxygen requirement. In contrast, acute coronary syndrome is characterized by an acute plaque rupture or hemorrhage, which induces an unstable situation that progresses to acute myocardial infarction when there is evidence of subsequent tissue necrosis due to reduced blood flow to the myocardium. CAD and prior myocardial infarctions are important factors for development of HF in a large number of patients (52). CAD is common, and around 10 000 patients were treated for myocardial

infarctions in Norwegian hospitals in 2020 (11). The prognosis of myocardial infarction has improved markedly in Norway during the last two decades due to a combination of factors: a reduction in the prevalence of CVD risk factors (smoking, cholesterol and hypertension), earlier and better detection of myocardial infarction, improvement in treatment with early percutaneous coronary angiography and angioplasty, and the introduction of new drugs (11, 14).

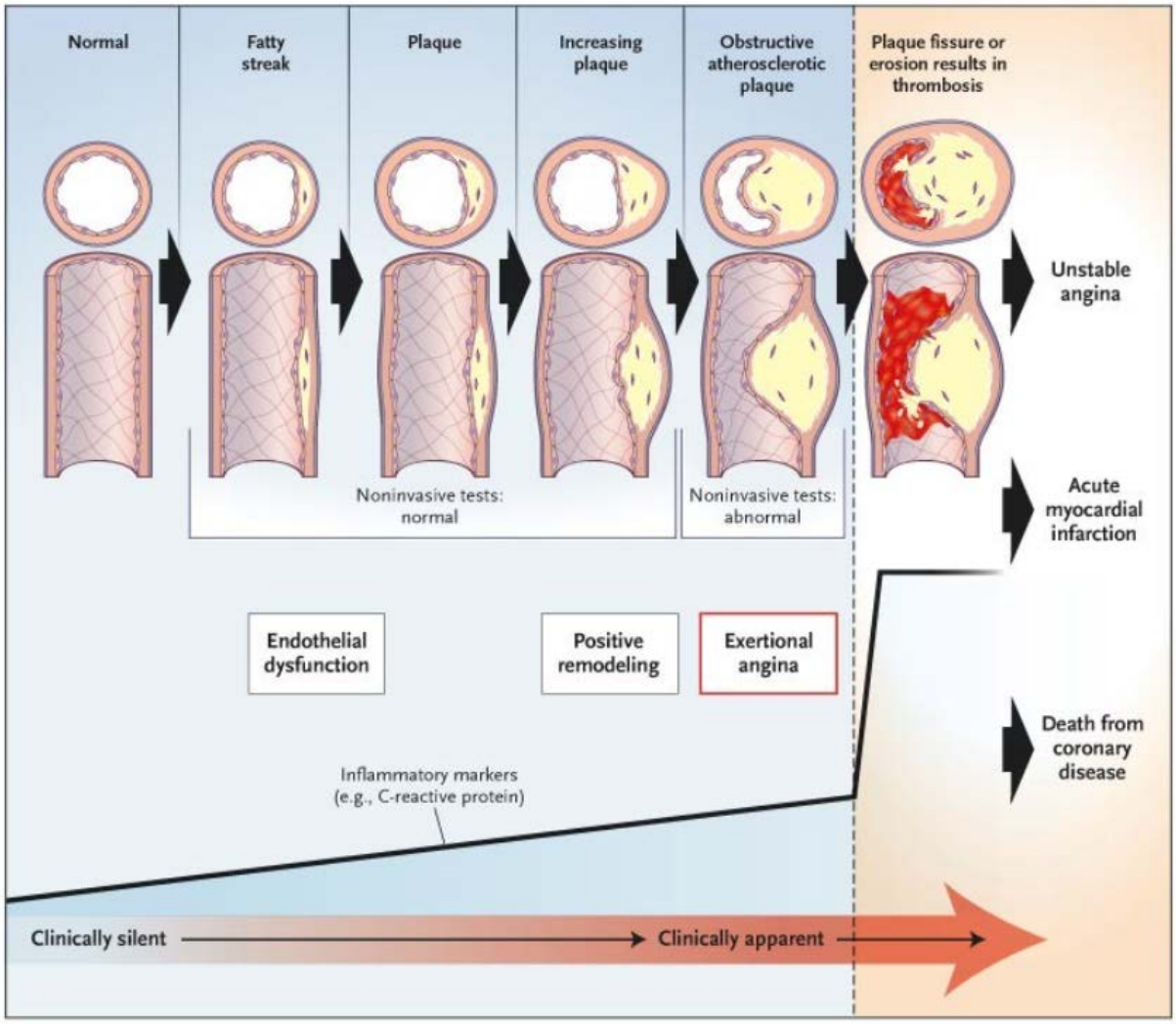

Figure 4. Illustration of the development of coronary atherosclerosis by Abrams N Eng J Med 2005 (20), Reprinted with permission of Massachusetts Medical Society.

6.3 Heart failure

Two main components are needed in a healthy heart to maintain adequate function: the ability of the heart to pump blood from the ventricles, referred to as systolic function, and the ability of the heart to relax in order to be filled with new blood, known as diastolic function. HF is a clinical syndrome causing typical symptoms like breathlessness, ankle swelling and fatigue, and may be accompanied by clinical signs such as elevated jugular venous pressure, pulmonary crackles, and peripheral edema (52). HF can be divided into right- and left-sided HF. Most patients suffer from LV HF, which is caused by reduced cardiac output (systolic dysfunction) and/or elevated intra-cardiac pressure (diastolic dysfunction) (52). Functional changes of the LV, for example after myocardial infarction, may lead to reduced ejection fraction (EF) and inability to pump out the required oxygenated blood to the body. This is called HF with reduced EF (HFrEF; LV EF ≤40%) or HF with mildly reduced EF (HFmrEF; LV EF 41-49%) and results in fatigue, dyspnea, dizziness and asthenia. Structural changes of the myocardium, such as LV hypertrophy and fibrosis following inadequate antihypertensive treatment or aortic stenosis, cause myocardial stiffness and a decrease in LV compliance. This can result in high intra-cardiac pressure, since the LV only can be filled adequately by an increase of atrial and LV filling pressure. Such a clinical condition, which includes an apparently normal LV systolic function, as assessed by ejection fraction, is referred to as HF with preserved EF (HFpEF; LV EF >50%). A rise in filling pressures of the left side causes a passive increase of pressures in the veins coming from the lung to the LV, which again may cause pulmonary congestion and dyspnea. Furthermore, a passive rise in the pulmonary artery pressure (secondary pulmonary hypertension) may occur, resulting in edema of lower extremities, ascites and increased jugular venous pressure.

The prevalence of HF in developed countries is 1-2 %, and increases with age (55). CAD, genetic disorders, hypertension, DM, arrhythmias and valvular pathologies are common causes of HF (55). HF has a dismal prognosis with a mortality rate equal to many types of cancer (56). Fortunately, the development of novel HF therapy, in particular for HFrEF and HFmrEF, during the last 25 years has reduced morbidity and mortality (57, 58). Historically, HF on the left side of the heart has been categorized into groups according to EF, because most clinical trials have included patients based on reduced EF (55). The intermediate group, HFmrEF was introduced in the HF guidelines of 2016 to encourage specific research on this grey area group and to improve treatment algorithm (55). While HFrEF is synonymous with HF with reduced LV systolic function, HFpEF is mainly a problem with increased LV filling

pressure, where LV systolic function is normal or mildly reduced. HFpEF is a syndrome composed of a heterogeneous group of patients, who often are elderly, female, obese, and suffers from DM, hypertension and/or atrial fibrillation (59, 60). Data regarding the prevalence of HFpEF compared to HFrEF are conflicting. Some studies have reported an almost equal distribution of the two main HF subtypes, while other studies have reported a much lower prevalence of HFpEF compared to HFrEF (61-65). According to the newest HF guidelines, there has been a belief that the prognosis is better for HFpEF than HFrEF (52). This notion is supported by data from the large MAGGIC meta-analysis that showed a lower mortality rate for HFpEF than HFrEF (62). However, other observational studies have shown no difference in mortality for those with HFpEF compared to HFrEF (56, 63). Four main types of medication reduce mortality and morbidity in patients with HFrEF, and these drugs should be implemented in all patients with HFrEF: beta blockers, angiotensin converting enzyme inhibitor or angiotensin receptor/neprilysin inhibitor, aldosterone antagonists, and SGLT2 inhibitors (52). No specific randomized controlled trials have been performed on HFmrEF patients. However, the current guidelines recommend the clinician to consider treating HFmrEF patients with the same four main types of medication which are recommended for HFrEF patients (52). Until recently, only therapies in patients with HFrEF demonstrated to reduce mortality. Despite several attempts to target treatment specifically towards HFpEF, none of the large randomized-controlled HFpEF trials, reached their primary endpoints (66-70). However, some of the studies met secondary endpoints, including that HF hospitalizations were reduced for patients receiving spironolactone in the TOPCAT trial (67) and patients receiving candesartan in the CHARM-Preserved trial (66). There was also a clear trend towards reduced HF hospitalizations for sacubitril/valsartan in the PARAGON-HF trial, although the study narrowly missed the primary endpoint (70). However, the DELIVER trial, demonstrated recently that SGLT2 inhibitor reduces the risk of CV death or worsening HF also for patients with HFmrEF and HFpEF (71). Many patients with HFpEF have comorbidities like hypertension, CAD, DM and/or atrial fibrillation, and treatment should also target these underlying conditions, including by the use of HF medications such as angiotensin converting enzyme inhibitors, angiotensin II inhibitors, beta blockers, aldosterone inhibitors and SGLT2 inhibitors (52).

6.4 Echocardiography

The first moving image of the heart by ultrasound was an M-mode image recorded in 1953 by the two Swedish inventors of echocardiography, Edler and Hertz (72). The invention was driven forward by the need for better preoperative assessment of mitral valve stenosis, and has been called “one of the truly groundbreaking and remarkable innovations of the 20th century” (72). Today echocardiography is widely used in clinical work and cardiac research, and it offers an easy accessible and noninvasive real-time imaging of the heart. The traditional modalities used are M-mode, 2-dimensional (2D) echocardiography and Doppler imaging (73, 74). These conventional modalities allow us to assess cardiac chamber dimensions and function, hemodynamics, valvular pathology and pericardial fluid. The echocardiography methods are constantly evolving, and during the last two decades, three-dimensional echocardiography and strain by speckle tracking imaging have been developed and implemented in clinical cardiology, which further have improved cardiac assessment (75, 76).

Several echocardiographic methods have been developed to assess systolic and diastolic function of the LV. The systole begins when the pressure in the LV becomes higher than in the left atrium, which causes the mitral valve to close and the aortic valve to open. The systole ends after LV has pumped out blood through the aortic valve, and the intraventricular pressure subsequently falls, leading to closure of the aortic valve (Figure 5) (77). The diastole is the time between the aortic valve closure and the mitral valve closure when the LV wall relaxes, the transmitral pressure gradient increases and allows for the filling of blood to the LV from the left atrium.

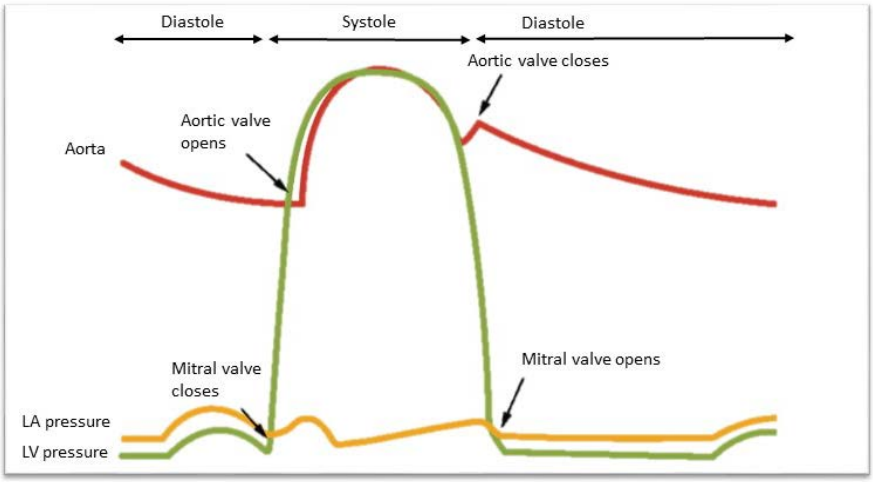

Figure 5. Pressure curves of the left ventricle (LV), left atrium (LA) and aorta during the systole and diastole, and its relation to the aortic- and mitral valve opening and closure.

Understanding the architecture and movements of the LV is essential to understand the various echocardiographic indices for systolic assessment and their strengths and limitations. The muscular fibers of the heart are arranged in an intricate fashion, and the exact details of the architecture has been studied for centuries (78). Three muscular layers make up the main components: The superficial (subepicardial) layer has muscle fibers oriented in a longitudinal and oblique direction in the LV depending on the location in the LV, and continues across the right ventricle in a circular direction. The thicker middle layer (myocardium) of the LV has muscle fibers oriented in a circular fashion mainly around the base of the LV and is not present towards the apex of the LV. The muscle fibers of the inner (subendocardial) layer run longitudinally where they support the origin of the papillary muscles, while the fibers cross more obliquely when they are deeper and between the trabeculae (77). Both the subepicardial and the subendocardial muscle fibers create a vortex at the apex of the LV and right ventricle. This complex alinement of the muscle fibers of the heart (Figure 6) facilitates the contraction of the LV in several directions: Longitudinal contraction from base to a more stationary apex, circumferential contraction with thickening of the myocardium towards the LV cavity, and a twisting motion both counter-clockwise and clockwise (77, 79).

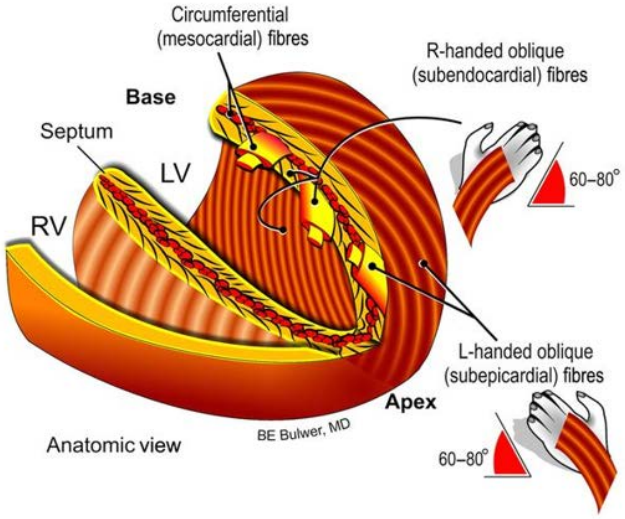

Figure 6. Illustration of myocardial fiber orientation with the subepicardial and subendocardial fibres oriented in opposing oblique directions, and the mid-myocardial muscle fibers oriented in a circumferential direction. Cikes et al. Eur Heart J 2016 (79). Reprinted with permission from Oxford University Press and Copyright Clearance Center.

6.4.1 LV ejection fraction

The most common way to assess systolic function is by LV EF, a method developed during the 1950s to the 1970s that measures the fraction of blood volume pumped out of the LV during systole (80, 81). EF is calculated as follows:

$$EF = \frac{(\text{end-diastolic volume} - \text{end-systolic volume})}{\text{end-diastolic volume}} \times 100$$

The volumes are measured by tracing of the LV endocardial border at end-diastole (the largest LV volume during the cardiac cycle) and end-systole (smallest volume) in apical four-chamber (4CH) and two-chamber (2CH) views (Figure 7). In order to calculate volumes from 2D area measurements and to adjust for the elliptical shape of the ventricular lumen, the biplane method of disks summation was developed (known as the modified Simpson's biplane method) (73). A reduced EF below 40% is a robust prognostic factor and has been a key inclusion criterion for the large therapeutic HF trials (79). Based on results from these trials, HF guidelines advice on treatment dependent on the EF value (52). This makes EF solidly implemented in clinical cardiologic assessment worldwide. However, there are many limitations to this widely used marker of LV function: EF is not a direct measure of myocardial function, but rather of the volumetric change in the LV, and is highly dependent on heart rate, preload and afterload (82). It is important to take into account that the calculation of LV volume size by this method is based on the assumption of geometrical volumes based on acquisition of only two 2D LV area (not volume) planes, and that this volume assumption does not directly reflect what is going on in the LV myocardium. A subject with reduced LV myocardial function can still have a normal EF as long as the ratio of the volumes remains the same (83). I.e. a small woman with a small LV cavity and hypertrophic myocardium, may present with a normal EF although the actual stroke volume and systolic function is reduced. Furthermore, an EF measurement does not reflect contraction disturbances like dyssynchrony or regional hypokinesis, which is of importance in the assessment of LV function (83). Thus, LV contraction is more complex than what a single EF measurement reflects. Finally, the inter-observer variability of EF estimation is high, of more than 10% (84, 85). All in all, EF by 2D echocardiography therefore seems to function best as a marker of more pronounced global LV systolic dysfunction and has well-established prognostic value below 40-45% (86). However, it is often insufficiently sensitive to identify

mild and moderate reduction in LV systolic function, and is not a good prognostic marker when within normal or only slightly reduced values (86). In the evaluation of patients undergoing cardio-toxic chemotherapy, 2D EF is therefore no longer recommended as the first choice to examine for subtle myocardial injury (87).

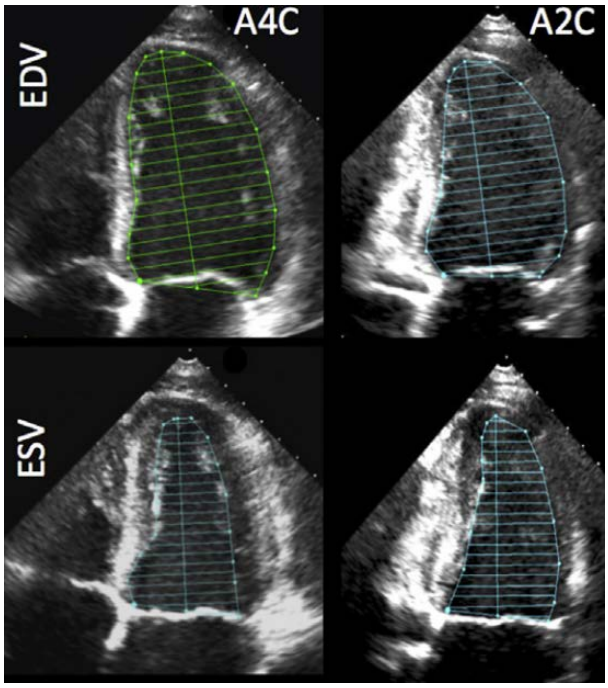

Figure 7. Measurement of the end-diastolic (ED) area plane (volume) and end-systolic (ES) area plane (volume) is performed by tracing the blood-tissue interface in apical 4CH and 2CH views (referred to as A4C and A2C in figure) in order to calculate EF. The volumes are calculated by the summation of disks method. Lang et al. Eur Heart J Cardiovasc Imaging (73). Reprinted with permission from Oxford University Press and Copyright Clearance Center.

6.4.2 Myocardial strain

Due to the limitations of EF, myocardial strain has been developed during the last decades as a direct way of measuring myocardial contraction and systolic function (88). Strain, synonymous with deformation in the echocardiographic setting, is a measure of the deformation of the myocardium during contraction and is reported as the percentage change (lengthening or shortening) of the myocardium (89). The heart is a three dimensional structure, and the deformation of the myocardium during contraction can be measured in three directions: Longitudinal, circumferential (both shortening) and radial (increase in length/thickness) (Figure 8).

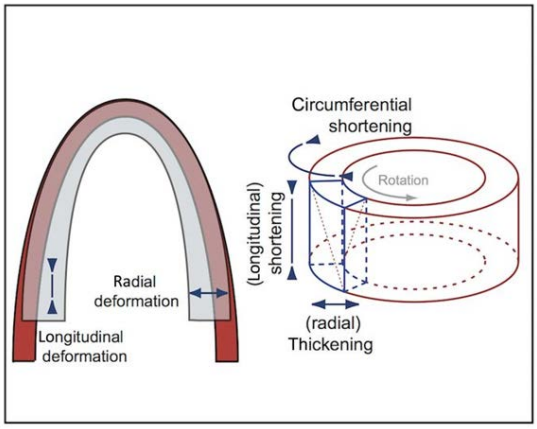

Figure 8. *Left:* Red shape is the myocardium before contraction, grey shape is the myocardium during contraction. *Right:* Longitudinal, circumferential and radial deformation during contraction. Cikes et al. Eur Heart J 2016 (79). Reprinted with permission from Oxford University Press and Copyright Clearance Center.

The first methods to measure strain were by M-mode and tissue Doppler imaging, however, none of the methods were widely used in clinical cardiology and had limitations (90). In contrast, strain using 2D speckle tracking imaging has been refined to permit strain measurements in clinical practice. 2D speckle tracking imaging is a method where the software selects "natural acoustic markers moving with the tissue" in 2D recordings and tracks these natural markers (speckles) frame-by-frame through the cardiac cycle (91, 92) (Figure 9).

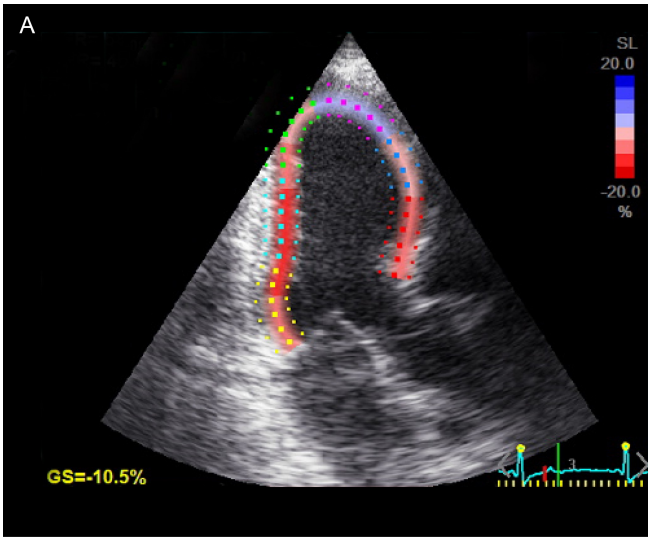

Figure 9. Apical long-axis view with speckles (colored dots) marking grey-scale speckles in the myocardium. The speckles follow the movement of the myocardium through a cardiac cycle. The yellow marks on peak R in the ECG (right bottom corner) define the start and end of the cardiac cycle. Each color of the speckles represents the different strain segments. Aagaard et al. Eur Heart J Open (93). Copyright by the Authors.

The most established way to assess speckle tracking imaging strain is by global longitudinal strain (GLS) (partly shown in Figure 9), which measures the deformation of the myocardium mostly in the longitudinal direction in three apical views (apical long axis view [APLAX], 4CH and 2CH). In this way, GLS better quantitates cardiac wall motion than EF measurements by the Simpson's biplane method (73, 94). Since the first articles on strain by speckle tracking imaging were published in 2002 and 2004, the method has been validated and studied in a wide range of cardiac and systemic illnesses (95-99). Studies have shown GLS to be an overall better predictor of mortality and major adverse cardiac events than EF (96, 98), but implementation into clinical cardiac practice has been slower than originally expected. GLS is more sensitive to changes in LV systolic function, and can detect subtle LV dysfunction (stage B HF) when EF is within normal range (83). A reason for its earlier detection of LV systolic dysfunction, is that GLS mainly reflects the longitudinal muscle fibers of the endocardium, which are more susceptible to damage than the circumferential myocardial layer that EF primarily reflects (83). GLS can also detect subclinical LV dysfunction among patients with DM and hypertension, where reduced GLS predicts a worse prognosis (100, 101). Due to its ability to detect subtle myocardial dysfunction, GLS is now well-implemented in cardio-oncology and the cardiac assessment of chemo-toxicity during cancer treatment (87, 102, 103). The limitations of GLS is primarily related to the good image quality required to obtain GLS measurements, which affects the feasibility. There were concerns regarding the reproducibility among different vendors, and recommendations were established to standardize strain imaging to reduce the variability (94, 104). A study by the Task Force to standardize deformation imaging showed good reproducibility of GLS measurements (105).

6.4.3 LV mechanical dispersion

Mechanical dispersion is a method, based on GLS measurements, to objectively assess the synchronism of the LV contraction pattern (2, 106). GLS is the average strain from APLAX, 4CH and 2CH, and the ventricular wall in each view is divided into several strain segments (Figure 10). The myocardial deformation of each LV segment during contraction yields a strain curve, where peak negative strain is the maximal contraction or deformation of the segment, and time from Q/R on the electrocardiogram (ECG) to peak negative strain is the contraction duration. If the LV segments contract synchronously, the peak negative strain of all segments will occur at approximately the same time in the cardiac cycle (Figure 10, left).

On the other hand, a dyssynchronous contraction results in peak negative strain of the different LV segments occurring more dispersed throughout the cardiac cycle (Figure 10, right).

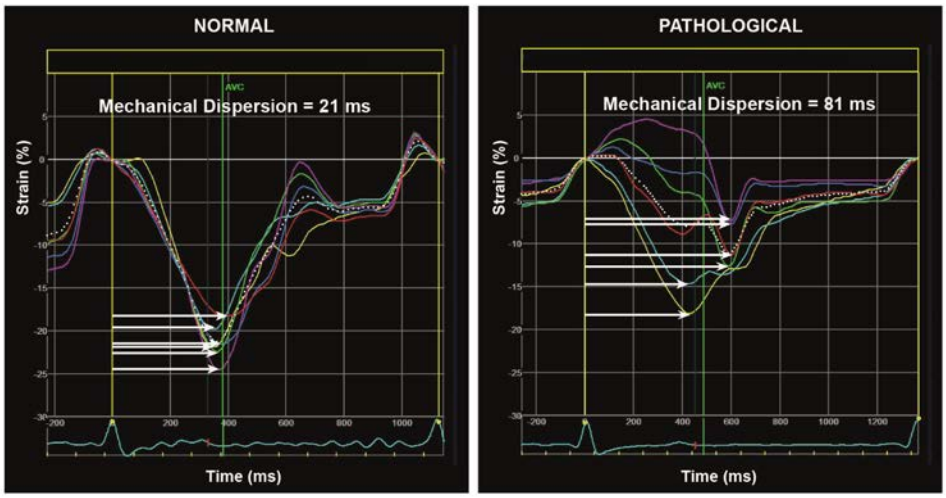

Figure 10. Example of strain curves with normal (left) and pathological (right) mechanical dispersion. The strain curves are from one apical view. White horizontal arrows show the contraction time (peak negative strain). AVC, aortic valve closure. Aagaard et al Eur Heart J Cardiovasc Imaging (107). Reprinted with permission from Oxford University Press and Copyright Clearance Center.

Mechanical dispersion is defined as the standard deviation (SD) of the contraction time of all strain segments, also if peak negative strain occurs after the end of systole (aortic valve closure). This novel dyssynchrony index has been proven associated with ventricular arrhythmias and sudden cardiac death in several specific cardiac diseases and a recent meta-analysis found that mechanical dispersion of 60 ms is an appropriate cutoff value for predicting arrhythmic events (1). Among patients with non-ischemic dilated cardiomyopathy, hypertrophic cardiomyopathy, and after acute myocardial infarction, mechanical dispersion was higher among subjects who experienced ventricular arrhythmias compared to those without any event (2, 99, 108). The same studies showed that mechanical dispersion was a strong and independent predictor of ventricular arrhythmic events, and superior to EF. Sudden cardiac death is often the first symptom of ventricular arrhythmias, and prediction of who is in need of an implantable cardioverter-defibrillator as a primary prevention is challenging (109). Currently, EF $\leq$ 35% is the only criterion assisting in the decision making for implantable cardioverter-defibrillator as a primary prevention (class 1A indication) (110, 111). However, many subjects with EF $\leq$ 35% will never experience ventricular arrhythmias during their lifetime, and most subjects who suffer from sudden cardiac death have a better EF than 35%

(112). Mechanical dispersion may therefore be a promising index for improving the identification of subjects at risk of ventricular arrhythmias and sudden cardiac death. While we currently have increasing evidence of the predictive abilities of mechanical dispersion in cardiac-specific diseases, less is known about mechanical dispersion in the general population. Upon commencing this thesis, there was no established reference value for mechanical dispersion and no information on its predictive value in the general population. A recent Danish population study has found that mechanical dispersion is associated with CV death, but not with non-CV death among a general population of Copenhagen city (113). However, they did not have specific information regarding sudden cardiac death, and further studies are needed to know whether the echocardiography index can be used to predict sudden cardiac death in subjects from the general population.

6.5 Circulating cardiac biomarkers

Circulating biomarkers are of immense importance in CV research and clinical practice as they provide information on physiological and pathological processes, can be used to assess the response to pharmacological interventions, and are easily accessible, affordable and noninvasive strategies for frequent follow-up of patients (114). The most established cardiac biomarkers are cardiac troponins (cTn), which reflect myocardial injury, and natriuretic peptides which are released in response to myocardial stretch (115).

6.5.1 Cardiac troponins

Troponin is a protein complex of three subunits (troponin C, I and T) which is part of the contractile apparatus in skeletal and cardiac muscle cells (Figure 11) (116). Cardiac troponins (cTn) are specific isotopes that are only found in cardiac myocytes and not in skeletal muscles. While the isotopes cTnC and skeletal TnC are identical and cannot be distinguished from each other, cTnI and cTnT are only found in cardiac myocytes and differ genetically and immunologically from their respected skeletal isotopes. Thus, elevated concentrations of cTnI and cTnT can be detected in peripheral blood in the case of myocardial injury, and have been a main part of the diagnostic work-up of acute myocardial infarction, heart failure and cardiac diseases since they were introduced around the new millennium (117-120).

Assays with increasing sensitivity for detection of cTn have been further developed during the last two decades (Figure 12). The high-sensitivity assays for cardiac troponins (hs-cTn), also known as the fifth generation assays, enable both early detection of hs-cTnI and hs-

cTnT release, and detection at 10- to 100-fold lower concentrations than with the previous assays (121-123). While the previous generations of assays detected troponin concentrations above the diagnostic threshold for acute myocardial infarction (99th percentile), the high-sensitivity assays detect troponin concentrations among a large proportion of healthy individuals (124). The hs-cTnI and T are now widely implemented in clinical practice in Europe and the US, and has improved rule-in and rule-out diagnostic strategies in suspected acute myocardial infarction (121, 122, 125). In the general population, hs-cTns are strongly associated with a poor outcome, and may be a marker of subclinical myocardial injury (126-129).

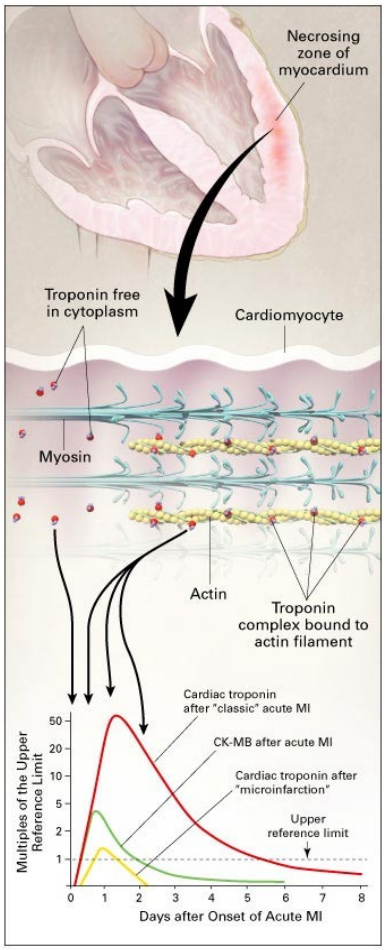

Figure 11. Troponins are part of the contractile apparatus in the cardiac myocyte, and the majority is bound to the myofilament except for a small amount which is found free in the cytoplasm/cytosol. The illustration also shows release of troponins in response to necrosis. Reproduced with permission from Antmann et al. N Engl J Med 2002 (130). Copyright Massachusetts Medical Society.

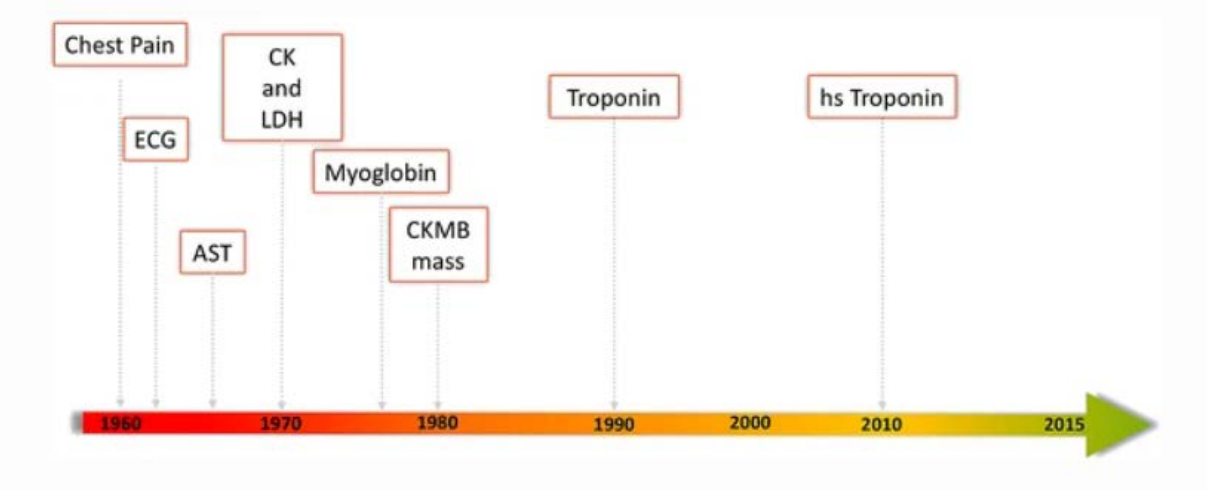

Figure 12. Timeline of biomarkers used for the purpose of diagnosing acute myocardial infarction. The discovery and implementation of troponin in clinical cardiology was pivotal. Reprinted with permission from Garg et al. Intern Emerg Med (http://creativecommons.org/licenses/by/4.0/) (123).

6.5.2 B-type natriuretic peptides

Natriuretic peptides are a group of hormones that are produced and released from the myocardium into the bloodstream during myocardial stretch, including volume overload and increased tension in the walls of the heart (atrium and ventricle) (131). They were discovered in the 1980s, and as the name implies, the peptides lead to natriuresis that cause a decrease in the plasma volume and reduced blood pressure that further reduce cardiac wall stress (132). There are several natriuretic peptides, but only the B-type natriuretic peptide (BNP) will be described here. The prohormone of BNP (proBNP) is primarily released by the ventricles, but there is also some release from atrial tissue (133). A small amount of proBNP is stored free (in granules) in the cytosol, and the release of proBNP in response to stimulus is largely dependent on upregulation of genetic expression, which occurs rather quickly. In the case of chronic stretch of the myocardium due to chronic heart failure, there is an upregulation of the gene expression (134). ProBNP is further enzymatically cleaved into two fragments, the active part of the peptide, BNP, and the inactive part, N-terminal-proBNP (NT-proBNP) (135) (Figure 13).

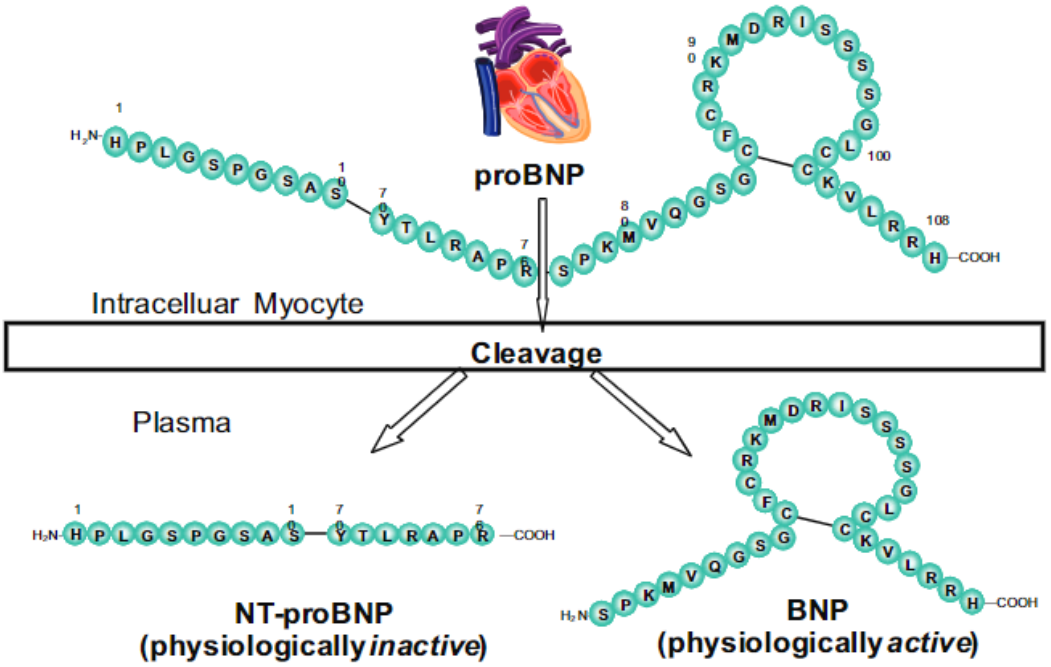

Figure 13. Illustration by Omland, Crit Care Med. 2008 (135), of the cleavage of prohormone proBNP into BNP (the biologically active fragment) and NT-proBNP (the inactive fragment). Reprinted with permission from Wolters Kluwer Health, Inc and Copyright Clearance Center.

BNP, as the active hormone, acts through several mechanisms: BNP reduces plasma volume by increasing diuresis and natriuresis. BNP also reduces blood pressure by inhibiting the renin-angiotensin-aldosterone system and the sympathetic nervous system, and by inducing peripheral vasodilatation. Furthermore, BNP reduces myocardial fibrosis and hypertrophy by inhibiting cardiac and vascular myocyte growth (132, 133). Figure 14 displays the actions of BNP and the organs influenced by BNP.

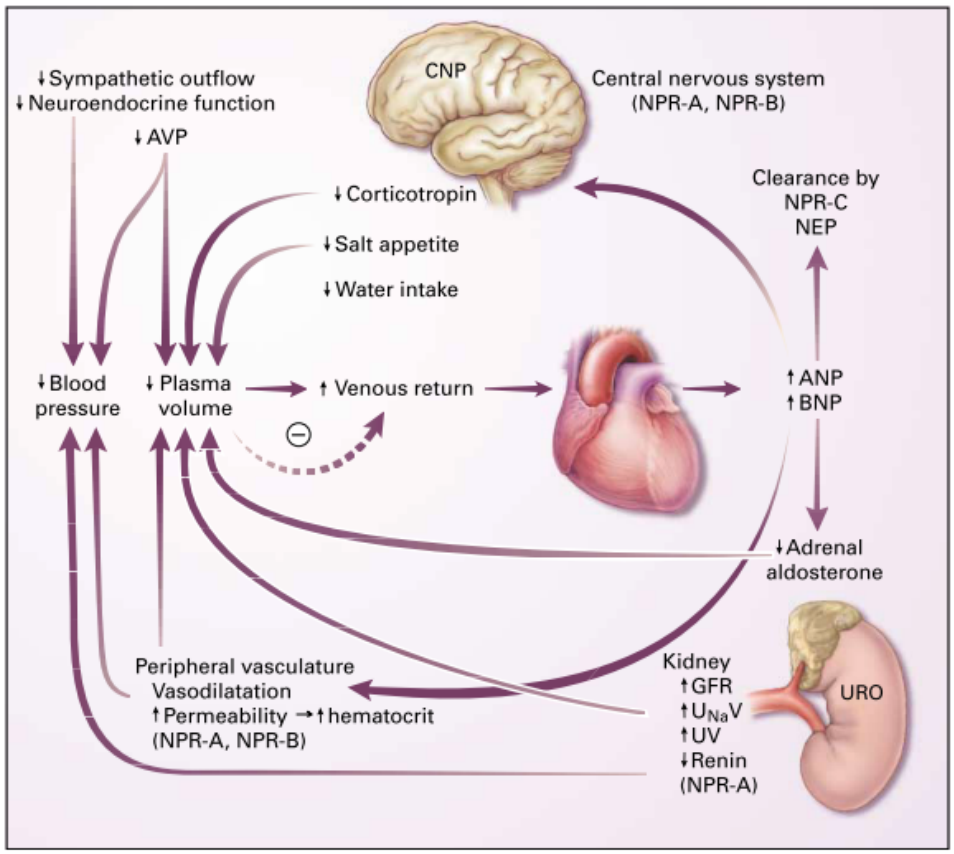

Figure 14. Physiologic effects of natriuretic peptides in response to stimulus/increased venous return to the heart. Reproduced with permission from Levin et al. N Engl J Med 1998 (132). Copyright Massachusetts Medical Society.

The concentration levels of both BNP and NT-proBNP can be measured in peripheral blood and are well-known biomarkers of heart failure (52). Elevated levels of natriuretic peptides are increased in congestive heart failure and are associated with increasing ventricular dysfunction, elevated cardiac filling pressures and arrhythmias (136, 137). Furthermore, circulating concentrations of NT-proBNP are strongly associated with CV disease and death in the general population, also at levels below the threshold for diagnosing heart failure (138, 139). The different natriuretic peptides and their ability to detect LV dysfunction have been studied in several general population cohorts with diverging results (140, 141). However, both BNP and NT-proBNP can detect LV dysfunction to some degree, and their predictive ability improves with increasing ventricular dysfunction and with the presence of symptomatic heart failure (142-145).

7 Thesis Aims

7.1 General aim

The general aim of this thesis was to provide new information related to the novel echocardiographic method, mechanical dispersion by 2D speckle tracking imaging, both in the general population and in a population of patients with stable CAD.

7.2 Main research questions

- Paper 1: In a general middle-aged population, what is the reference value for mechanical dispersion, and does mechanical dispersion associate with risk factors for CVD?
- Paper 2: In a general population, is mechanical dispersion associated with biomarkers of subclinical myocardial injury and dysfunction, hs-cTnT and NT-proBNP, respectively? Are risk factors for CVD in early mid-life associated with mechanical dispersion measured two decades later?
- Paper 3: In a population with stable CAD, does mechanical dispersion associate with poor long-term prognosis? How is the predictive ability of mechanical dispersion compared to established biomarkers and echocardiographic indices of CVD?

8 Materials and Methods

8.1 Study populations and design

8.1.1 The Akershus Cardiac Examination (ACE) 1950 Study (Paper 1-2)

The ACE 1950 Study invited all community dwellers born in 1950 in Akershus County, Norway, to participate in a cardiovascular survey. We included 3706 study participants from 5827 subjects that received invitation (64%) between 2012 and 2015 at two study sites, Akershus University Hospital and Bærum Hospital (146). We designed the study as a prospective cohort study, and we have permission for follow-up until year 2050. At the baseline examination, participants underwent a thorough evaluation of cardiovascular risk factors and disease by the use of validated questionnaires and physical examination including additional tests like ECG, spirometry, and tests of cognitive function. We also performed ultrasound of the carotid arteries and echocardiography, using both traditional and novel techniques for recordings and analyses (107, 147). We collected fasting blood samples for biochemical analyses, like blood glucose, lipids and renal function, and collected blood for biobanking, which later has been used for analyzing several circulating cardiac biomarkers. The participants gave written informed consent before study inclusion, and the consent permits linkage of data from previous Norwegian population surveys. The study was approved by the Regional Ethics Committee with reference number 2011/1475 and complies with the Declaration of Helsinki. The study population of Paper 1 consists of the 2529 participants from the ACE 1950 Study baseline examination with data on mechanical dispersion by 2D speckle tracking strain (see flow chart, Figure 15).

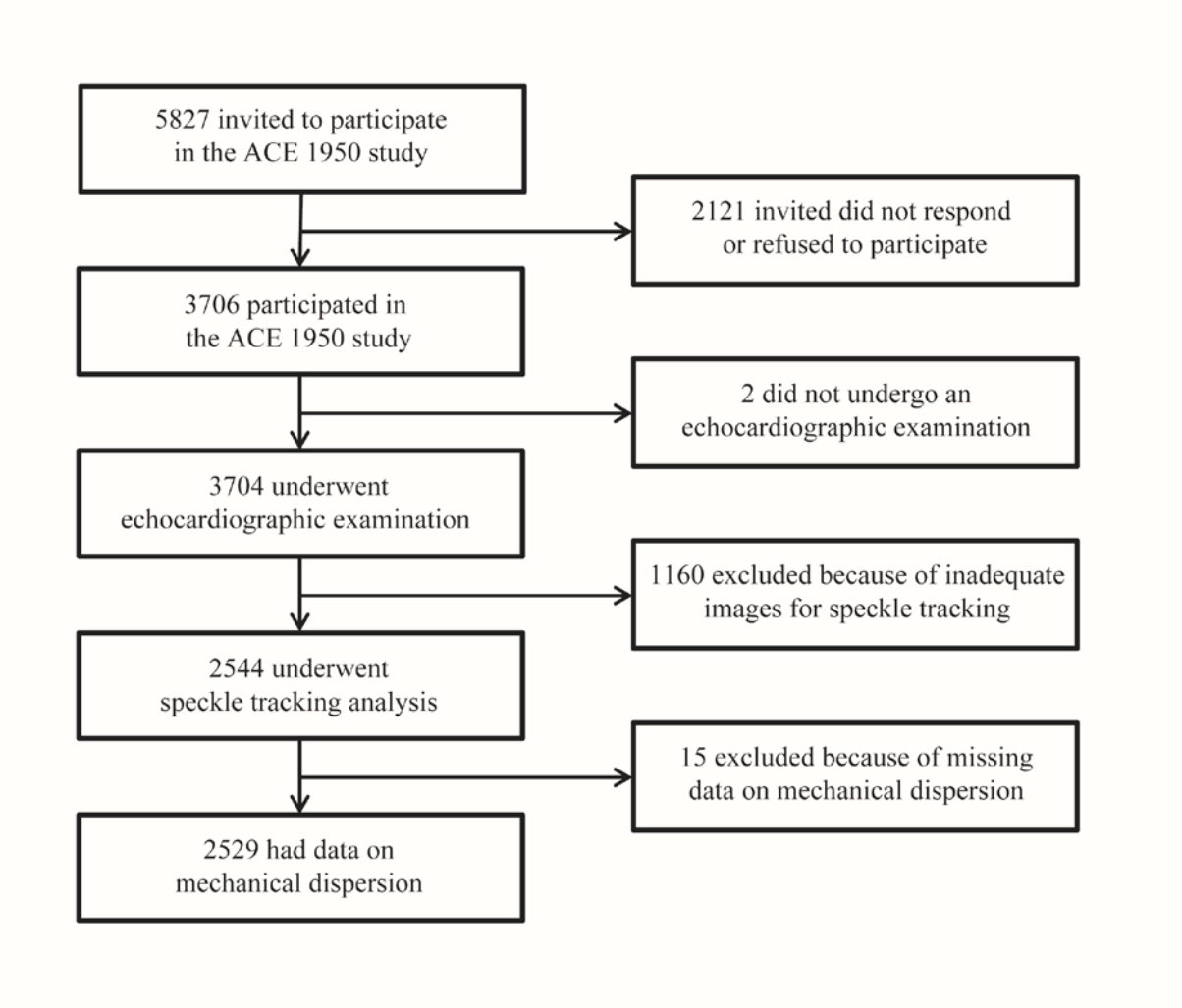

Figure 15. Flow chart of the study inclusion of the ACE 1950 sub-study in Paper 1 (107). Reprinted with permission from Oxford University Press and Copyright Clearance Center.

8.1.2 The Age 40 Program (Paper 2)

Between 1985 and 1999, a nationwide cardiovascular screening survey entitled "The Age 40 Program" was conducted in Norway by the National Health Screening Service (148). The study aimed to explore cardiovascular risk factors and disease among 40-year olds, and to provide intervention to those at high-risk. In total, 74% of the total study participants from the ACE 1950 Study also attended the Age 40 program between 1990 and 1994. The ACE 1950 Study steering committee has received permission to use data from the Age 40 program and to link these data to the ACE 1950 Study database.

The study population of Paper 2 consists of participants from the ACE 1950 Study with both analyses of mechanical dispersion and measurements of hs-cTnT and NT-proBNP (n=2527).

Of the 2527 subjects included in Paper 2, 1906 subjects (75%) had previously attended the Age 40 Program. For sub-group analyses, we included data on CV risk factors from the Age 40 Program to examine the associations between risk factors measured almost 25 years earlier and mechanical dispersion (Figure 16). We excluded one participant from sub-group analysis who had premature myocardial infarction before attending the study visit in the Age 40 program (established CAD).

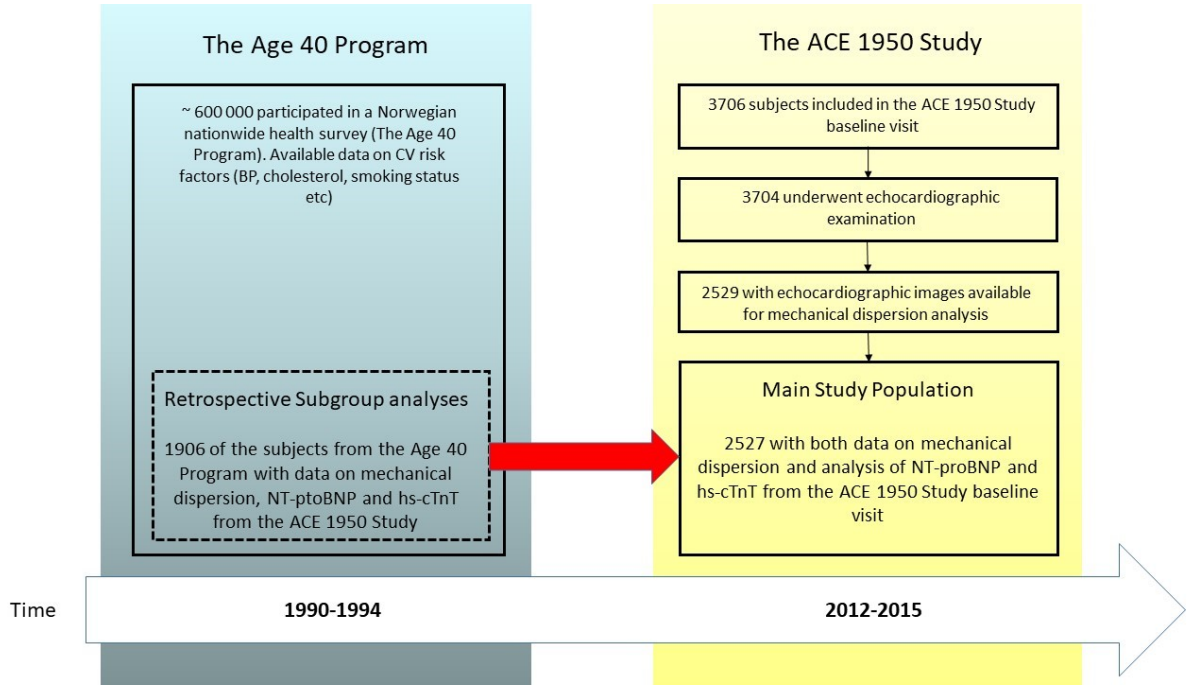

Figure 16. Flow-chart of the study inclusion of the ACE 1950 Study and of the retrospective sub-group analyses with data from the Age 40 Program in Paper 2 (93). Copyrights by the Authors.

8.1.3 Stable CAD Cohort (Paper 3)

In Paper 3, 160 patients with stable CAD were included and examined one year after successful coronary artery intervention. The study was performed between 2008 and 2009 in a tertiary coronary care center (Oslo University Hospital, Rikshospitalet), and patients were included in the study when they came for a one-year follow-up echocardiography (149). On study inclusion, the participants underwent echocardiography examination and peripheral venous blood collection for analysis of cardiac biomarkers (149). The indications for coronary artery intervention were non-ST-segment elevation myocardial infarction, unstable angina pectoris or chronic coronary syndrome (stable angina pectoris), and the intervention

was performed by percutaneous coronary intervention or by coronary artery bypass graft surgery. Participants with the following conditions were excluded: ongoing atrial fibrillation, valvular disease, left bundle branch block (LBBB), ventricular paced rhythm, and recurrent angina or other cardiovascular events between revascularization and the time of study inclusion. The primary endpoint was all-cause mortality, and the secondary endpoint was a composite endpoint of all-cause mortality, hospitalization for acute myocardial infarction or new-onset HF during the follow-up period. Follow-up data were collected by reviewing patient's hospital charts or by telephone interview with either the patients or relatives. None of the study subjects were lost to follow-up.

8.2 Echocardiography (Paper 1-3)

The transthoracic echocardiography recordings on the baseline visit of the ACE 1950 Study (Paper 1 and 2) were performed on Vivid E9 machines (GE Ultrasound Horten, Norway), with M5S probe, by four trained physicians and two echocardiography technicians (107). A senior cardiologist, specialized in echocardiography, was in charge of training the physicians and technicians to perform both the recordings and analyses in a similar fashion and to a good standard. He defined the protocols for image acquisition and analyses and supervised during the process of study inclusion and analysis. The pre-determined protocol for image recording was to obtain four cardiac cycles during breath-hold at end-expiration for subjects in sinus rhythm or six cardiac cycles for subjects with atrial fibrillation. Standard 2D images, M-mode, tissue velocity imaging, and pulsed and continuous Doppler were recorded, and we also obtained three dimensional LV recordings. Images from the following views were obtained: Parasternal long- and short-axis, apical 4CH and 2CH views and APLAX, and right ventricular focused apical 4CH view.

In the stable CAD cohort (Paper 3), the echocardiography recordings were performed with a Vivid E7 machine (GE Ultrasound, Horten, Norway) at study inclusion in 2008-2009. Images from three apical views (4CH, 2CH and APLAX) were obtained. The echocardiography images in both the ACE 1950 Study and the stable CAD cohort were recorded and analyzed according to contemporary guidelines (73, 74).

8.2.1 Cardiac dimensions, systolic and diastolic function

All echocardiography images from the ACE 1950 Study baseline visit (Paper 1 and 2) were analyzed off-line using GE EchoPAC version 201, between May 2015 and July 2016, by the

same six persons who had performed the image acquisition. The images were analyzed according to a predefined protocol. Most echocardiographic indices were analyzed from three cardiac cycles, and the final value is the average of the three. However, if some of the cycles had poor image quality, only cycles with good image quality were analyzed. LV dimensions were assessed in parasternal long-axis or short-axis view by M-mode, and LV mass was calculated with the formula from Devereux et al (150). EF was assessed by the Simpson biplane method. All indexed parameters were calculated using body surface area by the Mosteller formula (151). The main diastolic parameters analyzed, were the mitral inflow peak early diastolic velocity (E) and peak late diastolic velocity (A) by pulsed Doppler. We also calculated the ratio between E and A. By tissue velocity imaging, we measured peak early diastolic velocity (e'), where the e' value used is the average of the basal septal and lateral e'. We calculated the E/e' ratio and analyzed maximal tricuspid velocity and left atrial volume index (end-systolic volume/body surface area) (73). The echocardiography images in Paper 3 were analyzed off-line in 2015 by a single observer (B.A.K.) using EchoPAC version 12 (GE Healthcare). In this paper, LV volumes (EDV and ESV) and EF by Simpson biplane were analyzed in two cardiac cycles for all participants.

8.2.2 Global longitudinal strain and mechanical dispersion

Myocardial strain, measured as GLS by 2D speckle tracking imaging, and mechanical dispersion were analyzed in both the ACE 1950 Study (paper 1 and 2) and the Stable CAD cohort (paper 3) using the three apical views (4CH, 2CH and APLAX). In the ACE 1950 Study, GLS was analyzed semi-automatically by automatic function imaging method using a 17-segment model averaging measurements of two cardiac cycles. The endocardial border was traced automatically by EchoPAC, and speckles were tracked frame by frame during the cardiac cycle. The operator adjusted the marker manually if segments did not track the myocardium properly and adjusted the region of interest if the speckles did not properly fit the myocardial thickness. If more than one segment per image view or more than two segments in total failed to track properly, the analysis was excluded. In the Stable CAD Study, quantitative strain analysis (Q-analysis), where the operator initially defined the LV base and apex, was used for the GLS and mechanical dispersion analyses. The region of interest was adjusted manually to fit the myocardium and ensure proper tracking during the cardiac cycle. If more than two segments per image view failed to track properly, the analysis was excluded. A total of six excluded segments per analysis were tolerated before the analysis was excluded.

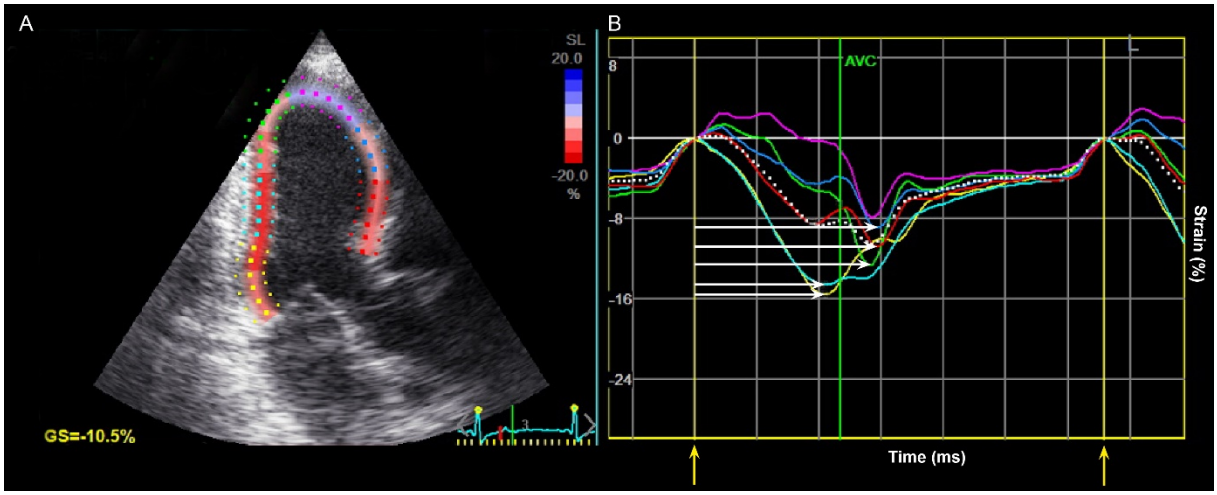

Figure 17. (A) shows strain tracing of left ventricle in apical long axis view, leaving a value of global strain (GS). (B) shows the strain curves for each colored strain segment which the LV is divided into. White horizontal arrows show time to peak negative strain of each segment. Yellow vertical arrows mark peak R on ECG and start and end of a cardiac cycle. AVC, aortic valve closure. Aagaard et al Eur Heart J Open (93). Copyright by the Authors.

A 17-segment model was used in both cohorts (referred to as 16-segments in paper 3), where each segment yields a peak negative strain value and the time from Q/R on the ECG to peak negative strain, is called contraction duration (marked as white horizontal arrows in Figure 17). Both GLS and mechanical dispersion were calculated by the software: GLS is the average value of all strain segments, and mechanical dispersion defined as SD of the contraction duration of all strain segments, regardless if peak negative strain occurred after the aortic valve closure (after end of systole).

8.2.3 Variability testing

Intra-observer and inter-observer variability of the strain measurements were tested using the intraclass correlation coefficient (ICC), which is the strictest form of variability calculation. ICC between 0.75 and 1.00 is considered excellent reliability, ICC 0.50 to 0.75 is considered moderate reliability and ICC below 0.50 is considered poor reliability. Two observers (E.N.A and B.A.K.) performed the variability testing of GLS and mechanical dispersion measurements in both the ACE 1950 Study and the Stable CAD Study. In the ACE 1950 Study, 15 randomly selected subjects were analysed for GLS and mechanical dispersion, and the analyses were repeated after a few weeks. Intra-observer ICC for GLS and mechanical dispersion were 0.97 and 0.87 (E.N.A.) and 0.87 and 0.89 (B.A.K). Inter-observer ICC for GLS and mechanical dispersion were 0.86 and 0.89 (E.N.A.) and 0.94 and 0.89 (B.K.),

respectively. In the Stable CAD Study, 10 randomly selected patients were analysed for GLS and mechanical dispersion and the analyses were repeated after a few weeks. Intra-observer ICC coefficients for the measurements of B.A.K. were 0.84 for GLS and 0.88 for mechanical dispersion, and inter-observer ICC were 0.90 and 0.93 (E.N.A.).

8.3 Biochemical analyses (Paper 2 and 3)

Circulating cardiac biomarkers have been analyzed in both cohorts included in the current thesis. In the ACE 1950 Study (Paper 2), fasting peripheral blood was collected at the baseline visit, centrifuged at room temperature, and serum was frozen at - 80°C. Both biomarkers were analyzed between October 2017 and January 2018 at Akershus University Hospital. Concentrations of both biomarkers were measured on Cobas Platform 8000, e801 (Roche Diagnostics, Rotkreuz, Switzerland). The proBNP II assay was used to measure NT-proBNP, and the STAT hs-Troponin T assay was used for hs-cTnT. The limit of detection for NT-proBNP was 5.0 ng/L and the limit of blank was 3.0 ng/L. For hs-TnT, the limit of blank was 3.0 ng/L and limit of blank 2.5 ng/L. Concentrations that were below limit of blank, were given a concentration of 2.5 ng/L for NT-proBNP and 1.5 ng/L for hs-TnT.

At the day of the echocardiography recordings in the Stable CAD cohort (Paper 3), peripheral blood was drawn from the patient, and serum was then stored at -70°C. Concentrations of NT-proBNP and hs-cTnI were later analyzed: NT-proBNP was analyzed on a Modular E170 platform (Roche Diagnostics) with the Elecsys reagents, and hs-TnI was measured on ARCHITECT STAT (Abbott Diagnostics, Abbott Park, IL). For NT-proBNP, limit of detection was 5 ng/L and the 97.5th percentile was defined by Roche as cutoff level of pathology, which was 263 ng/L. Limit of detection for hs-cTnI was 1.9 ng/L and levels above the 99th percentile were defined as pathological, which equals a concentration of 26 ng/L (152).

8.4 Clinical variables

8.4.1 Clinical variables from the ACE 1950 Study population (Paper 1-2)

The main variables used in Paper 1 and 2 from the ACE 1950 Study were collected and defined based on self-reported questionnaires and data from the baseline examination. CAD was self-reported as either previous myocardial infarction, percutaneous coronary

intervention or coronary artery bypass graft surgery. Heart rate, QRS duration, rate corrected QT interval time, LBBB and right bundle branch block were measured automatically from the 12-lead ECG (AT-101, Schiller or MAC 5500 HD, GE Healthcare), which was taken in supine position after 10 min of rest. The atrial fibrillation variable was based on self-report or diagnosed from the baseline ECG, and two physicians later validated the diagnosis. Blood pressure was measured by an automatic monitor Carescape V100 (GE Healthcare) after 5 minutes of rest in a seated position. Hypertension was based on self-reported use of anti-hypertensive medication or mean systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg from the 2nd and 3rd recording in seated position. Obesity was defined as BMI ≥ 30 g/m^2, and DM was defined as either self-reported diagnosis or the use of antidiabetic medication or elevated glucose tests at baseline (HbA1c ≥6.5% and or? fasting blood glucose ≥7 mmol/L). Renal failure was defined as estimated glomerular filtration rate <60 ml/min/1.73m^2. Chronic obstructive pulmonary disease (COPD) was based on post-bronchodilatory spirometry forced expiratory volume 1/forced vital capacity <0.64 in men or <0.66 in women on the baseline study visit, or self-reported in participants that did not perform lung function testing. Current smoking was defined as self-reported daily smoking. Lipid levels were measured from fasting venous blood, and hypercholesterolemia was defined as the use of statins or total cholesterol >6.2 mmol/L or low-density lipoprotein cholesterol >4.1 mmol/L.

8.4.2 Clinical variables from the Age 40 Program (Paper 2)

Information on clinical conditions like treatment for hypertension, DM, previous myocardial infarction, physical activity and smoking status was collected through a questionnaire answered by the study participants. Heart rate and BP were measured after two minutes of rest. Three measurements were made, and the average of the 2nd and 3rd measurement was used. For these measurements, an automatic device (DINAMAP, Criticon, Tampa, USA) was used by a trained nurse. An inactive lifestyle was defined as reading, watching television or other sedentary activities in leisure time and less than 4 hours of low-to-moderate intensive physical activity per week. Current smoking was defined as daily smoking. The lipid concentrations measured were total cholesterol and triglycerides, which were measured in non-fasting blood-serum by an enzymatic method.

8.5 Statistical analyses

Statistical analyses in this thesis were analyzed using IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc), MedCalc Statistical Software version 18.2 or R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and STATA 16 (StataCorp LP, College Station, TX, USA). Statistical significance was defined as $P < 0.05$.

8.5.1 Baseline analyses

Continuous variables were presented as mean ± SD or median (interquartile range [IQR]), and categorical variables as numbers (percentages [%]). Groups of continuous variables were compared using independent samples Student's t test or Mann-Whitney *U* test. Categorical variables were compared with Chi-Square tests. Comparison of paired samples were made by the Wilcoxon Signed Rank test for continuous variables and by the McNemar's Test for categorical variables. Baseline characteristics for Paper 1 and 2 were compared according to the median value of mechanical dispersion (<38 ms and ≥38 ms). Correlations between variables were calculated by the Pearson method (Paper 3) and by the Spearman's rank correlation (Paper 1-2). The biomarkers hs-cTnT, hs-cTnI and NT-proBNP have a skewed distribution, and were log-transformed prior to parametric tests (Pearson method) and regression analyses.

8.5.2 Multivariable linear regression analyses

Multivariable linear regression analyses are used to examine associations between a dependent variable and predictor variables (independent variables), while adjusting for other independent variables that may influence the associations. Different methods may be used to select the independent variables used in a model and to perform the analysis. The simultaneous, the hierarchical and the stepwise methods are all different methods for performing the multivariable linear regression analysis (153). An important issue is that the number of independent variables included in a model depends on the size of the study population, and a general recommendation has been made that there should be 20 or more observations (study subjects) per variable that is included in the model. Accordingly, a large study population may not have any restriction to the number of independent variables used in an analysis, while researchers with smaller cohorts need to take this recommendation into account and restrict the number of variables in the models.

Paper 1

Due to the high number of included subjects in the study population of Paper 1 (n = 2529) and Paper 2 (n = 2527) and the large number of variables available (> 200 – 250), we chose to use an approach with *a priori* selected variables. This method was chosen rather than selecting the variables for the multivariable regression analysis through the level of significance in primary univariate linear regression analyses.

The general purpose of Paper 1 was to explore how mechanical dispersion was distributed in the general population among healthy subjects and those with CV risk factors, and one of the specific aims were to identify factors associated with mechanical dispersion. Mechanical dispersion was selected as the dependent variable, and the predictor variables were clinical conditions associated with CVD: CAD, hypertension, DM and obesity. In addition we added variables known to be associated with CVD (age, sex, hypercholesterolemia, renal function, current smoking, COPD and C reactive protein) and variables that may influence mechanical dispersion (atrial fibrillation, heart rate, LBBB and right bundle branch block). In a second multivariable model we added echocardiographic indices for cardiac structure and function (LV mass index, EF, GLS, e', E/e', left atrial volume and maximal tricuspid velocity) to assess how they would influence the associations between the predictor variables and mechanical dispersion. For the multivariable regression analysis, we chose the first order analysis using a forward selection procedure.

Paper 2

In Paper 2, almost the same population as Paper 1, the first hypothesis was that clinical CV risk factors in the early forties are associated with mechanical dispersion two decades later. The second hypothesis was that mechanical dispersion in the mid-sixties is associated with cardiac biomarkers of subclinical myocardial injury and dysfunction in cross-sectional analysis. To assess the first hypothesis, we used mechanical dispersion as dependent variable and available CV risk factors from the Age 40 Program as independent variables. Similar to Paper 1, we selected the variables *a priori* that were related to CV risk: age at the Age 40 Program visit, resting heart rate, systolic and diastolic blood pressure, BMI, inactive lifestyle, hypertensive medication, DM, current smoking, non-fasting serum total cholesterol and triglyceride concentrations. We chose to use the enter method in SPSS, including all selected variables into the multivariable analysis simultaneously. For the same reason as in Paper 1, we chose not to select the variables through univariate regression analysis, but rather select variables *a priori* based on prior knowledge related to factors that could influence mechanical

dispersion. In addition, we performed three sensitivity analyses: (*1*) Selecting variables through univariate regression analysis and entering only variables with a *P*-value <0.05. (*2*) Adjusting the main multivariable model for established CAD at the ACE 1950 Study baseline visit, and (*3*) adjusting the main multivariable model for length of follow-up time between the Age 40 Program visit and the ACE 1950 baseline visit.

In order to test whether mechanical dispersion in the mid-sixties is associated with cardiac biomarkers of subclinical myocardial injury and dysfunction (second hypothesis), we used hs-cTnT and NT-proBNP as dependent variables and mechanical dispersion as a predictor variable, and adjusted for all variables from the ACE 1950 Study baseline visit. GLS and EF were also used as predictor variables, both in separate models for each echocardiographic index and in a combined model that included all three echocardiographic indices. We adjusted for the study site at the ACE 1950 Study baseline visit, demographic data and variables selected *a priori* due to known association with CV risk. We hypothesized that variables associated with CV risk will also be associated with both mechanical dispersion and cardiac biomarker concentrations. We also adjusted for statin therapy, as it may attenuate associations with hs-cTnT (154). Similar to the first hypothesis testing, we used the enter method in SPSS without a preselection of variables through univariate regression analysis. We performed the multivariable regression analyses with the following hierarchical method: Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex, study site, higher education level, BMI, renal function, fasting total cholesterol, high-density lipoprotein cholesterol, DM, hypertension, CAD, statin therapy and current smoking. We chose this method because we wanted to assess the effect on the associations in each model.

Paper 3

The Stable CAD Study population with 160 patients is smaller than the cohort included in paper 1 and 2. Due to the restricted number of variables that should be included in the final model, we performed linear regression analyses differently for this study. The hypothesis was that mechanical dispersion might be a promising marker of subtle myocardial dysfunction and long-term prognosis in patients with stable CAD. Variables associated with GLS and mechanical dispersion (dependent variables) were assessed by univariate linear regression analysis and presented if P <0.1. Furthermore, the associations with hs-cTnI and NT-proBNP (dependent variables) and EF, GLS and mechanical dispersion (independent predictor variables) were assessed through univariate and multivariable linear regression analyses by a forward selection procedure. In the multivariable linear regression analysis, each LV

echocardiographic index was adjusted for the remaining two indices. Due to the low number of study subjects, we did not adjust for other covariates.

8.5.3 Establishing a reference value for mechanical dispersion (Paper 1)

As a second aim in Paper 1, we wished to establish a reference value, or an upper limit of normal for mechanical dispersion in subjects recruited from the general population. At the time, no established upper limit of normal was available for mechanical dispersion by 2D speckle tracking imaging. The echocardiographic index had mostly been studied in populations with established cardiac diseases, and often in cohorts with conditions that increases the risk of ventricular arrhythmias and sudden cardiac death (2, 3, 99, 108, 155). Still, to facilitate possible transfer of mechanical dispersion into clinical practice, the clinician will need to have reference values separating normal results from pathologic results. Based on the method for calculating reference values for 2D echocardiography indices provided by the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) in the 2015 guidelines for echocardiography chamber quantification (73), we defined a healthy sub-group of our study population using similar exclusion criteria as the Task Force. The healthy subgroup was defined as all subjects in the ACE 1950 Study with following conditions excluded: Hypertension (>140/90 mmHg), DM, obesity, renal failure, COPD, atrial fibrillation, stroke, CAD, EF<50%, moderate and severe valvular disease, valvular surgery, LBBB, right bundle branch block, atrioventricular block type II-III, cardio- and vasoactive treatment, and the use of statins. Upper limit of normal for mechanical dispersion was calculated as the value of mean + 2 SD in the healthy subgroup.

8.5.4 Survival models (Paper 3)

The survival models used in Paper 3 are the Cox proportional hazard regression model and the Kaplan-Meier survival analysis. Survival analyses are statistical methods used to assess the time to an event to occur. As described previously, the primary end-point was all-cause mortality and the secondary endpoint was a composite endpoint of all-cause mortality, hospitalization for acute myocardial infarction or new-onset HF during the follow-up period.

The Cox regression method assesses the probability of the outcome at a specific time for a given value of the independent variables (156). The effect of the independent variable is denoted as hazard ratio, where a positive value reflects a high impact of the variable on the outcome. In the Cox proportional hazard regression analyses of Paper 3, the echocardiographic indices EF, GLS and mechanical dispersion were used as independent variables with primary and secondary endpoints as outcome (dependent) variables. The

echocardiographic indices were entered into the models both as continuous variables and with the variables dichotomized according to the cut-off values displayed in Table 1. As for the multivariable linear regression analyses, we adjusted for the remaining echocardiographic LV variables in the multivariable Cox proportional hazards regression model.

Table 1. Overview of cut-off values used in Paper 3.

Variable	Good value	Poor value	Reference
EF	≥53 %	<53 %	Lang et. al (73)
GLS	≤ -18 %	>-18 %	Lang et. al (73)
Mechanical dispersion	≤64 ms	>64 ms	Rodrigues et al. (157) Haland et al. (108) Haugaa et al. (2)
hs-cTnI	≤26 ng/L	>26 ng/L	Apple et al. (124)
NT-proBNP	≤263 ng/L	>263 ng/L	According to contemporary cut-off value provided by the manufacturer (Roche)

EF, ejection fraction; GLS, global longitudinal strain; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

A Kaplan-Meier survival plot describes the time until a study subject reaches the outcome, and may be shown with dichotomized variables that may explain the difference in i.e. survival (Figure 18) (156). In Paper 3, we used the variables EF, GLS, mechanical dispersion, and log-transformed hs-cTnI and NT-proBNP, dichotomized as in Table 1. The associations between the respective variables and the endpoints were compared by the log-rank test.

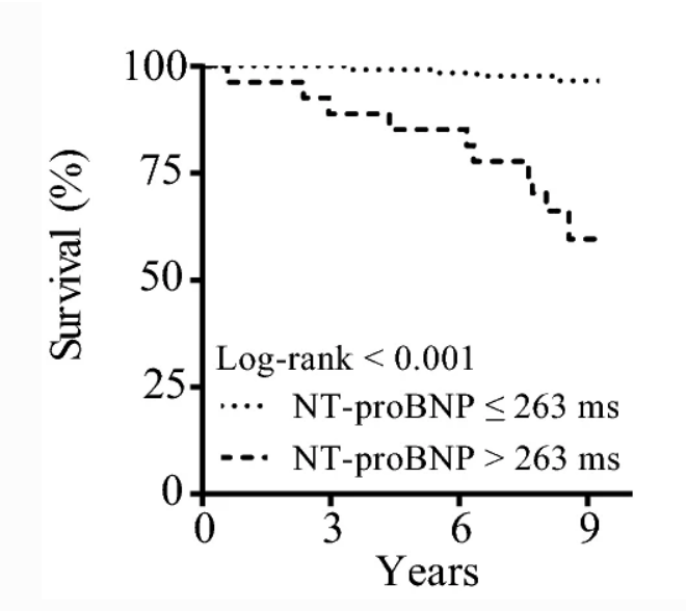

Figure 18. Kaplan-Meier plot by Kvisvik et al Int J Cardiovasc Imaging 2019 (158). The survival of a population depicted with a Kaplan-Meier plot, where the Y axis the probability of survival and the X axis is the time. A drop in the survival curve shows an actual event occurring at that time. Modified and reprinted with permission from Springer Nature and Copyright Clearance Center.

8.5.5 Prognostic performance of the LV indices and the biomarkers (Paper 3)

Receiver operating characteristics analysis by measurement of the area under the curve is a way of measuring the ability of a test to correctly diagnose a condition or predict an outcome in medical research. Figure 19 gives an example of the receiver operating characteristics curve: The Y-axis represents the true positive rate (sensitivity) and the X-axis represents the false positive rate (1-spesificity) of the test. The closer the curve is to the upper left corner (true positive rate of 100%) or the lower right corner (false positive rate of 100%), the better is the diagnostic ability of the test. In paper 3, receiver operating characteristics area under the curve analyses were made to assess the prognostic ability of the biomarkers hs-cTnI and NT-proBNP and the LV indices EF, GLS and mechanical dispersion in the prediction of the primary and secondary endpoint. The prognostic ability between the variables were compared by the DeLong test (159).

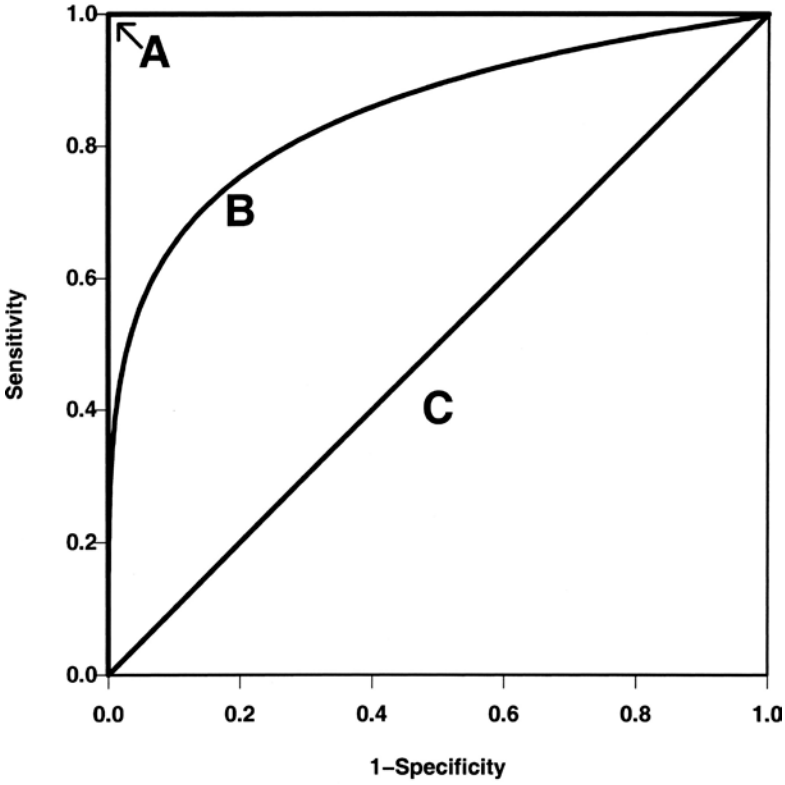

Figure 19. The receiver operating characteristics curve with the area under the curve diagnostics, Zou et al. Circ. 2007 (160). Reprinted with permission from Wolters Kluwer Health, Inc and Copyright Clearance Center.

In the same article we also used net reclassification improvement and integrated discrimination index to further assess the hypothesis that mechanical dispersion might be a marker of long-term prognosis in patients with stable CAD. Net reclassification improvement is a method to better calculate the incremental value of a biomarker or variable compared to the area under the curves (161, 162). Net reclassification improvement is a method that calculates how well a new test or variable can reclassify subjects from false negative to true positive compared to the original test. The integrated discrimination index is derived from net reclassification improvement and is a measure of how the prediction may be increased by adding a variable to the existing model or test. The integrated discrimination index is expressed as a discrimination slope in %. Mechanical dispersion was added to net reclassification improvement and integrated discrimination index models together with EF, GLS, hs-cTnI and NT-proBNP, respectively, to investigate if mechanical dispersion had incremental value to other variables.

9 Summary of results

9.1 Paper 1

A total of 2529 subjects in their mid-sixties from the general population of Akershus County, Norway were included. Female and male subjects were equally represented, mean age (SD) was 64 ± 0.6 years, and 59.1% had hypertension, 6.7% had DM, and 5.9% reported history of CAD. Mechanical dispersion was normally distributed with a median (IQR) value of 38.0 (29.8-47.0), range 9.0-181.5 ms. Although within the normal range, there was a significant between-group difference with a slight reduction in systolic and diastolic function shown by a reduced EF, GLS and e' and increased E/e' in the above-median group of mechanical dispersion. Compared to the healthy sub-group, mechanical dispersion was significantly higher in subjects with hypertension, DM and CAD (Figure 20). In a multivariable linear regression analysis, CAD, hypertension, DM and obesity were independently associated with increasing mechanical dispersion. However, adjusting also for echocardiographic variables, only CAD and hypertension were associated with high mechanical dispersion.

In total, 594 subjects were included in the healthy reference population. Mean value (SD) of mechanical dispersion was 35.7 (± 12.7) ms and upper limit of normal was calculated to be 61 ms.

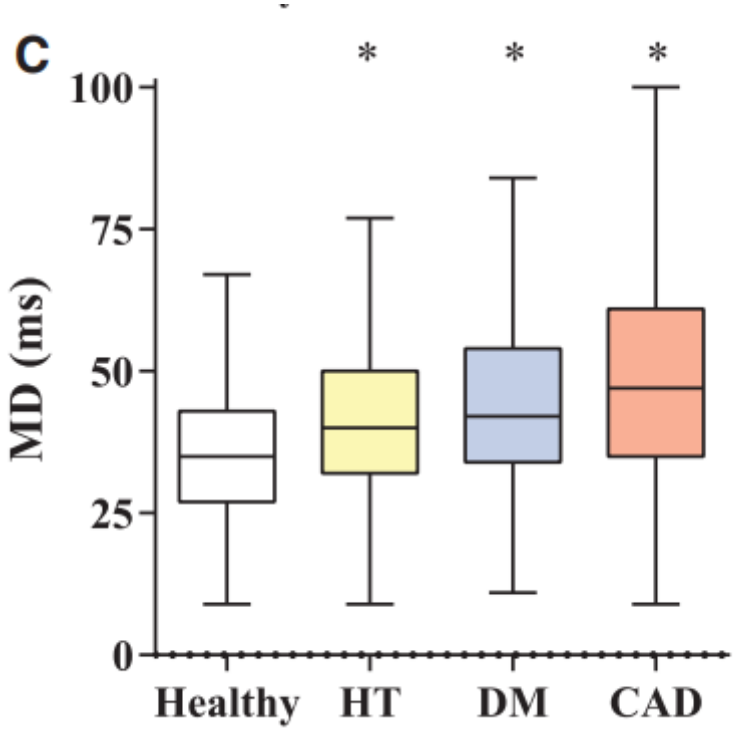

Figure 20. Comparison of mechanical dispersion among the groups. Comparisons were made between the healthy group and hypertension, DM and CAD. CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; MD, mechanical dispersion. *P<0.001. Aagaard et al Eur Heart J Cardiovasc Imaging (107). Reprinted with permission of Oxford University Press and Copyright Clearance Center.

9.2 Paper 2

In total, 2527 of the 3706 subjects from the ACE 1950 Study had measurements of mechanical dispersion and hs-cTnT and NT-proBNP measurements, and we included these participants in the current study. Among these, 1906 (75%) subjects also had available data from the Age 40 Program. Participants were median 40 years old when examined in the Age 40 Program, and 21 participants (1.1%) were treated for hypertension and two participants (0.1%) had been diagnosed with DM. In the final multivariable linear regression analysis, BMI and concentrations of triglycerides at age 40 were independently associated with higher mechanical dispersion two decades later, while heart rate was independently associated with lower mechanical dispersion.

Among the cross-sectional data of subjects in their mid-sixties from the ACE 1950 Study, median (IQR) value of hs-cTnT was 6.0 (4.0-8.0) ng/L and of NT-proBNP 54 (33.8-93.0) ng/L. There was a significant between-group difference for hs-cTnT according to infra- or supra-median mechanical dispersion value, and hs-cTnT concentrations correlated with mechanical dispersion. For NT-proBNP, there was no between-group difference according to median value of mechanical dispersion and we found no significant correlation between NT-proBNP concentrations and mechanical dispersion. In multivariable linear regression analyses, mechanical dispersion was independently associated with both hs-cTnT and NT-proBNP concentrations. In combined multivariable models which included EF, GLS and mechanical dispersion in the same analyses, only mechanical dispersion was independently associated with hs-cTnT. In contrast, all three echocardiographic indices were independently associated with NT-proBNP concentrations. Figure 21 shows a graphical abstract of the study and the main results.

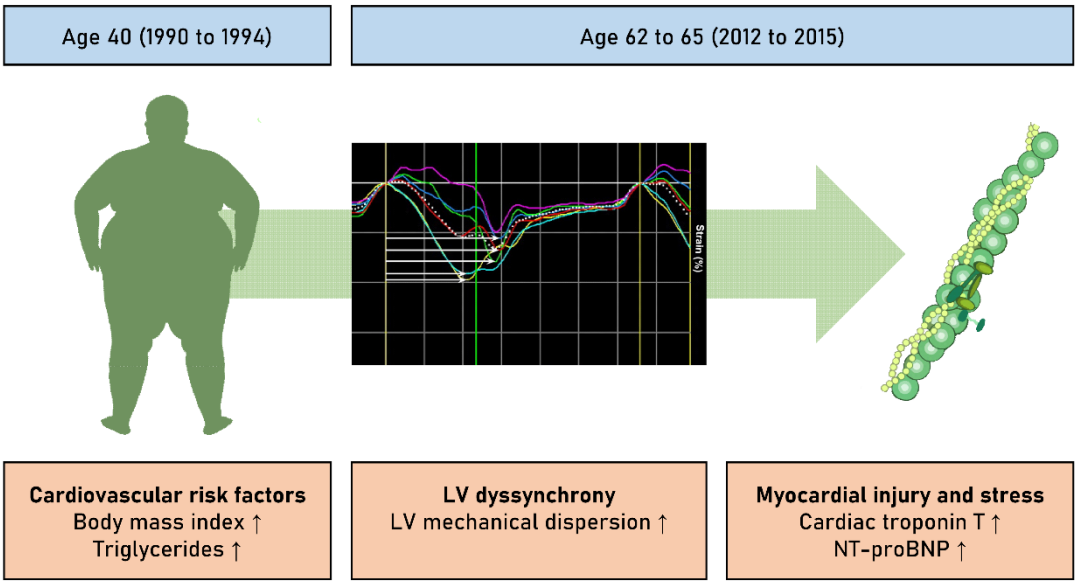

Figure 21. Graphical abstract of the findings in Paper 2 (93). Increased levels of triglycerides and body mass index at age 40 were associated with increased mechanical dispersion in the mid-sixties, and mechanical dispersion was cross-sectionally associated with hs-cTnT and NT-proBNP in the mid-sixties. Copyright by the Authors.

9.3 Paper 3

We included 160 patients: 90 were included after non-ST-segment myocardial infarction, 26 due to unstable angina pectoris, and 44 patients had chronic coronary syndrome. In total, 126 of the study participants (79%) were vascularized by percutaneous coronary intervention and 34 (21%) by coronary artery bypass graft surgery. In total, 153 patients (96%) had sufficient quality of the echocardiographic images for 2D speckle tracking imaging strain analysis, and 97% of the strain segments could be analyzed. Median (IQR) value of mechanical dispersion was 46 (37-54) ms. More than 80% of the population had normal LV function as assessed by EF (>53%), while only 44% had GLS values that are considered normal (below -18%). hs-cTnI concentrations were higher than the limit of detection in 70% of the population, and 1.9% had levels above the 99th percentile. NT-proBNP concentrations were detected in 99% of the patients and 17% of the patients demonstrated levels above the 97.5th percentile.

Mechanical dispersion correlated moderately with hs-cTnI and NT-proBNP, while EF and GLS did not correlate with the biomarkers. Mechanical dispersion was the only LV index independently associated with hs-cTnI and NT-proBNP in multivariable linear regression analyses after adjusting for the two other echocardiography LV indices. During median (IQR) 8.4 (8.2-8.8) years, 14 subjects died, 12 were hospitalized for recurrent AMI, and three patients were hospitalized for new-onset HF. Mechanical dispersion was the only echocardiographic index that differed between patients with and without clinical events (Figure 22). hs-cTnI and NT-proBNP concentrations were significantly higher in the groups who reached the primary and secondary endpoints. In reclassification assessment, mechanical dispersion demonstrated incremental prognostic ability for both primary and secondary endpoint when added to EF, GLS and hs-cTnI concentrations, but did not provide incremental prognostic ability to NT-proBNP. Mechanical dispersion > 64ms identified patients with poor prognosis for both all-cause mortality and composite endpoint.

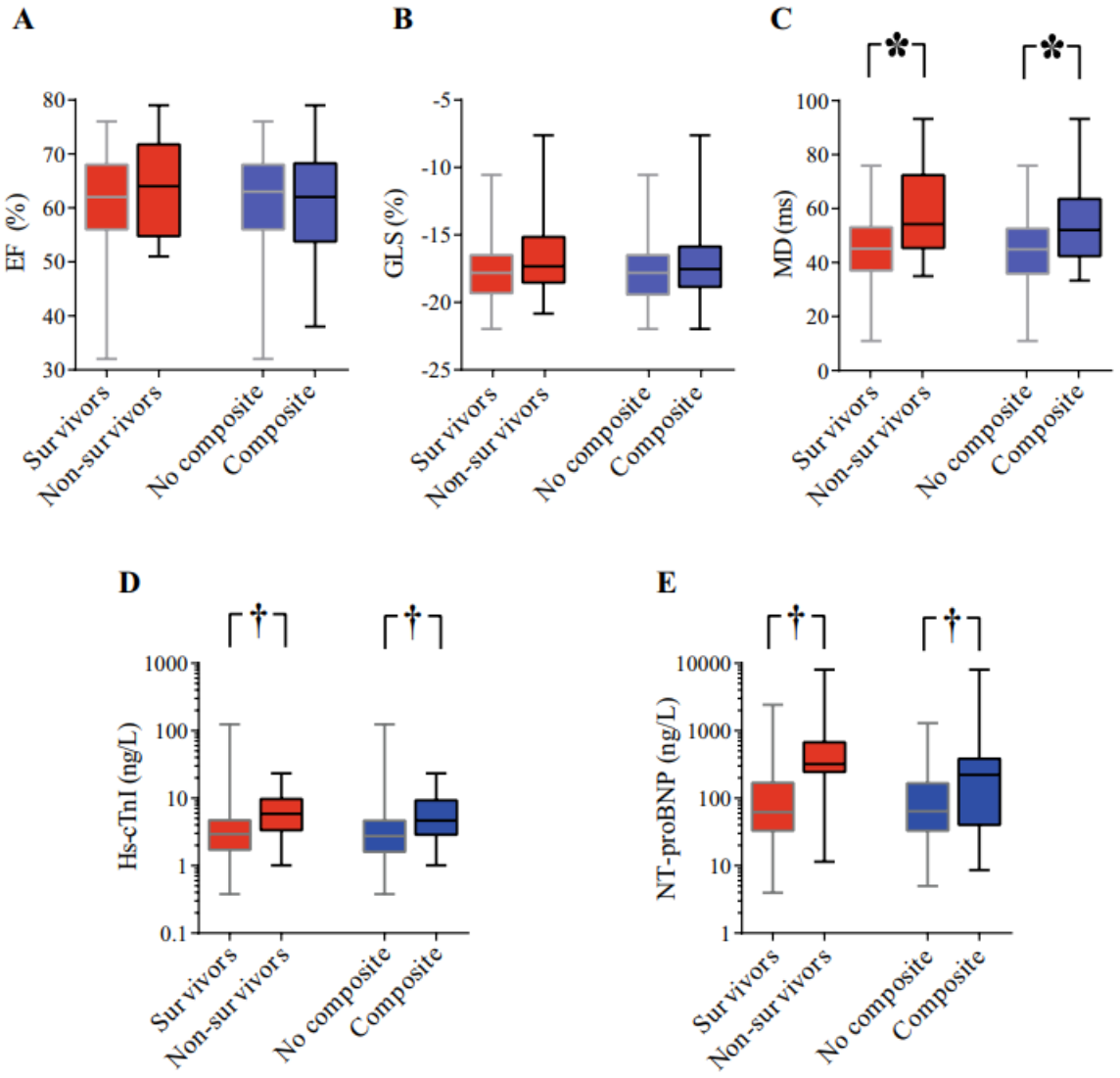

Figure 22. Comparisons of patients that reached the primary endpoint (all-cause mortality) and secondary endpoint (all-cause mortality and hospitalization for recurrent acute myocardial infarction or new-onset HF) versus those who did not reach the endpoints, according to EF, GLS, MD, hs-cTnI and NT-proBNP. * $p<0.05$, † $p<0.01$. Kvisvik et al. Int J Cardiovasc Imaging 2019 (158). Reprinted with permission from Springer Nature and Copyright Clearance Center.

10 Discussion of methodology

10.1 Study design

All three studies of the thesis are designed as prospective observational cohort studies and the results are therefore hypothesis generating. In order to test causality in medical studies, a randomized controlled trial should ideally be performed. However, observational studies may also provide useful evidence (163). In paper 1 we used cross-sectional data from the ACE 1950 Study baseline visit in order to calculate the upper limit of normal (ULN) for mechanical dispersion and to assess which risk factors for CVD associate with mechanical dispersion. It should be emphasized that the results are applicable primarily to 64 year old subjects. Hence, studies in cohorts with other age categories, nationalities and ethnicities are needed to validate our results and to extend the results to other groups. In paper 2 we have longitudinal data on the associations between risk factors at age 40 years and mechanical dispersion 24 years later, and in Paper 3 we have follow-up data with endpoints 8.4 years after the primary echocardiography examination. The sample size of the Stable CAD cohort is moderate (n=160) and the results should be validated in additional cohorts of stable CAD patients.

10.2 Random errors

There are two main categories of errors that may occur when conducting a study: random and systematic errors. Random errors, are errors that are due to chance and which may alter the measurements in a study in either direction with equal probability (164). A large sample size decreases the probability of the random error affecting the result substantially. Systematic errors are incorrect results due to bias, which distort the results in one direction (164). Random errors are often considered less serious in nature than systematic errors.

The sample size of the cohorts in Paper 1 and 2 is large, which will reduce the impact of random errors (e.g. typing the wrong number into the database) to overall results. The study inclusion, tests and physical examination of the ACE 1950 Study were also standardized and performed by experienced and trained research personnel, which reduces the risk of both random and systematic errors. We constructed a digital data system to fit the study variables in order to reduce the potential random errors that can occur when moving data between different databases. Similarly, we used a macro made specifically for the

echocardiography analyses to transfer the results in a controlled manner and to include into the database.

Due to the large sample size, spurious associations may potentially occur. In Paper 1 we found EF to be positively associated with increasing mechanical dispersion in the cross-sectional multivariable regression analysis. In contrast, previous studies have found worsening LV function to be associated with increasing LV dyssynchrony (113, 165), which indicate that the result in our study may not be correct. The mechanism behind spurious findings is that large sample size increases the risk of statistical significance despite no association truly existing. In our cohort EF was narrowly dispersed and most participants had normal EF, therefore most changes were of minor magnitude and with a large sample size, these factors together could explain the likely spurious result for the direction of the association between EF and mechanical dispersion. Other results in our work are more in line with prior work and basic understanding of cardiac function and therefore appear robust (157, 166).

Due to the smaller sample size of the Stable CAD cohort, a random (individual) error could potentially have a larger effect on the overall results than in a study with larger sample size. On the other hand, random errors may be easier to identify while establishing the database, and there is a lower chance of spurious findings due to less statistical power.

10.3 Systematic errors

10.3.1 Selection bias

If the association between exposure and outcome is different between the group of participants included in the study and those that did not participate, the error is called selection bias. Non-response bias occurs when there is a difference between the participants who agreed to participate versus non-responders.

In the ACE 1950 Study, we had a participation rate of 64%, which is similar to other Norwegian contemporary population studies, such as the Tromsø 6 study (66%) and the HUNT 3 study (54%) (167, 168). There has been a decline in participation rate in population studies during the last decades (169). The 2121 subjects that did not respond or chose to decline to participate in the ACE 1950 Study, may represent a selection bias, and it is believed that individuals who do not participate in epidemiologic studies generally have poorer health status than subjects who agree to participate in studies (170). However, except for sex and

residential address we have no information on the subjects that did not participate in the ACE 1950 Study, and therefore we cannot assess non-response bias for our cohort. In paper 2, 75% of the 2527 study subjects had already participated in the Age 40 Program 24 years earlier. This indicates a willingness to participate in studies, and potentially a more health-conscious behavior than among the non-responders of the two studies.

In paper 1 and 2 the main study population consisted of subjects with available mechanical dispersion analyses. There is a selection bias between the group included in the study and those without sufficient image quality for strain analyses, as the excluded subjects had more risk factors and comorbidities, including higher BMI, and higher prevalence of atrial fibrillation, obesity, DM, hypertension and CAD. To some surprise, there were no between group differences among current smokers and subjects with chronic obstructive pulmonary disease. The selection bias could potentially cause a type 2 error (wrongfully accepting the null hypothesis by not finding an association between the exposure and outcome). Despite the selection bias, we found that CVD risk factors associate with mechanical dispersion, and we believe that this association would only have been strengthened by including subjects with more risk factors into the analysis.

In the Stable CAD cohort, we included 160 patients. These patients were recruited at a scheduled follow-up one year after coronary artery revascularization, and included patients from either a group with chronic coronary syndrome (stable angina cohort) or patients originally treated invasively for non-ST elevation acute coronary syndrome (unstable angina pectoris or non-ST-segment myocardial infarction; ACS cohort) (171, 172). Both the stable angina cohort and the ACS cohort had pre-specified that strain echocardiography and GLS were focus of the studies. Accordingly, all subjects underwent an echocardiographic examination with special focus to obtain good and specified image quality required for strain analyses. For the same reason, the subjects with atrial fibrillation, LBBB, ventricular paced rhythm, valvular disease at the time of the initial assessment were excluded from the studies. Unfortunately, no information exists on other patients originally considered for inclusion and therefore I cannot assess whether the included patients are representative for the total cohort of such patients, or whether selection bias is a problem here.

10.3.2 Information bias

Information bias occurs due to incorrectly collected information, which we can reduce by using standardized and validated questionnaires and experienced and well-trained study personnel. Both the ACE 1950 Study and the Age 40 Program relied on self-reported

information regarding disease, smoking status, physical activity and other variables, which could lead to recall bias. Variables from the ACE 1950 Study that are fully or partially based on self-report include history of CAD, prior diagnosis of DM and smoking status, and all of these variables could potentially be influenced by recall bias. However, through a population study in Olmsted County, we know that the recall bias depends on the condition reported, and that agreement between self-reported condition and medical records was good for myocardial infarction, DM and hypertension (173). In contrast, correlation between self-reported condition and medical records was lower for HF, which is a complex condition. The variable for hypertension in the ACE 1950 Study was based on the use of hypertensive medication at the time of baseline examination or elevated systolic blood pressure and/or diastolic blood pressure at the baseline visit. Consequently, subjects that were using i.e. beta blockers or ACE inhibitors due to HF or to optimize due to regional LV contraction disturbances after myocardial infarction, may have been subjected to misclassification bias and categorized as hypertension. There is a possibility that this could influence the outcome for the association between hypertension and increased mechanical dispersion in Paper 1, which thereby would be classified as a type 1 error. However, based on the recruited population with overall low prevalence of established CVD and echocardiographic examinations in all subjects not detecting gross LV pathology in the majority of the population, such misclassification of hypertension diagnosis will only be applicable in a small minority and thereby will most likely not represent a major problem in our cohort.

In Paper 3, we collected the clinical variables reported as baseline data from medical records combined with patient interview at the time of study inclusion. The variables are considered reliable, and we do not suspect any recall bias. The endpoints of all-cause mortality and recurrent myocardial infarction or new-onset HF were collected through review of the medical records or by telephone interview, and none were lost to follow-up. Information obtained through telephone interview regarding recurrent myocardial infarction or new-onset HF is more prone to recall bias, but we tried to alleviate this problem by crosslinking self-reported information from the participants with other available information.

10.4 Validity

Internal validity refers to whether the results of a study are true for the specific population that we examined. To increase internal validity, good study design, protocols and data collection

are important, in addition to collect and process reliable variables (including missing variables) and to perform statistical analyses that truthfully answer the research questions.

External validity represents whether the results of a study can be generalized to other populations (174). Studies should be performed in different populations to increase external validity. Without good external validity, the results cannot be transferred to other populations. In Paper 1, we determined the ULN for mechanical dispersion. We have examined a homogeneous population of Caucasian subjects in their early sixties, but as studies in other populations show similar results, our results may still prove valid across age-groups and ethnicities (see Discussion of Results).

10.5 Echocardiography

Echocardiography is a widely used method in both clinical cardiology and research to assess the function and dimensions of the heart. As described in the introduction of this thesis, the imaging method comes with certain limitations, especially regarding variability due to hemodynamic changes in the same person when examined at different times, potential variability of the recordings between the investigators, and variability of the analyses and results (inter- and intra-observer variability). We performed echocardiography imaging in both the ACE 1950 Study and the Stable CAD cohort. In both cohorts, the echocardiography was performed by a limited number of trained physicians and echocardiography technicians, and after a predefined protocol, in order to reduce the potential variability. For the same reason, the analyses were also performed according to a predefined protocol. Due to the high number of images collected in the ACE 1950 Study, and because we were six investigators analyzing the images, we had regular meetings supervised by the senior cardiologist specialized in echocardiography, to calibrate how we performed the analyses and rule out potential systematic errors and differences. Similarly, the images were analyzed by one investigator in the Stable CAD cohort, who was also supervised by a senior cardiologist with echocardiography as a subspecialty. After the image collections were performed, it has become an increasing focus on test-retest variability in echocardiography studies (175). Regrettably, this was not performed in neither studies, and we are therefore unable to investigate whether special hemodynamic conditions or other factors were causing variations between a study participant's recordings. Furthermore, although we measured resting BP on the same day (either before or after) of the echocardiography recordings in the ACE 1950

Study, we do not have a BP value in immediate relation to the image obtainment, which could have been useful to assess causes of variation.

10.5.1 Mechanical dispersion

Mechanical dispersion by 2D speckle tracking strain, was the main variable assessed in this thesis and merits further methodological discussion. In the ACE 1950 Study, we quantified mechanical dispersion in 68% of the total cohort with echocardiographic images, while 96% of the patients in the Stable CAD cohort had recordings adequate to quantitate mechanical dispersion. There are several reasons for the discrepancy between the two studies: A main reason was the different exclusion criteria between the two studies relating to echocardiographic images. In the ACE 1950 Study, only one excluded strain segment per apical view and no more than two segments in total were accepted before we excluded the patient from quantification of mechanical dispersion (94). In the Stable CAD cohort, we quantitated mechanical dispersion in all patients, except patients with more than two excluded strain segments per apical view or six excluded strain segments in total (73). Both protocols were anchored by recommendations from the European Society of Cardiology Cardiovascular Imaging and American Society of Echocardiography, the former by a position paper on deformation parameters and the latter by the guidelines for cardiac chamber quantification by echocardiography (73, 94). We chose a stricter protocol for exclusion criteria in the ACE 1950 Study to avoid strong influence on the overall result for mechanical dispersion from single segments that tracked poorly. Poorly tracking segments will result in a deformation value that is worse than the real strain value in the participant, i.e. worse GLS, and the result for one segment could potentially have a major impact on the overall result for mechanical dispersion. By using a strict criterion for the GLS analysis, we intended to increase the accuracy of our findings and thereby to increase internal validity. Of note, increased internal validity may come at the cost of reduced external validity. However, our GLS and mechanical dispersion values are similar to the results in other cohorts, which supports external validity for our results to subjects in the same age group and demographics (1, 73, 157, 176). In the Stable CAD cohort, we allowed more segments to track poorly before we excluded the patient from the study. Apical segments usually have a better strain value than basal segments. Thus, the region from which you exclude segments, will influence the overall GLS (94). In the Stable CAD cohort we could quantitate mechanical dispersion in 97% of the strain segments, which is a high proportion of participants. Still, median GLS of -17.7% in this cohort is

within the range of normal values for GLS, and we consider also this cohort to have good internal validity (177).

The feasibility of 68% for GLS and mechanical dispersion in the ACE 1950 Study may be considered as low. However, several large international studies show the same feasibility for the speckle tracking indices**:** The TOPCAT echocardiography sub study had a feasibility of strain analysis (from a 12 segment model, i.e. only two apical views) of 64% (165). In MADIT-CRT, 59% of those included in the main study had images sufficient for strain analysis (also from only two apical views) (178). The community study Northern Manhattan Study (NOMAS) reported a feasibility of 72% for GLS by a 12 segment model, and the large Norwegian population study, the HUNT Study, had a feasibility of ~60% for strain using both a 16 and 18 segment model (179, 180). In the ACE 1950 Study we used a 17 segment model, analyzing images from three apical views, which is similar to the HUNT study. Common for these studies and the ACE 1950 Study, is that none of these studies included feasibility of speckle tracking strain analysis as a main aim when performing the echocardiography recordings and analyses. This differs from studies that only included participants when the echocardiographer actually was able to obtain images considered suitable (during off-line examination) for speckle tracking strain analysis (181). In the Stable CAD cohort we could analyze GLS and mechanical dispersion in 96% of the patients, which is a high percentage compared to the other studies previously referenced. The main explanation for this is that the selection process leading to study participant inclusion assured image quality suitable for strain analysis.

10.6 Cardiac biomarkers

In Paper 2, hs-cTnT and NT-proBNP analyses were handled by a few selected and trained research personnel at Akershus University Hospital, in order to limit the chances of random errors. In Paper 3, the analyses of hs-cTnI were analyzed later by a limited number of personnel at Drammen Hospital, while NT-proBNP was analyzed at the clinical laboratory by regular hospital staff at Oslo University Hospital, Rikshospitalet. The serum used for the analyses of hs-cTnT and NT-proBNP in the ACE 1950 Study was stored at -80°C and was not thawed until the analyses were performed. For hs-cTnI and NT-proBNP, the serum was stored at -70°C and was not thawed until the analyses were performed. There has been a concern regarding potential degradation in samples that have been pre-frozen. However, studies show

that there is little degradation of hs-cTnT, hs-cTnI and NT-proBNP when stored at -80°C (182, 183).

10.7 Statistical considerations and confounding

I have described the strategy for selecting independent variables in the multivariable linear regression analyses in the methods section of this thesis. We tried to build multivariable models by carefully assessing the variables that could affect predictors and the outcome (confounders), both by using knowledge from previous research and logical thinking of factors that could influence mechanical dispersion. The cohort used in paper 1 and 2 was large and many variables were available. We therefore found it most correct to choose variables *a priori*, rather than selecting them through a process where all variables significantly associated with the dependent variable in univariate regression analyses ae included in the final multivariable model. Paper 3 consisted of a much smaller cohort of 160 patients. Due to the lower number of study participants, there was a limit to the number of variables that could be added to the multivariable linear regression model, and we chose to only add the LV indices of systolic function in the model. In paper 1 and 3 we used the forward selection procedure, while in paper 2 we used the simultaneous ("Enter" in SPSS) procedure to perform the multivariable linear regression analyses. The automatic selection procedures have received much criticism: adding increasing number of variables to the models increases the likelihood of coincidental statistical relationship and the procedure may exclude confounders in the final model (184). In paper 1 we found that EF was independently associated with increasing mechanical dispersion in the final multivariable model, meaning that a better LV systolic function is associated with a more dyssynchronous LV contraction pattern. We concluded that this finding probably was spurious, and this could be a result of the increasing number of variables used in the final multivariable model. In paper 2, heart rate at age 40 was not associated with mechanical dispersion in univariate regression analysis. We had decided to include the variable in the final model (*a priori* selection) despite the level of significance in the univariate analysis, and heart rate was subsequently associated significantly with mechanical dispersion in the multivariable analysis. This phenomenon is called "suppression", where potentially important variables will go unrecognized in a univariate screening, and this may occur when using the forward selection procedure or the univariate selection method (185).

A **confounder** is a variable that influence both the predictor and the outcome variable, and may attenuate or augment the association between the predictor and outcome. In order to ensure internal validity, the confounders should be identified and adjusted for in multivariable analyses (186). We can also reduce the effect of confounders by stratifying the population or by defining specific exclusion criteria for the study population. In paper 1 and 2 we tried to carefully identify potential confounders in the statistical plan made a priori. However, there may still be residual confounding from data that we have not collected in the ACE 1950 Study and the Age 40 Study, which may affect the results. An **intermediary variable** is a variable (e.g. DM) that may be caused by the predictor variable and is on the effect pathway between the predictor (e.g. obesity) and the outcome (e.g. mechanical dispersion, Figure 23). Adjusting for the intermediary variable may weaken the association between the predictor and the outcome. In paper 1 the aim was to examine if obesity, DM, hypertension and CAD were associated with worse mechanical dispersion. Accordingly, we included all the predictor variables in the same multivariable models. However, DM may be an intermediary variable for obesity and the multivariable analysis may therefore have attenuated the true association between obesity and mechanical dispersion. Similarly, hypertension may be an intermediary variable for DM and mechanical dispersion, and may therefore attenuate the relationship between DM and mechanical dispersion. Although these interactions may theoretically have affected our results, in real-life, patients present with several of these comorbidities, and therefore our analysis is a realistic approach that should capture real-life scenarios.

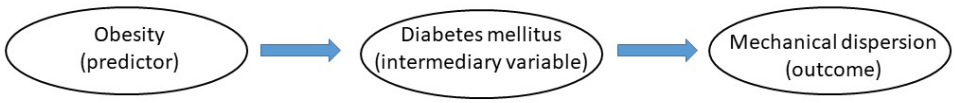

Figure 23. Direct acyclic graph illustrating the role of an intermediary variable.

In paper 3, we tried to reduce the confounding by defining a set of exclusion criteria that could affect mechanical dispersion (e.g. LBBB). The sample size was rather small, which increases the chance of both type 1 and type 2 errors. Because of the sample size and a study population with less severe cardiac disease compared to previous studies on mechanical dispersion (1), there was a low number of primary endpoints (n=14). Accordingly, there was a chance of overfitting when including three variables in the final Cox regression analysis. In

order to be transparent, we included the unadjusted results in the paper. However, our results need to be externally validated as we had a limited sample size and a low number of endpoints.

10.8 Ethical considerations

We registered the ACE 1950 Study on www.clinicaltrials.gov (registration number NCT01555411) prior to inclusion of the first participant in the study. The study was approved by the Regional Ethics Committee, with reference number 2011/1475. The steering committee of the ACE 1950 Study have received permission from the Ethics Committee to link the data from the ACE 1950 Study with data from the Age 40 Program. We also have permission to follow the study participants of the ACE 1950 Study prospectively until year 2050. The study in paper 3 was approved by the Regional Ethics Committee. Participants from all three cohorts have provided written informed consent before being included into the studies. The manufacturers of the biomarker assays, the machine and software used for the echocardiography, are all commercially available, and the manufacturers have had no role in study design or conduction. We performed the studies according to the Declaration of Helsinki.

When performing prospective epidemiological studies, the aim of the studies is often ideally to observe a general population over time without interventions by the researchers. However, it would be considered unethical to not report severe pathology of the study participants, and the line between not intervening and intervening may be overlapping in some cases. In order to handle this issue in an objective and organized manner, we made a detailed protocol for type and severity of pathologies that should be followed by the dedicated echocardiographic team or referred for cardiac work-up. For example, if echocardiography detected moderate aortic valve stenosis, the protocol was to perform follow-up echocardiography according to clinical practice at Bærum Hospital and Akershus University Hospital.

11 Discussion of main findings

During the work of this thesis, I have explored the marker of LV dyssynchrony, mechanical dispersion, in middle-aged subjects from the general population and in patients with chronic coronary syndrome. There was limited information in the literature regarding mechanical dispersion in the general population when I started the work, including no generally accepted reference values for mechanical dispersion. This thesis should therefore add valuable insight into mechanical dispersion, as we published an upper limit of normal for the age-specific cohort. We also found hypertension and established CAD to be associated with higher mechanical dispersion values in the general population. In addition, high BMI and triglycerides around age 40 years were associated with increased mechanical dispersion measured 20 years later. We also found mechanical dispersion to associate with hs-cTnT and NT-proBNP concentrations in subjects aged 62-65 years (cross-sectional data). Finally, among stable CAD patients, mechanical dispersion associated with poor long-term prognosis while EF and GLS did not. Mechanical dispersion provided incremental prognostic ability when added to EF, GLS and hs-cTnI, but not when added to NT-proBNP. Mechanical dispersion >64 ms identified patients with poor prognosis.

11.1 Limit of normality and pathology for mechanical dispersion (Paper 1)

In paper 1, we found that 61 ms was the upper limit of normal for mechanical dispersion in our cohort. The value is based on a large reference population of 594 men and women, which is larger than in previous studies (157, 187-189). To compare, echocardiographic images from 201 men and 319 women were used as the reference population for the current calculations of EF reference values (73). The contribution from the rather large ACE 1950 Study population could therefore be valuable, both for identifying reference values and to broaden our knowledge on the pathophysiology associated with high mechanical dispersion. Other groups have reported similar results for upper limit of normal of mechanical dispersion, although their reference populations were smaller. The data of these studies have been put up for comparison in table 2.

Table 2. Overview on studies of upper limit of normal (ULN) for mechanical dispersion

First author	*Year*	*Sample size*	*Age, years*	*Mechanical dispersion*	*ULN*
Conca (187)	2009	120	44	28.9 ± 11.52	57 ms*
Morris (190)	2012	106	42	27.4 ± 11.7	50 ms†
Rodriguez-Zanella (157)	2017	303 51	42 (median) >60	34 ± 10 41 ± 10	56 ms* 64 ms*
Perry (189)	2019	200	70 (median)	53.5 ± 11	75 ms‡
Aagaard (107)	2020	594	64	35.7 ± 12.7	61 ms‡

*ULN calculated as 97.5th percentile. †ULN calculated as mean+1.96 SD. ‡ULN calculated as mean+2 SD. Age and mechanical dispersion are presented as mean ± SD unless otherwise stated.

Conca et al. reported in 2009 reference values for echocardiographic indices of LV synchrony, including mechanical dyssynchrony measured by 2D speckle tracking strain (mechanical dispersion), in a population of 120 subjects from Ticino (Lugano, Switzerland) (187). Mean age was 44 years and upper limit of normal, calculated as the 97.5th percentile, was 57 ms. Morris et al. reported an upper limit of normal of 50 ms for mechanical dispersion, calculated as mean + 1.96 SD (from 106 healthy subjects with mean age 42 years) (188). In 2017 Rodriguez-Zanella et al. published reference values for mechanical dispersion and examined its predictors (157). The sample-size was 334 subjects of whom 51 were older than 60 years. Upper limit of normal for the age group older than 60 years was reported as 64 ms, which was also calculated as the 97.5th percentile. The 97.5th percentile and 1.96 SD above mean should ideally yield the same value. However, if mechanical dispersion is not perfectly normally distributed in the population, the two values will differ slightly. In our study, we calculated the upper limit of normal as mean + 2 SD, which is also the method used in a study by Perry et al. (189). Despite slightly different methods used to calculate upper limit of normal in these studies, the differences in all the reported reference values are not numerically large. We know from paper 1 that increasing age is independently associated with increasing mechanical dispersion, and the upper limit of normal from paper 1 and from Rodriguez-Zanella et al. is in line with what could be expected according to age. Most of the aforementioned studies used EchoPAC software (GE Healthcare, Horten, Norway) to perform the speckle tracking strain analyses, and data have been lacking from other software producers. However, the recent

Australian study by Perry et al. used the TOMTEC software (TOMTEC, Unterschleissheim, Germany) and presented upper limit of normal of mechanical dispersion of ≥75 ms (189).

It should be emphasized that the upper limit of normal of 61 ms for the general population found in paper 1 does not reflect a cutoff value to predict incident ventricular arrhythmias. The data we presented were cross-sectional and therefore without information regarding clinical end-points. However, we plan to examine the predictive value of mechanical dispersion for incident cardiac death when we have follow-up data in our study. Several studies have examined the association between high mechanical dispersion and ventricular arrhythmias, and shown that mechanical dispersion can predict arrhythmic events in a wide range of cardiac diseases (1). One seminal study from 2010 examined the predictive ability of mechanical dispersion by speckle tracking strain in patients that had suffered myocardial infarction (2). In this study, mechanical dispersion >70 ms was associated with future fatal ventricular events (2). A meta-analysis from 2019 concluded that mechanical dispersion was superior to GLS and EF to predict ventricular arrhythmic events and that mechanical dispersion >60 ms identified subjects at risk of ventricular arrhythmia (1). The studies included in the meta-analysis, were primarily on patients with cardiomyopathies or who had suffered a myocardial infarction. The aforementioned study by Perry et al. evaluated the ability of mechanical dispersion to predict the risk of ventricular arrhythmias and sudden cardiac death in > 900 patients with moderate to severe LV dysfunction (EF <45%) irrespective of the cause (189). Interestingly, their upper limit of normal of 75 ms calculated from the healthy control group, was also the cutoff value for pathology that predicted fatal ventricular arrhythmic events. Based on these findings, and the evidence leaning towards an increased risk of ventricular arrhythmias at values of mechanical dispersion above 60-75 ms, it seems that the upper limit of normal of 61 ms in our general population study may also be a cutoff level for pathology and the prediction of incident ventricular arrhythmias. To date, there is limited information on mechanical dispersion and its ability to predict ventricular arrhythmias and sudden cardiac death in the general population. A recent publication from the Copenhagen Heart Study found that, in a general Danish population, mechanical dispersion >51 ms was associated with CV death but not with non-CV death (113). These researchers also found that mechanical dispersion had incremental prognostic value to established risk prediction scoring systems in multivariable statistical analysis. However, there was no information regarding the specific causes of CV death, and additional studies are needed to investigate whether mechanical dispersion has a role in specifically predicting ventricular arrhythmias and sudden cardiac death in the general population.

11.2 Determinants of mechanical dispersion and its predictive abilities (Paper 1-3)

In paper 1, we found that CAD, hypertension, DM and obesity were independently associated with increased mechanical dispersion. Adjusting also for echocardiographic indices in a multivariable model, the associations with DM and obesity were attenuated and no longer significant, while CAD and hypertension remained associated with mechanical dispersion. In paper 2, we showed that increasing BMI and triglyceride concentration measured at age 40 years were independently associated with increasing mechanical dispersion two decades later. The associations remained after adjusting for established CAD at age 64 years, which suggests that the CV risk factors are not only associated with mechanical dispersion through established ischemic heart disease alone, but also additional pathways. In paper 3, we found that mechanical dispersion was independently associated with all-cause mortality and composite endpoint among patients with stable CAD during long-term follow-up.

There is limited information on the association between established CAD and mechanical dispersion in the general population. The previously mentioned publication on mechanical dispersion in the Copenhagen Heart Study did not report specifically on this subject (113). They did, however, show in the baseline table, a higher prevalence of previous myocardial infarction among subjects with the highest tertile of mechanical dispersion compared to the lowest. That CAD was independently associated with increased mechanical dispersion in paper 1 is not surprising. Ischemia may cause destruction of myocardial cells leading to scar tissue formation in the myocardium and areas of focal fibrosis. Such areas with fibrosis may induce dyssynchronous contraction pattern of the LV (191). The model of myocardial fibrosis as an underlying driver for dyssynchronous LV contraction is supported by a recent study by Abou et al. of 96 patients with first time acute ST-segment elevation myocardial infarction (STEMI) that were treated with percutaneous coronary intervention (192). This retrospective study investigated the correlation between the presence of scar tissue on cardiac MRI assessed by late gadolinium enhancement (LGE), and mechanical dispersion by 2D strain echocardiography. Scar tissue on LGE was assessed as the total scar burden, defined as signal intensity ≥35% of maximal myocardial signal intensity, infarct core (defined as ≥50% of maximal signal intensity) and the border zone (defined as 30-50% of maximal signal intensity). The researchers found that mechanical dispersion correlated with infarct core ($r=0.517$, $p<0.001$), total scar burden ($r=0.497$, $p<0.001$) and border zone ($r=0.298$, $p=0.003$). Median value of mechanical dispersion was 53.5 ms, and patients with values

above median had a higher event rate for the combined endpoint of all-cause mortality or appropriate implantable cardioverter-defibrillator therapy than patients with mechanical dispersion below median value. Mechanical dispersion also demonstrated higher area under the curve for the prediction of the combined endpoints than GLS, total scar burden, infarct core, border zone and EF. Their findings support a model that mechanical dispersion may be a marker of LV fibrosis after myocardial infarction. However, mechanical dispersion predicted outcomes better than scar burden itself and may therefore reflect additional myocardial pathophysiology leading to LV contraction disturbances and increased risk of ventricular arrhythmias.

Several studies on mechanical dispersion have been performed among patients suffering from acute myocardial infarction, including both STEMI and non-STEMI patients (2-4). These studies all demonstrate that mechanical dispersion can predict ventricular arrhythmias after myocardial infarction regardless of EF. However, less is known about mechanical dispersion as a prognostic marker in patients with chronic coronary syndrome. In the Stable CAD cohort, we did not have specific data regarding ventricular arrhythmic events, but we showed that mechanical dispersion predicted long-term prognosis of all-cause mortality and hospitalization due to recurrent myocardial infarction or HF regardless of EF, GLS and hs-cTnI. In this study, the median (IQR) mechanical dispersion was 46 (37-54) ms, which was lower than in the STEMI population of Abou e al., likely reflecting a population with less severe CVD (192). The Stable CAD cohort was a heterogeneous group of patients that underwent revascularization due to either non-ST-elevation myocardial infarction, but also due to unstable angina pectoris or chronic coronary syndrome. STEMI occurs when there is an occlusion of a coronary artery, and the risk for myocardial damage is high (193). Median value of mechanical dispersion in the STEMI population may be higher than in the Stable CAD patients as myocardial damage is usually more severe in STEMI patients, thereby leading to scar tissue formation and later focal contraction abnormalities (segmental dyskinesia). Despite the risk of myocardial damage, HF and death due to myocardial infarction, it is worth emphasizing that mechanical dispersion was still superior to GLS and EF in prediction of primary and secondary endpoints in the Stable CAD cohort. This reflects that mechanical dispersion may be a good predictive marker also in patient groups with less severe cardiac disease, which is an important finding in our work and novel information to prior studies performed in subjects with more established and severe CVD (1).

In paper 1, we also show that hypertension was independently associated with mechanical dispersion in the general population in cross-sectional analysis, also after

adjustment for LBBB, right bundle branch block and LV mass index. In paper 2, diastolic blood pressure in early forties showed a tendency towards an association with increased mechanical dispersion ($p = 0.05$) measured two decades later, although it did not reach the level of statistical significance. Hypertension that is not properly treated, commonly causes LV concentric hypertrophy and can lead to LBBB in selected individuals (194). LBBB and LV hypertrophy may both cause dyssynchronous LV contractions due to mechanical and electrical alterations in the heart. However, hypertension remained associated with increased mechanical dispersion, despite adjustment for LBBB, right bundle branch block and LV mass index. Hence, other, yet unknown mechanisms may also explain the association between hypertension and increased mechanical dispersion. Hypertension is a major risk factor for CAD, which seems associated with increased mechanical dispersion. Whether dyssynchrony due to hypertension may be a result of atherosclerotic disease and/or more direct fibrotic alterations in the myocardium, is currently not known. A study on mechanical dispersion in patients with hypertrophic cardiomyopathy supports the notion that mechanical dispersion may be linked to myocardial fibrosis (108). In this study by Haland et al., 150 patients with hypertrophic cardiomyopathy and 50 healthy controls were assessed with 2D strain echocardiography and cardiac MRI. The extent of fibrosis was defined as the sum of areas with LGE present on MRI, and quantified as the proportion of the whole LV myocardium, %LGE. The occurrence of ventricular arrhythmias was assessed by implantable cardioverter-defibrillator and 24-48 hours ECG monitoring. The researchers found that mechanical dispersion and %LGE correlated moderately ($r=0.52$, $p<0.001$), while the correlation for GLS and %LGE was weak ($r=0.27$, $p=0.01$). Mechanical dispersion was a strong and independent predictor of ventricular arrhythmias, also in multivariable analysis that adjusted for the presence of LGE.

We also report associations between other CV risk factors and mechanical dispersion. In paper 1 and 2, we found increasing BMI and high triglyceride concentrations at age 40 to be associated with increasing mechanical dispersion when quantitated 20 years later. In cross-sectional analysis at age 62-65 years, obesity and DM were also associated with increasing mechanical dispersion before adjusting for echocardiographic indices of cardiac dimensions and function. Few studies on this subject exist from the general population. A publication from the Belgian population study (FLEMENGHO) found that BMI was independently associated with increasing mechanical dyssynchrony by tissue velocity imaging assessment, and Rodriguez-Zanella et al. found BMI to be associated with mechanical dispersion in univariate linear regression analysis (157, 166). Data from the Copenhagen Heart Study

showed significantly higher BMI and total cholesterol concentrations among subjects with high compared to low mechanical dispersion (113). In the same study, there was no between group difference for DM, and they did not report on triglyceride concentrations. Hypertension, DM, obesity and increased cholesterol and triglyceride levels are all risk factors for CAD and could potentially be associated with mechanical dispersion through the pathophysiological development of atherosclerosis. However, in paper 2, we performed a sensitivity analysis where we also adjusted for CAD at age 64 years, and this did not affect the associations between BMI and triglyceride concentrations at age 40 years and mechanical dispersion measured two decades later. In paper 1, obesity and DM were independently associated with increased mechanical dispersion, also when CAD was included in the same multivariable model. The pathobiology underlying the increasing mechanical dispersion in participants with hypertension, DM, increasing BMI, obesity and high triglyceride concentrations, is probably multifactorial. An editorial on the publication by Haland et al. on mechanical dispersion and its correlation to fibrosis among patients with hypertrophic cardiomyopathy, stated that mechanical dispersion could reflect replacement and interstitial fibrosis, together with macro- and microvascular ischemia (108, 195). This view is intriguing and may explain our results, however, more research is needed in order to confirm this hypothesis.

11.3 Mechanical dispersion and cardiac biomarkers (Paper 2-3)

One of the aims of this thesis was to assess whether mechanical dispersion is associated with the biomarkers of subclinical myocardial injury (hs-cTnT) and dysfunction (NT-proBNP) in the general population, and we found that mechanical dispersion was independently associated with both hs-cTnT and NT-proBNP after adjusting for CVD risk factors (paper 2). We also aimed to assess the predictive value of mechanical dispersion compared to EF, GLS, hs-cTnI and NT-proBNP for stable CAD patients, and found that mechanical dispersion have incremental prognostic ability to EF, GLS and hs-TnI, but not to NT-proBNP (paper 3).

Although biomarkers are influenced by non-cardiac factors such as renal dysfunction, studies in the general population show that NT-proBNP concentrations reflect LV dysfunction, especially when EF is less than 40% (144, 145). Data from Olmsted County, Minnesota, have also demonstrated that BNP can predict subclinical LV dysfunction (143). However, for mild LV dysfunction, the natriuretic peptides are less sensitive, which should be taken into account when interpreting our results (141, 145). Both hs-cTnT and hs-cTnI are used in the diagnosis of acute myocardial infarction and are markers of myocardial injury (196). We know from the

large general population studies, ARIC and the Dallas Heart Study, that hs-cTnT can predict CAD, HF and mortality in individuals free from CVD at baseline, and that hs-cTnT is independently associated with structural heart disease measured on MRI (126, 128). These studies have also shown that the presence of hs-cTnT increases with age, and that concentrations of hs-cTnT were detected in 25 % in the adult population, age 30-65 years (the Dallas Heart Study), and in 66.5% among middle-aged and older individuals, age 54-74 years (ARIC). Similar results have been found for hs-cTnI in a large population study from Scotland (n= 15 340) (129). They found that hs-cTnI concentrations could be measured in 74.8% of all study subjects (mean age 48.9 years) and that hs-cTnI was a strong and independent predictor of CVD events (129).

In paper 2, we found mechanical dispersion to be independently associated with hs-cTnT and NT-proBNP concentrations when measured in subjects 62-65 years, but these associations were of modest strengths, and we did not find a significant correlation between mechanical dispersion and NT-proBNP concentrations. One explanation for the modest strength of the associations, may be that the ACE 1950 Study population consists of predominately healthy individuals without LV dysfunction or myocardial injury, which is demonstrated by normal values of the echocardiographic indices of LV function and the cardiac biomarkers (median EF 56%, median GLS -20.2%, median hs-cTnT 6.0 ng/L and median NT-proBNP 54.0 ng/L). Another explanation is that the biomarkers and mechanical dispersion may possibly display different aspects of pathophysiology in cardiac disease, and the results may reflect that neither hs-cTnT and NT-proBNP concentrations nor mechanical dispersion capture all aspects of cardiac disease. Mechanical dispersion is most of all a functional marker of the segmental movement and dyssynchronous contraction pattern of the LV, which can be due to several underlying conditions influencing the electrical conduction system and the mechanics of LV contraction, including focal and interstitial fibrosis. Cardiac troponins are also associated with myocardial fibrosis and LV structural changes (197), and the associations between mechanical dispersion and hs-cTnT concentrations could originate from the reflection of common underlying pathobiology, most notably myocardial fibrosis or LV structural changes. However, there is a need for additional experimental and clinical studies to establish possible common pathobiology more in detail.

In the Stable CAD cohort, mechanical dispersion correlated moderately with both hs-cTnI and NT-proBNP concentrations ($r=0.442$, $p<0.001$ and $r=0.390$, $p<0.001$, respectively), while in the ACE 1950 Study the correlations between mechanical dispersion and the biomarkers were either weak or non-significant ($r=0.084$, $p<0.001$ for hs-cTnT and $r=0.029$,

p=0.149 for NT-proBNP). The difference in these results could be due to a population with more pronounced cardiac disease among the stable CAD patients. NT-proBNP concentrations were elevated above 97.5th percentile in 17% of the stable CAD patients, and median (IQR) value was higher and with a larger spread that in the ACE 1950 Study (74 [34-205] ng/L vs. 54 [33.8-93.0] ng/L). Among the stable CAD patients, we also found that mechanical dispersion was superior to EF, GLS and hs-cTnI, but not to NT-proBNP concentrations in predicting adverse outcome. NT-proBNP is well-documented as an excellent prognostic marker, superior to conventional CVD risk factors and LV dysfunction measured by EF (198), and our results provide additional evidence for this model for NT-proBNP.

12 Conclusion and perspectives

12.1 Conclusions

The main conclusions of this thesis are as follows:

1. CAD and hypertension are independently associated with increasing mechanical dispersion among 64 year olds in a large general population, and upper limit of normal for mechanical dispersion in this age group is 61 ms.

2. In subjects from the general population, increasing BMI and triglyceride concentrations at age 40 are independently associated with increasing mechanical dispersion 2 decades later.

3. In subjects in their mid-sixties from the general population, mechanical dispersion is independently associated with the biomarkers reflective of myocardial injury and dysfunction, hs-cTnT and NT-proBNP, respectively.

4. Among patients with stable CAD, mechanical dispersion associate with long-term prognosis of all-cause mortality and composite endpoint, while GLS and EF did not. Mechanical dispersion was found to have incremental prognostic value to EF, GLS and hs-cTnI, but not to NT-proBNP among patients with stable CAD.

12.2 Perspectives and future research

This thesis has provided results that expand the current knowledge on mechanical dispersion and strengthens the notion of mechanical dispersion as a useful prognostic marker. Our results on the upper limit of normal has validated and strengthened the findings from previous studies, and it seems that ~ 60-65 ms is a robust reference value for middle-aged subjects. There are indications that the reference value may also predict poor prognosis and maybe even future arrhythmic events in subjects from the general population, however, more research is needed before mechanical dispersion possibly can be used in the implantable cardioverter defibrillator assessment of subjects without known CVD and in a screening setting. Based on what we currently know, mechanical dispersion can be used in a clinical echocardiographic setting for evaluating cardiac disease, and especially in the diagnostic work-up of patients with syncope

suspicious of ventricular arrhythmia. Finding increased mechanical dispersion in such a situation, should elicit attention and trigger investigations regarding the potential for future ventricular arrhythmias.

We have also provided new knowledge on the prognostic ability of mechanical dispersion in patients with stable CAD. These findings will need to be validated in larger cohorts. However, in the clinical follow-up of patients with stable CAD and increased mechanical dispersion, the clinician should consider to perform further examinations, including measuring NT-proBNP concentration and maybe perform 24-72 hours ECG registration and clinically assess reasons for the dyssynchronous LV contractions. If, for example, the increased mechanical dispersion in such a case is due to HFrEF or LV dilatation, the medical treatment should be optimized, and the patient scheduled for a follow-up echocardiography. Although not widely implemented in a clinical setting, mechanical dispersion may add useful information in a clinical assessment where many different variables are being used, and especially when the conventional diagnostic tests point in diverging directions.

Our work also provides information about risk factors for CVD associated with increased mechanical dispersion. The reason for these associations and whether these findings have clinical implications is currently unknown. Further studies are needed where individuals with these conditions are followed prospectively regarding cardiac death, in particular sudden cardiac death or ventricular arrhythmic events. In addition, it would be interesting to evaluate these patients again with a new mechanical dispersion assessment and cardiac MRI, to investigate the presence of myocardial fibrosis and the relationship to the CVD risk factors and to mechanical dispersion. Finally, in order for mechanical dispersion to be implemented in general clinical cardiology, the dyssynchrony index will need to show incremental value to established diagnostic and prognostic tests and scoring systems.

13 References

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ORIGINAL ARTICLE
Epidemiology & Prevention

Associations between cardiovascular risk factors, biomarkers, and left ventricular mechanical dispersion: insights from the ACE 1950 Study

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Aims Mechanical dispersion measures left ventricular contraction heterogeneity and is associated with the risk of sudden cardiac death. However, the associations between mechanical dispersion and cardiovascular risk factors in early mid-life, and established biomarkers of sub-clinical myocardial injury and dysfunction are not known. We aimed to examine this in the general population.

Methods and results During 2012–15, we included 2527 Norwegian individuals from the general population born in 1950, with measurements of mechanical dispersion by 2D speckle tracking echocardiography and concentrations of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) available. Mechanical dispersion was calculated as the standard deviation of the contraction duration of 17 strain segments. We assessed the associations between mechanical dispersion, concentrations of hs-cTnT and NT-proBNP, and cardiovascular risk factors collected at a national health screening survey two decades earlier. At echocardiography baseline, median age was 64 (interquartile range 63.5–64.5) years, 49.8% were women, 59.1% had hypertension, and 5.9% reported established coronary artery disease. Median mechanical dispersion was 38.0 (29.5–47.0) ms, median hs-cTnT concentration 6 (4–8) ng/L, and the median NT-proBNP concentration 54 (34–93) ng/L. Mechanical dispersion was associated with both hs-cTnT and NT-proBNP concentrations in multivariable models adjusted for clinical and echocardiographic variables. High body mass index, serum triglyceride concentrations, and low resting heart rate at Age 40 were independently associated with increased mechanical dispersion two decades later.

Conclusion Established risk factors at Age 40 are associated with mechanical dispersion two decades later, and mechanical dispersion is cross-sectionally associated with biomarkers of subclinical myocardial injury and dysfunction.

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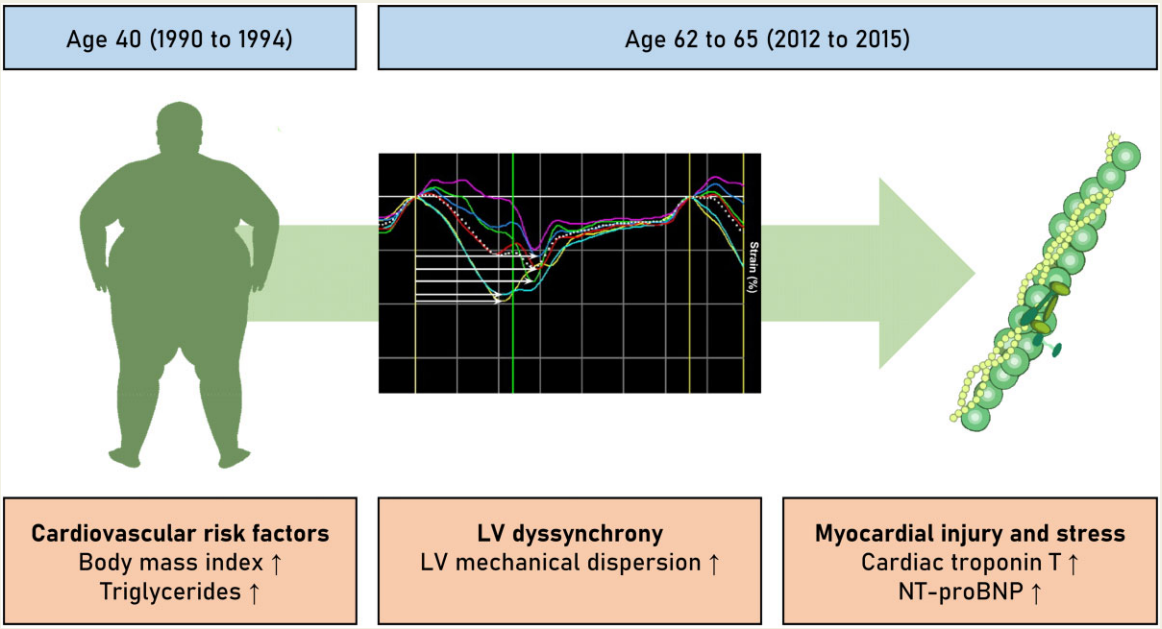
Graphical Abstract



Keywords Mechanical dispersion • Two-dimensional speckle tracking echocardiography • Myocardial strain • Cardiac biomarkers • General population

Introduction

Heart failure is one of the most common causes of morbidity and mortality in the Western world.[1] Circulating biomarkers identify subjects at increased risk of heart failure[2] but are less accurate to identify specific pathophysiologic mechanisms like the risk of future ventricular arrhythmias.[3] Recently, novel imaging-based risk markers by echocardiography like mechanical dispersion have been identified, which seem to predict incident ventricular arrhythmias and death in patients with established cardiovascular (CV) disease.[4]

Mechanical dispersion measures the heterogeneity of the contraction pattern of the left ventricle (LV) and is derived from global longitudinal strain (GLS) by two-dimensional speckle tracking echocardiography (2D STE). A higher value of mechanical dispersion reflects a more dyssynchronous LV contraction pattern, which may increase the risk of ventricular arrhythmias.[4] We have previously shown that in the general population, coronary artery disease (CAD) and hypertension are associated with higher mechanical dispersion.[5] Additionally, a recent publication reports that mechanical dispersion in the general population was associated with cardiac death.[6] CV risk factors during early adulthood may impact the progression of mechanical dispersion, but currently, no information is available regarding the association between clinical risk factors in the early forties and mechanical dispersion at age ~65 years.

Mechanical dispersion has also been proposed to reflect fibrosis and electromechanical changes in the myocardium, but whether this transcends to middle-aged subjects from the general population is not known.[7,8] Cardiac biomarkers like high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are considered surrogate markers for subclinical myocardial injury and dysfunction.[9–13] We propose that mechanical dispersion is associated with cardiac biomarkers of subclinical myocardial injury and dysfunction.[14–16] Using a cohort of late mid-life individuals recruited from the general population, the current study aimed to test the hypotheses that (1) clinical CV risk factors in the early forties are associated with mechanical dispersion two decades later, and (2) mechanical dispersion measured in mid-sixties correlates cross-sectionally with cardiac biomarkers of subclinical myocardial injury and dysfunction.

Methods

Study population

The study design and methods of the Akershus Cardiac Examination (ACE) 1950 Study have been described previously.[17] In short, all residents of Akershus County, Norway, born in 1950 were invited to participate in a prospective population-based health examination study. In total, 3706 individuals participated (participation rate 63.6%), and were extensively evaluated regarding CV risk factors and disease with a baseline study visit performed for all participants. The study participants were aged 63–65 years at study inclusion, which was performed between 2012 and 2015 at two study sites (Akershus University Hospital and Bærum

Hospital). In the present study, we included participants with echocardiographic recordings avaiable for mechanical dispersion analyses by 2D STE ($n = 2529$) that also had available measurements of the biomarkers hs-cTnT and NT-proBNP ($n = 2527$). Previously, 1906 (75.4%) of the participants from the present study had also attended another Norwegian nationwide health survey that included self-assessed questionnaires, clinical examination, and non-fasting blood sampling (The Age 40 Program, *Figure 1*). The survey was conducted by the National Health Screening Service and aimed to investigate the CV risk profile of 40-year-olds. This national survey was performed between 1990 and 1994 for participants born in 1950, approximately two decades before the baseline visit of the ACE 1950 Study. Accordingly, we have measured and self-reported data on CV risk factors in the early forties from the majority of our participants, and prior to the potential development of CV disease. One participant with a self-reported history of premature myocardial infarction at the Age 40 Program was excluded from the analysis.

The ACE 1950 Study participants provided written informed consent before study inclusion and the consent also permitted linkage of data from previous Norwegian health studies. The study complies with the Declaration of Helsinki and was approved by the Regional Ethics Committee with reference number 2011/1475, and is registered at Clinicaltrials.Gov with registration number NCT01555411.

Echocardiography at the ACE 1950 Study baseline visit

We performed transthoracic echocardiography using Vivid E9 (GE Healthcare, Horten, Norway) and images were stored digitally and later analysed off-line using EchoPac version 201 (GE Healthcare, Horten, Norway). The methods for echocardiography recordings and analyses were performed according to a predefined study protocol and have previously been described in detail.[5] LV systolic function was assessed by LV ejection fraction (EF) according to the modified Simpson's biplane method, and GLS and mechanical dispersion were determined by 2D STE. GLS was analysed semi-automatically by tracing the mid-wall myocardium in three apical views, averaging peak systolic strain values from 17 strain segments.[18,19] Two cardiac cycles were measured. The region of interest was adjusted to fit the myocardial thickness, and the operator manually adjusted segments that failed to track. Segments that subsequently failed to track properly were excluded, and the whole analysis was excluded if more than one segment per image view, or more than two segments in total failed to track properly. Peak systolic strain was defined as maximal peak negative strain during systole, where the start of systole was defined by R wave on the electrocardiogram (ECG) and end of systole defined by the aortic valve closure in apical long-axis view. Mechanical dispersion was calculated automatically by EchoPac as the standard deviation (SD) of contraction duration of 17 strain segments. Contraction duration was defined as the time from R wave on ECG to peak negative strain, regardless of the aortic valve closure (*Figure 2*).

LV mass was calculated from M-mode measurements according to the method described by Devereux *et al.*[20] Diastolic function was assessed by the average of septal and lateral peak early diastolic velocity by tissue velocity imaging (e'), the ratio between peak early diastolic velocity (E) by pulsed Doppler and e' (E/e'), maximal tricuspid regurgitation velocity (TR V_{max}) and left atrial (LA) volume index (end-systolic volume/body surface area). Indexed measures were calculated using body surface area by the Mosteller formula.[21] Cardiac dimensions and established indices of systolic and diastolic function were analysed according to current guidelines.[19,22]

Intra-observer and inter-observer variability testing were performed by two observers (E.N.A. and B.K.) in 15 randomly selected patients for GLS and mechanical dispersion, and expressed by intra-class correlation values.

Circulating biomarkers and blood sampling at the ACE 1950 Study baseline visit

Fasting peripheral venous blood samples were drawn on the same day as the echocardiographic recordings in the ACE 1950 Study, centrifuged at

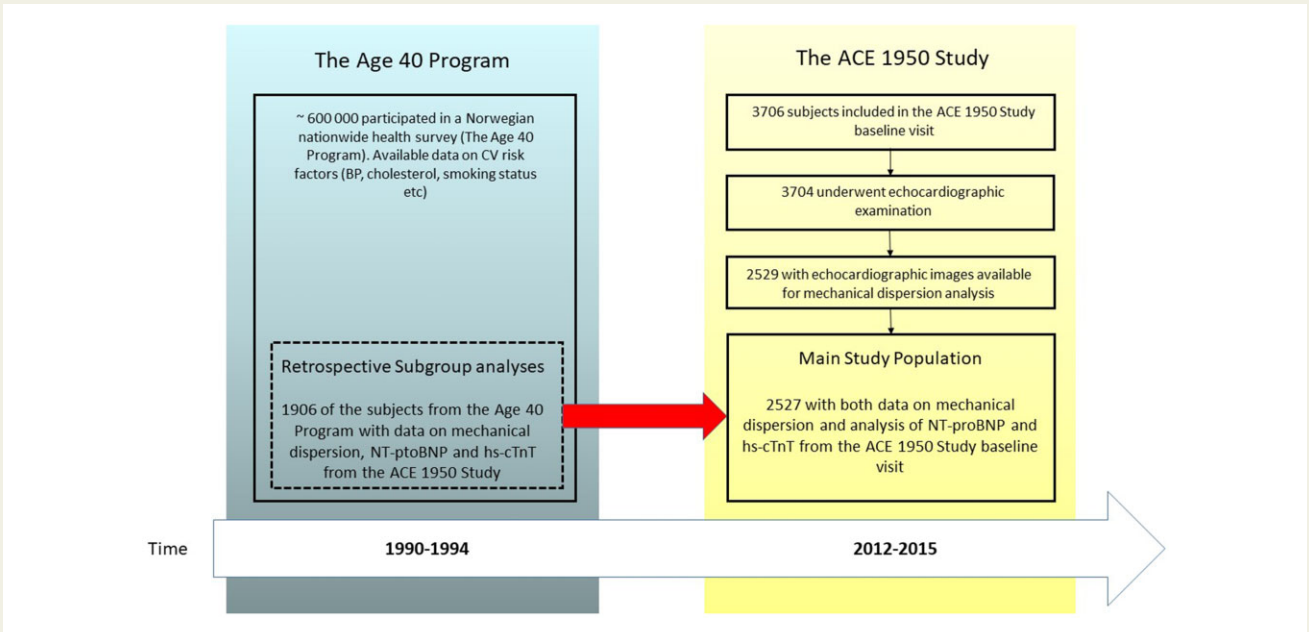


Figure 1 Overview of the study population, including timeline. The ACE 1950 Study was performed when the participants were 64 years old, and the Age 40 Program when the participants were 40 years old.

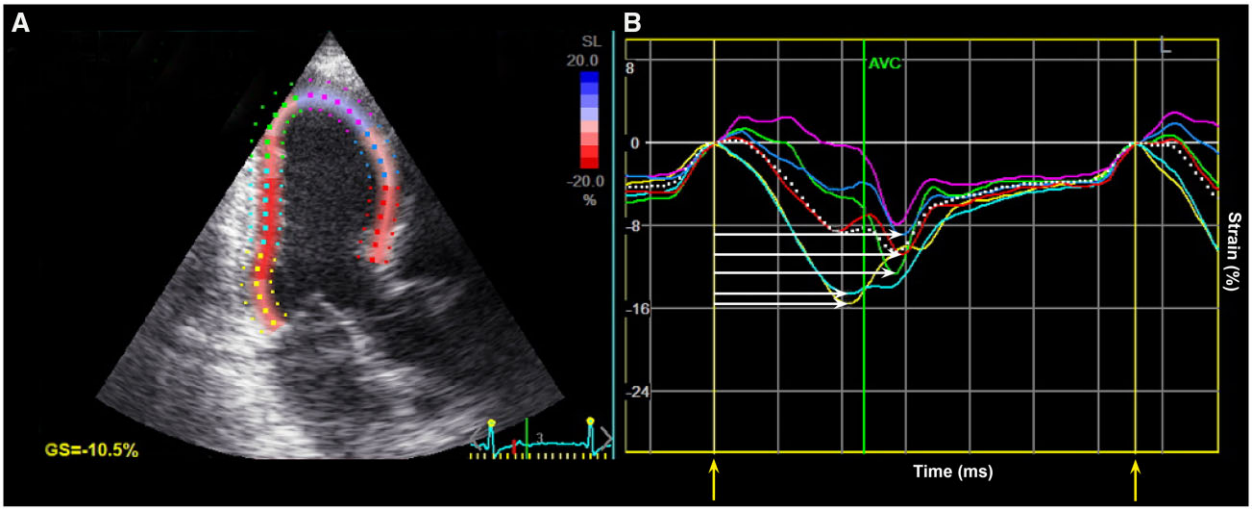


Figure 2 (*A*) Strain tracing of apical long-axis view. (*B*) Strain curves from same image. Yellow vertical arrows indicate R on the electrocardiogram. White horizontal arrows demonstrate contraction duration per strain segment. Mechanical dispersion was defined as standard deviation of contraction duration of all segments. AVC, aortic valve closure.

room temperature and serum was frozen at -80°C. NT-proBNP and hs-cTnT concentrations are considered stable when stored at -80°C.[23,24] Both biomarkers were analysed between October 2017 and January 2018 at Akershus University Hospital, Norway. NT-proBNP and hs-cTnT concentrations were measured on Cobas Platform 8000, e801 (Roche Diagnostics, Rotkreuz, Switzerland) using the proBNP II assay and the STAT hs-Troponin T assay. For NT-proBNP, the limit of detection (LoD) was 5.0 ng/L and the limit of blank (LoB) was 3.0 ng/L, and for hs-cTnT LoD was 3.0 ng/L and LoB was 2.5 ng/L. Study participants with concentrations below the LoD were given a concentration of 2.5 ng/L for NT-proBNP and 1.5 ng/L for hs-cTnT.

Details regarding serum cholesterol variables and renal function are found in Supplementary material online, *Methods*.

Clinical variables at the ACE 1950 Study and Age 40 Program study visits

Demographic and clinical variables from the ACE 1950 Study participants have been previously reported.[5] Details concerning variables from the ACE 1950 Study baseline visit and the Age 40 Program are presented in the Supplementary material online, *Methods*.

Statistical analysis

Baseline characteristics were reported according to the median value of mechanical dispersion (38 ms) in our cohort. Continuous variables were reported as median (interquartile range), and categorical variables as absolute numbers (percentages). Comparisons of groups were made by the Mann–Whitney *U* test for continuous variables and by χ^2 tests for categorical variables. Comparisons of paired samples were made by the Wilcoxon Signed Rank test for continuous variables and by the McNemar's Test for categorical variables. Due to a highly right-skewed distribution, hs-cTnT and NT-proBNP concentrations were transformed by the natural logarithm prior to regression analyses. hs-TnT and NT-proBNP concentrations were used as dependent variables to assess the associations with mechanical dispersion, GLS and LVEF in multivariable linear regression analyses. We assessed the associations of mechanical dispersion, GLS, and LVEF with hs-cTnT and NT-proBNP separately for each echocardiographic index and in analyses in which all three indices were included. We adjusted for the study sites at the ACE 1950 Study baseline visit, demographic data and *a priori* selected variables associated with CV risk. We also adjusted for current statin therapy, as it may attenuate associations with cardiac troponins.[25] We performed the regression analysis in the following fashion: Model 1, unadjusted; Model 2, adjusted for age and sex; and Model 3, adjusted for age, sex, study site, higher education level, body mass index (BMI), estimated glomerular filtration rate (eGFR), total cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes mellitus, hypertension, CAD, statin therapy, and current smoking.

We performed linear regression analyses using data from the Age 40 Program to determine whether CV risk factors in the early forties were associated with increased mechanical dispersion in the mid-sixties. Mechanical dispersion obtained at the ACE 1950 Study baseline visit was used as a dependent variable, and we performed univariate and multivariable linear regression analysis with *a priori* selected variables obtained at the Age 40 Program visit: Age at the Age 40 Program visit, sex, resting heart rate, systolic and diastolic blood pressure, BMI, inactive lifestyle, hypertensive medication, diabetes mellitus, current smoking, and non-fasting serum total cholesterol and triglyceride concentrations. We performed three sensitivity analyses on the associations between CV risk factors and mechanical dispersion: (1) Entering only variables with a *P*-value <0.05 in univariate analysis in to the final multivariable analysis, (2) additionally adjusting the multivariable model for established CAD at the ACE 1950 Study baseline visit and (3) additionally adjusting the multivariable model for length of follow-up time between the Age 40 Program and the ACE 1950 Study baseline.

Statistical significance was defined as $P < 0.05$, and we used IBM SPSS Statistics for Windows, version 25.0 and STATA 16 (StataCorp LP, College Station, TX, USA) for the analyses.

RESULTS

Baseline characteristics in the ACE 1950 Study stratified according to median value of mechanical dispersion

Of 2527 participants included in the present study, median age was 64 [interquartile range (IQR) 63.5–64.5] years, 49.8% were women, 59.1% had hypertension, and 5.9% reported established CAD. The median (IQR) value for mechanical dispersion was 38.0 (39.5–47.0) ms and participants with supra-median mechanical dispersion were more often non-Caucasians, obese, and fewer had higher-education (*Table 1*). Participants with high mechanical dispersion values also had a higher prevalence of diabetes mellitus, hypertension, and CAD. The prevalence of current smoking at the ACE 1950 Study baseline visit did not differ between the groups.

Mechanical dispersion and conventional echocardiographic indices in the ACE 1950 Study

Median (IQR) values for LVEF were 56 (52–59)% and median GLS value was -20.2 (-21.8 to -18.5)% in the current study cohort. We found significant differences for echocardiographic indices of systolic function according to mechanical dispersion: LVEF 55 (52–59)% for participants with high mechanical dispersion vs. 56 (53–59)% for participants with low mechanical dispersion ($P = 0.002$) and GLS -19.7 (-21.4 to -17.8)% for participants with high mechanical dispersion vs. -20.6 (-22.2 to -19.2)% for participants with low mechanical dispersion ($P < 0.001$, *Table 2*). The diastolic parameters E/e', e', and LV mass index were also significantly different between participants with high and low mechanical dispersion. The correlation coefficient between mechanical dispersion and LVEF was -0.07 ($P < 0.001$), and the correlation coefficient between mechanical dispersion and GLS was 0.27 ($P < 0.001$). Mechanical dispersion was also significantly correlated with E/e', while GLS and LVEF did not correlate with E/e'. Numerically, correlation coefficients were higher for mechanical dispersion and LV mass index, E/e' and e' compared to the corresponding correlation coefficients for GLS and LVEF (Supplementary material online, *Table S1*). Variability analysis is reported in Supplementary material online, *Results*.

Associations between clinical risk factors in early mid-life and mechanical dispersion two decades later

The median age at participation in the Age 40 Cardiovascular Screening Survey was 40.0 (40.0–40.0) years and of the participants

Table 1 Characteristics at the ACE 1950 Study baseline visit according to median value of mechanical dispersion

	Better	Worse	
Mechanical dispersion	<38.0	≥38.0	*P*-value*
n	1253	1274	
Age (years)	63.9 (63.4–64.4)	64.0 (63.5–64.5)	<0.001
Female sex, n (%)	638 (50.9%)	620 (48.7%)	0.26
Caucasian ethnicity, n (%)	1234 (98.5%)	1240 (97.3%)	0.043
Higher education, n (%)	621 (49.7%)	554 (43.7%)	0.002
Body mass index (kg/m^2)	25.6 (23.4–28.1)	26.6 (24.5–29.1)	<0.001
Systolic blood pressure (mmHg)	134 (122–146)	139 (127–152)	<0.001
Diastolic blood pressure (mmHg)	76 (69–82)	77 (71–84)	<0.001
Heart rate (beats/min)	61 (55–68)	61 (55–67)	0.43
Current smoker, n (%)	187 (15.0%)	164 (12.9%)	0.14
COPD, n (%)	101 (8.1%)	83 (6.6%)	0.13
Obesity, n (%)	164 (13.1%)	235 (18.4%)	<0.001
Diabetes mellitus, n (%)	67 (5.4%)	103 (8.1%)	0.006
Hypertension, n (%)	648 (51.7%)	845 (66.3%)	<0.001
Coronary artery disease, n (%)	43 (3.4%)	105 (8.2%)	<0.001
Total cholesterol (mmol/L)	5.4 (4.8–6.1)	5.5 (4.7–6.2)	0.91
HDL cholesterol (mmol/L)	1.6 (1.3–1.9)	1.5 (1.2–1.8)	<0.001
eGFR (mL/min/1.73 m^2)	85.4 (75.5–92.5)	84.0 (74.7–92.2)	0.11
hs-cTnT (ng/L)	6.0 (4.0–8.0)	6.0 (4.0–9.0)	0.001
NT-proBNP (ng/L)	54.0 (33.8–90.0)	56.0 (33.8–93.0)	0.21
Beta blocker, n (%)	109 (8.7%)	172 (13.5%)	<0.001
ACEi or ARB, n (%)	243 (19.4%)	370 (29.0%)	<0.001
Statins, n (%)	279 (22.3%)	340 (26.7%)	0.011

Values are median (IQR) or *n* (%).
*Comparisons according to median value of mechanical dispersion.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2 Electrocardiographic and echocardiographic characteristics at the ACE 1950 Study baseline visit according to median value of mechanical dispersion

	Better	Worse	
Mechanical dispersion	<38.0	≥38.0	*P*-value*
n	1253	1274	
Atrial fibrillation, n (%)	36 (2.9%)	37 (2.9%)	0.96
Left bundle branch block, n (%)	1 (0.1%)	14 (1.1%)	0.001
Right bundle branch block, n (%)	10 (0.8%)	35 (2.7%)	<0.001
QRS duration (ms)	90 (84–98)	94 (86–100)	<0.001
QTc (ms)	419 (405–434)	424 (409–438)	<0.001
LV EF (%)	56 (53–59)	55 (52–59)	0.002
LV GLS (%)	-20.6 (-22.2–[-19.2])	-19.7 (-21.4–[-17.8])	<0.001
LV mass index	71.0 (62.4–82.4)	76.1 (65.7–89.5)	<0.001
LA volume index	26.1 (22.2–30.9)	26.0 (22.0–31.1)	0.82
e′ average (cm/s)	8.0 (7.0–9.0)	7.2 (6.2–8.2)	<0.001
E/*e′*	8.2 (6.9–9.6)	8.8 (7.5–10.4)	<0.001
TR V_{max} (m/s)	2.2 (2.1–2.4)	2.2 (2.1–2.4)	0.57

Values are median (IQR) or *n* (%).
*Comparisons according to median value of mechanical dispersion.
e′, peak early diastolic velocity by tissue velocity imaging; *E*, peak early diastolic velocity by pulsed Doppler; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; LV, left ventricular; QTc, rate corrected QT-interval. TR V_{max}, maximal tricuspid regurgitation velocity.

51.2% were women. Supplementary material online, *Table S2* reports baseline characteristics of our ACE 1950 cohort from the Age 40 Screening visit ($n = 1906$) and Supplementary material online, *Table S3* presents a comparison between baseline characteristics at the two study visits performed in 1990–94 and 2012–15. High BMI, serum triglyceride concentration, and low resting heart rate in early adult life were independently associated with increasing mechanical dispersion at the ACE 1950 Study baseline visit age 63–65 years (*Table 3*). A sensitivity analysis where only variables with $P < 0.05$ in the univariate regression analysis were included in a multivariable linear regression analysis did not change the results substantially: BMI and triglyceride concentrations remained independently associated with mechanical dispersion, while heart rate was not included in the final model (Supplementary material online, *Table S4*). Adjusting for CAD in the ACE 1950 Study and for follow-up time between the Age 40 Program and the ACE 1950 Study baseline did not alter the results (Supplementary material online, *Table S5* and *S6*).

Table 3 Associations between variables from the Age 40 Program and left ventricular mechanical dispersion

Independent variables from the Age 40 Study	Univariate linear regression		Multivariable linear regression	
	B (95% CI)	*P*-value	B (95% CI)	*P*-value
Age (years)	-1.88 (-3.85 to 0.09)	0.06	-0.80 (-3.07 to 1.48)	0.49
Female sex	-1.72 (-3.04 to -0.41)	0.010	1.02 (-0.57 to 2.61)	0.21
Heart rate (beats/min)	-0.03 (-0.08 to 0.02)	0.26	-0.07 (-0.13 to -0.01)	0.015
Systolic blood pressure (mmHg)	0.10 (0.05 to 0.15)	<0.001	0.03 (-0.05 to 0.10)	0.52
Diastolic blood pressure (mmHg)	0.15 (0.08 to 0.22)	<0.001	0.11 (0.00 to 0.22)	0.05
Treatment for hypertension	3.79 (-2.53 to 10.11)	0.24	1.75 (-4.55 to 8.05)	0.59
Body mass index (kg/m^2)	0.60 (0.38 to 0.82)	<0.001	0.35 (0.11 to 0.59)	0.005
Inactive lifestyle	0.56 (-1.15 to 2.27)	0.52	0.24 (-1.51 to 2.00)	0.79
Diabetes mellitus	-13.13 (-33.51 to 7.25)	0.21	-10.36 (-30.49 to 9.77)	0.31
Current smoking	-0.55 (-1.95 to 0.84)	0.44	-0.38 (-1.84 to 1.08)	0.61
Total cholesterol (mmol/L)	1.51 (0.84 to 2.17)	<0.001	0.73 (-0.03 to 1.48)	0.06
Triglycerides (mmol/L)	1.52 (0.96 to 2.08)	<0.001	0.91 (0.24 to 1.57)	0.007

B, unstandardized coefficient; CI, confidence interval.
In the multivariable linear regression analysis, all variables from univariate linear regression were included.

Cross-sectional associations between mechanical dispersion and hs-cTnT and NT-proBNP concentrations

Median (IQR) hs-cTnT and NT-proBNP concentrations in this substudy were 6.0 (4.0–8.0) ng/L and 54.0 (33.8–93.0) ng/L. hs-cTnT concentrations were higher in participants with high mechanical dispersion, while NT-proBNP concentrations did not differ significantly between the groups (*Table 1*). No correlation was found between mechanical dispersion and NT-proBNP, while only a weak correlation was found between mechanical dispersion and hs-cTnT (rho = 0.084, $P < 0.001$). When analysed in separate multivariable linear regression models, mechanical dispersion, GLS, and LVEF were all significantly associated with hs-cTnT concentrations (*Table 4*). In contrast, only mechanical dispersion was associated with hs-cTnT concentrations when all three echocardiographic indices were included in the same model (Supplementary material online, *Table S7*). For NT-proBNP, mechanical dispersion and LVEF were both associated with increasing concentrations when adjusting for demographic variables and CV risk factors (*Table 4*). These associations remained after adjusting for all three echocardiographic indices in the same model (Supplementary material online, *Table S7*).

Discussion

The principal findings from this large population-based study were that CV risk factors in the early forties are associated with increased mechanical dispersion two decades later and that mechanical dispersion is independently associated with cardiac biomarkers in the mid-sixties. Hence, our study lends support to the concept of mechanical dispersion as an early echocardiographic index of subclinical myocardial injury and dysfunction.

LV mechanical dispersion appears to be a promising echocardiographic index across different populations with CV disease. Increased mechanical dispersion reflects a heterogeneous contraction pattern that has been postulated to reflect pathology in the electrical conduction pathway or mechanical changes in the myocardium.[26] In line with this, mechanical dispersion has previously been found associated with ventricular arrhythmias and sudden cardiac death in patients with different types of established CV disease.[7,27–29] Recently, a Danish general population study also reported that mechanical dispersion predicted cardiac death, but not non-cardiac death, during median 11 years follow-up.[6] We have previously also found established CAD and hypertension to be independently associated with high mechanical dispersion values in subjects 62–65 years old from the general population.[5] We now validate and extend these observations by demonstrating an association between CV risk factors in early midlife and mechanical dispersion obtained over 20 years later. We also demonstrate independent associations between mechanical dispersion and NT-proBNP and hs-TnT concentrations, which are established cardiac biomarkers reflective of myocardial injury and dysfunction. Hence, mechanical dispersion could have the potential as a novel echocardiographic risk index across different populations, including subjects with sub-clinical CV disease. Still, there are a number of questions for mechanical dispersion that need to be resolved prior to widespread clinical use, including the pathobiology underlying the prognostic potential of mechanical dispersion in large population-based cohorts.

The current model for mechanical dispersion postulates that mechanical dispersion reflects a risk of future ventricular arrhythmias. However, the pathobiology underlying the increased risk of arrhythmias is not clear. Other groups have proposed that mechanical dispersion may reflect myocardial fibrosis. Pertinent to this point, mechanical dispersion has been found associated with myocardial fibrosis as assessed by cardiac magnetic resonance imaging and late gadolinium enhancement (LGE) in patients with hypertrophic cardiomyopathy.[7] Supporting a model of mechanical dispersion as an echocardiographic index of cardiac fibrosis, mechanical dispersion also correlated with LGE-quantified focal myocardial fibrosis in patients with first-time ST-segment elevation myocardial infarction.[30] The previously identified associations between increasing mechanical dispersion and established CAD and hypertension, which both are known to contribute to LV remodelling, also support a model of mechanical dispersion as reflective of cardiac fibrosis. We now add to this information by demonstrating independent associations between mechanical dispersion and established cardiac biomarkers of myocardial injury and dysfunctions in a population of subjects in the mid-sixties recruited from the general population primarily without established CV disease. In a study assessing the prognostic value of mechanical dispersion and NT-proBNP in stable CAD patients, mechanical dispersion had incremental prognostic value to LVEF and GLS.[31] These results support that mechanical dispersion may provide incremental information on cardiac structure and function compared to established echocardiographic indices, but this will need to be tested in more cohorts with prospective clinical endpoints, including in the general population. Prior to widespread clinical use in the general population, we will also need to know more about the appropriate therapeutic interventions to start in subjects with high mechanical dispersion. Currently, this is not known, but based on the model of mechanical dispersion as reflective of myocardial fibrosis, treating common risk factors throughout adult life will probably attenuate an increase in mechanical dispersion values in later life. Our results provide some indirect support for such a strategy as we now report associations between common CV risk factors in early mid-life (age 40 years) and mechanical dispersion measured more than 20 years later. This also relates to obesity as we and others identify high BMI as associated with increased mechanical dispersion values,[6] including when adjusted for established CAD in our multivariable statistical model. However, whether mechanical dispersion adds information to the use of common risk stratification models to predict incident CV disease in the general population is not known, and this will also need to be established before introducing mechanical dispersion as an echocardiographic index to screen for sub-clinical CV disease in the general population. Of note, we did not find risk factors for vascular disease, e.g., smoking, diabetes mellitus, and arterial hypertension, to be associated with mechanical dispersion. This result will need validation in other cohorts, but supports a model of mechanical dispersion being more reflective of LV remodelling and fibrosis than of CAD per se.

Strengths and limitations

A major strength of this study is the high number of participants with available echocardiograms as well as analyses of hs-cTnT and NT-

Table 4 Associations between LV mechanical dispersion, GLS and EF, and the biomarkers hs-cTnT and NT-proBNP, performed with the echocardiographic indices in separate multivariable linear regression analyses

Variables	Model 1		Model 2		Model 3	
	B (95% CI)	*P*-value	B (95% CI)	*P*-value	B (95% CI)	*P*-value
hs-cTnT (dependent variable)						
LV mechanical dispersion, per 10 ms increase	0.040 (0.024 to 0.057)	<0.001	0.032 (0.017 to 0.046)	<0.001	0.029 (0.015 to 0.043)	<0.001
LV GLS, per 1% increase	0.046 (0.036 to 0.055)	<0.001	0.020 (0.011 to 0.028)	<0.001	0.012 (0.004 to 0.021)	0.006
LV EF, per 5% increase	-0.087 (-0.109 to -0.066)	<0.001	-0.047 (-0.067 to -0.027)	<0.001	-0.026 (-0.045 to -0.006)	0.010
NT-proBNP (dependent variable)						
LV mechanical dispersion, per 10 ms increase	0.030 (0.010 to 0.051)	0.004	0.033 (0.013 to 0.053)	0.001	0.024 (0.003 to 0.045)	0.022
LV GLS, per 1% increase	-0.017 (-0.029 to -0.005)	0.004	-0.005 (-0.018 to 0.007)	0.39	-0.003 (-0.015 to 0.009)	0.65
LV EF, per 5% increase	-0.022 (-0.049 to 0.005)	0.12	-0.041 (-0.068 to -0.013)	0.004	-0.029 (-0.057 to -0.001)	0.044

Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex, study site, higher education level, body mass index, eGFR, total cholesterol, HDL cholesterol, diabetes mellitus, hypertension, coronary artery disease, statin therapy, and current smoking.
B, unstandardized coefficient; CI, confidence interval; EF, ejection fraction; GLS, global longitudinal strain; hs-cTnT, high-sensitivity cardiac troponin T; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

proBNP concentrations. The echocardiographic recordings and analyses were performed by several researchers and therefore represent a real-life scenario close to a clinical setting. We could link data from two age-specific studies, allowing us to assess the associations between variables at age 40 with mechanical dispersion two decades later. Survival bias may be present, as deceased participants of the Age 40 Program could not be included in the ACE 1950 cohort. Selection bias is additionally a limitation, as we do not have information on the individuals who refused to participate in the studies. We used peak R as the start of the cardiac circle as this was automatically detected by the software and because peak R more consistently can be detected compared to the start of QRS. We acknowledge that the start of QRS complex could have been chosen, but we do not believe this would have influenced our results. As we currently do not have follow-up data with endpoints for the ACE 1950 Study population, we are not able to investigate whether mechanical dispersion is associated with sudden cardiac death or ventricular arrhythmias in a general population. We plan to investigate this in the future.

Conclusion

In a large community-based cohort, we demonstrate that established CV risk factors in early adulthood are associated with worse mechanical dispersion in mid-life, and that mechanical dispersion is cross-sectionally associated with biomarkers of sub-clinical myocardial injury and dysfunction in middle age.

Lead Author Biography

Erika Nerdrum Aagaard, MD, has a medical degree from 2007 from The Jagiellonian University, Krakow, Poland. She is currently finishing her PhD at the University of Oslo and the Akershus University Hospital where she also works as a cardiology resident. She is passionate about cardiology in general and echocardiography specifically, with a main research focus on strain imaging and mechanical dispersion.

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Conflict of interest: T.O. has served on advisory boards for Abbott Diagnostics, Roche Diagnostics and Bayer and has received research support from Abbott Diagnostics, Novartis, Roche Diagnostics, Singulex and SomaLogic via Akershus University Hospital, and speaker's or consulting honoraria from Roche Diagnostics, Siemens Healthineers and CardiNor. H.R. has received personal fees from Novartis and Thermo Fischer BRAMS, CardiNor and SpinChip. T.B. has received speaker fees from Bayer, Boehringer Ingelheim, BMS and Pfizer (non-related to the submitted work). E.N.A. and the remaining co-authors have nothing to disclose.

Data Availability

The data set used in this study is not publicly available; the Data Protection Authority approval and patient consent do not allow for such publication. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application. More information is available on the study website (http://www.ace1950.no).

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SUPPLEMENTARY MATERIAL

to

Associations between Cardiovascular Risk Factors, Biomarkers and Left Ventricular Mechanical Dispersion: Insights from the ACE 1950 Study

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SUPPLEMENTARY METHODS

Blood sampling procedures at the ACE 1950 Study baseline visit

Total and high-density lipoprotein (HDL) cholesterol and creatinine were analyzed immediately by routine hospital laboratory and we calculated estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration formula (1). We defined renal failure as chronic renal disease stage 3; i.e. eGFR<60 ml/min/1.73m².

Clinical variables at the ACE 1950 Study and Age 40 Program study visits

Demographic and clinical variables from the ACE 1950 Study included age, sex, higher education level (level of university or equivalent), and current smoking. Body mass index (BMI) was calculated by weight (kg)/(height [m])^2 and obesity was defined as BMI ≥30 kg/m². Hypertension was defined as current use of antihypertensive medication or measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at the ACE 1950 baseline visit. The diagnosis of diabetes mellitus was based on either a self-reported diagnosis, current use of anti-diabetic medication, or measured elevated glucose tests (both HbA1c ≥6.5% and fasting blood glucose ≥7.0 mmol/L) at the ACE 1950 Study baseline visit. Participants were identified with coronary artery disease (CAD) if they reported prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting surgery. The diagnosis of chronic obstructive pulmonary disease (COPD) was based on either established diagnosis at the baseline visit or post-bronchodilatory spirometry FEV1/FVC <0.64 (men) or <0.66 (women) at the ACE 1950 Study baseline visit. Left bundle branch block and right bundle branch block were based on the electrocardiogram that was recorded at the ACE 1950 Study baseline visit. Atrial fibrillation (AF) was based on self-report or diagnosed from the baseline electrocardiogram, and was further validated from hospital records.

In the Age 40 Program, information regarding diabetes mellitus, treatment for hypertension, physical activity, and smoking status was provided through a questionnaire answered by the study participants. The variable inactive lifestyle was defined as reading, watching television, or other sedentary activity in leisure time and less than 4 hours of low-to-moderate intensive physical activity per week. Current smoking is defined as daily smoking. Heart rate, systolic, and diastolic blood pressure were measured after two minutes of rest, three measurements were performed with one-minute intervals, and the average of the second and third recording for the blood pressure was used. The heart rate variable used for the present analyses was the first of three recordings, as this variable had fewer missing values. Body mass index (BMI) was calculated as weight/height square (kg/m^2), and total cholesterol and triglycerides were measured in nonfasting blood-serum by an enzymatic method. The methods of this study have been described previously (2).

SUPPLEMENTARY RESULTS

Variability of strain analyses

Intra-observer intra-class correlation coefficients for GLS were 0.97 (95% CI 0.92-0.99; $p<0.001$) (E.N.A.) and 0.87 (95% CI 0.27-0.97; $p<0.001$) (B.K.), and for mechanical dispersion 0.87 (95% CI 0.68-0.96; $p<0.001$) (E.N.A.) and 0.89 (95% CI 0.71-0.96; $p<0.001$) (B.K.). Inter-observer intra-class correlation coefficients for GLS were 0.86 (95% CI 0.44-0.96; $p<0.001$) (E.N.A.) and 0.94 (95% CI 0.82-0.98; $p<0.001$) (B.K.), and for mechanical dispersion 0.89 (95% CI 0.65-0.97; $p<0.001$) (E.N.A.) and 0.89 (95% CI 0.71-0.96; $p<0.001$) (B.K.).

Supplementary Table S1. Correlations between echocardiographic indices, hs-cTnT and NT-proBNP.

Varibles	LV mechanical dispersion		LV GLS		LV EF	
	rho	*P* value	rho	*P* value	rho	*P* value
Circulating biomarkers:						
hs-cTnT	0.084	<0.001	0.201	<0.001	-0.149	<0.001
NT-proBNP	0.029	0.149	-0.108	<0.001	0.014	0.500
Echocardiographic indices:						
LV mechanical dispersion	-	-	0.265	<0.001	-0.073	<0.001
LV GLS	0.265	<0.001	-	-	-0.397	<0.001
LV EF	-0.073	<0.001	-0.397	<0.001	-	-
LV mass index	0.194	<0.001	0.101	<0.001	-0.101	<0.001
LVIDd index	0.054	0.007	-0.122	<0.001	-0.015	0.45
LA volume index	0.024	0.22	-0.089	<0.001	-0.066	0.001
E	-0.065	0.001	-0.238	<0.001	0.182	<0.001
e’	-0.320	<0.001	-0.254	<0.001	0.178	<0.001
E/e’	0.192	<0.001	-0.016	0.42	0.035	0.08
TR Vmax	0.004	0.85	-0.039	0.08	-0.054	0.015

Rho indicates Spearman’s rank coefficient. A indicates peak late diastolic velocity by pulsed Doppler, E, peak early diastolic velocity by pulsed Doppler; e’, the average of septal and lateral e’ peak early diastolic velocity by tissue velocity imaging; EF, ejection fraction; GLS, global longitudinal strain; hs-TnT, high-sensitivity cardiac troponin T; LA, left atrial; LV, left ventricular; LVIDd, left ventricular internal dimension end-diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TR Vmax, maximal tricuspid regurgitation velocity.

Supplementary Table S2. Clinical characteristics of participants at the time of inclusion in the Age 40 Program who are included in Ace 1950 subgroup analyses of (n=1906).

Age, years	40.0 (40.0-40.0)
Female sex, %	975 (51.2)
Heart rate (beats/min)	70 (61-78)
Systolic blood pressure (mmHg)	127 (119-136)
Diastolic blood pressure (mmHg)	78 (71-84)
Treatment for hypertension, %	21 (1.1)
Body mass index (kg/m^2)	23.7 (22.0-25.7)
Diabetes mellitus, %	2 (0.1)
Inactive lifestyle, %	345 (18.1)
Current smoking, %	645 (33.8)
Total cholesterol (mmol/L)*	5.3 (4.8-6.0)
Triglycerides (mmol/L)*	1.3 (0.9-1.9)

Values are median (IQR) or n (%). *Nonfasting.

Supplementary Table S3. Comparison of study characteristics from the Age 40 Program to the ACE 1950 Study baseline (n = 1906)

	Age 40 Program	ACE 1950 Study	P value
Heart rate, beats/min	70 (61-78)	61 (55-68)	<0.001
Systolic blood pressure, mmHg	127 (119-136)	136 (124-149)	<0.001
Diastolic blood pressure, mmHg	78 (71-84)	76 (70-83)	<0.001
Treatment for hypertension, n	21 (1.1%)	605 (31.7%)	<0.001
Body mass index, kg/m2	23.7 (22.0-25.7)	26.0 (23.7-28.6)	<0.001
Diabetes mellitus, n	2 (0.1%)	117 (6.1%)	<0.001
Current smoker, n	645 (33.8%)	261 (13.8%)	<0.001
Total cholesterol, mg/dL	5.3 (4.8-6.0)*	5.5 (4.7-6.1)	<0.001
Triglycerides, mg/dL	1.3 (0.9-1.9)*	1.1 (0.8-1.5)	<0.001

Values are median (IQR) or n (%). * Nonfasting.

Supplementary Table S4. Associations between variables from the Age 40 Program and left ventricular mechanical dispersion, only variables that were significant in the univariate analysis were included.

Independent variables from the Age 40 Study	Multivariable linear regression	
	B (95% CI)	P value
Age (years)	*	
Female sex	0.41 (-1.11 – 1.93)	0.59
Heart rate (beats/min)	*	
Systolic blood pressure (mmHg)	0.02 (-0.05 – 0.10)	0.54
Diastolic blood pressure (mmHg)	0.08 (-0.03 – 0.19)	0.15
Treatment for hypertension	*	
Body mass index (kg/m$^{2)}$	0.38 (0.14 – 0.62)	0.002
Inactive lifestyle	*	
Diabetes mellitus	*	
Current smoking	*	
Total cholesterol (mmol/L)	0.61 (-0.14 – 1.35)	0.11
Triglycerides (mmol/L)	0.87 (0.21 – 1.53)	0.010

B, unstandardized coefficient; CI, confidence interval. * not significant in univariate analysis.

Supplementary Table S5. Associations between variables from the Age 40 Program and left ventricular mechanical dispersion, adjusted for established CAD at the ACE 1950 Study baseline.

Independent variables from the Age 40 Study	Multivariable linear regression	
	B (95% CI)	P value
Age (years)	-0.81 (-3.08-1.46)	0.48
Female sex	1.31 (-0.28-2.89)	0.11
Heart rate (beats/min)	-0.07 (-0.13 to -0.02)	0.014
Systolic blood pressure (mmHg)	0.02 (-0.05-0.10)	0.53
Diastolic blood pressure (mmHg)	0.11 (-0.00-0.22)	0.06
Treatment for hypertension	1.53 (-4.74-7.80)	0.63
Body mass index ($kg/m^{2)}$	0.34 (0.10-0.58)	0.005
Inactive lifestyle	0.28 (-1.46-2.03)	0.75
Diabetes mellitus	-10.45 (-30.47-9.58)	0.31
Current smoking	-0.73 (-2.19-0.73)	0.33
Total cholesterol (mmol/L)	0.53 (-0.22-1.29)	0.17
Triglycerides (mmol/L)	0.88 (0.22-1.54)	0.009

B, unstandardized coefficient; CI, confidence interval. All variables from univariate linear regression were included.

Supplementary Table S6. Associations between variables from the Age 40 Program and left ventricular mechanical dispersion, adjusted for length of follow-up time between the Age 40 Program and the ACE 1950 Study baseline

Independent variables from the Age 40 Study	Multivariable linear regression	
	B (95% CI)	P value
Age (years)	0.24 (-2.16-2.63)	0.85
Female sex	0.98 (-0.61-2.57)	0.23
Heart rate (beats/min)	-0.07 (-0.13 to -0.01)	0.015
Systolic blood pressure (mmHg)	0.03 (-0.05-0.10)	0.53
Diastolic blood pressure (mmHg)	0.12 (0.01-0.23)	0.040
Treatment for hypertension	1.78 (-4.51-8.07)	0.58
Body mass index ($kg/m^{2)}$	0.32 (0.08-0.56)	0.009
Inactive lifestyle	0.12 (-1.63-1.87)	0.89
Diabetes mellitus	-8.65 (-28.78-11.49)	0.40
Current smoking	-0.45 (-1.91-1.01)	0.54
Total cholesterol (mmol/L)	0.68 (-0.07-1.43)	0.08
Triglycerides (mmol/L)	0.92 (0.26-1.58)	0.007

B, unstandardized coefficient; CI, confidence interval. All variables from univariate linear regression were included.

Supplementary Table S7. Associations between LV mechanical dispersion, GLS and EF, and the biomarkers hs-cTnT and NT-proBNP, performed with the echocardiographic variables in the same multivariable linear regression analyses.

Variables	Model #1 B (95% CI)	Model #2 B (95% CI)	Model #3 B (95% CI)
hs-cTnT (dependent variable)			
LV mechanical dispersion, per 10 ms increase	0.019 (0.002-0.036)‡	0.025 (0.010-0.041)†	0.026 (0.011-0.041)†
LV GLS, per 1% increase	0.032 (0.021-0.043)*	0.008 (-0.002-0.018)	0.004 (-0.005-0.014)
LV EF, per 5% increase	-0.052 (-0.076 to -0.029)*	-0.037 (-0.058 to -0.015)†	-0.019 (-0.040-0.002)
NT-proBNP (dependent variable)			
LV mechanical dispersion, per 10 ms increase	0.046 (0.024-0.067)*	0.041 (0.020-0.063)*	0.028 (0.006-0.049)‡
LV GLS, per 1% increase	-0.036 (-0.050 to -0.022)*	-0.023 (-0.037 to -0.009)†	-0.015 (-0.029 to -0.001)‡
LV EF, per 5% increase	-0.053 (-0.083 to -0.022)†	-0.058 (-0.088 to -0.027)*	-0.039 (-0.069 to -0.008)‡

*p<0.001. † p<0.01. ‡ p<0.05. Model #1, unadjusted; model #2, adjusted for age and sex; model #3, adjusted for model #2 and study site, higher education level, body mass index, eGFR, total cholesterol, HDL cholesterol, diabetes mellitus, hypertension, coronary artery disease, statin therapy, and current smoking.

B, unstandardized B; CI, confidence interval. Other abbreviations as in Supplementary Table S1.

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ORIGINAL PAPER

Mechanical dispersion as a marker of left ventricular dysfunction and prognosis in stable coronary artery disease

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Abstract

Assessment of global longitudinal strain (GLS) is superior to ejection fraction (EF) in the evaluation of left ventricular (LV) function in patients with stable coronary artery disease (CAD). However, the role of mechanical dispersion (MD) in this context remains unresolved. We aimed to evaluate the potential role of MD as a marker of LV dysfunction and long-term prognosis in stable CAD. EF, GLS and MD were assessed in 160 patients with stable CAD, 1 year after successful coronary revascularization. Serum levels of high-sensitivity cardiac troponin I (hs-cTnI) and amino-terminal pro B-type natriuretic peptide (NT-proBNP) were quantified as surrogate markers of LV dysfunction. The primary endpoint was defined as all-cause mortality, the secondary endpoint was defined as the composite of all-cause mortality and hospitalization for acute myocardial infarction or heart failure during follow-up. Whereas no associations between EF and the biochemical markers of LV function were found, both GLS and MD correlated positively with increasing levels of hs-cTnI ($R = 0.315$, $P < 0.001$ and $R = 0.442$, $P < 0.001$, respectively) and NT-proBNP ($R = 0.195$, $P = 0.016$ and $R = 0.390$, $P < 0.001$, respectively). Median MD was 46 ms (interquartile range [IQR] 37–53) and was successfully quantified in 96% of the patients. During a median follow-up of 8.4 (IQR 8.2–8.8) years, 14 deaths and 29 secondary events occurred. MD was significantly increased in non-survivors, and provided incremental prognostic value when added to EF and GLS. NT-proBNP was superior to the echocardiographic markers in predicting adverse outcomes. MD may be a promising marker of LV dysfunction and adverse prognosis in stable CAD.

Keywords Stable coronary artery disease · Speckle tracking echocardiography · Myocardial strain · Mechanical dispersion · High-sensitivity troponin I · Amino-terminal pro-B-type natriuretic peptide

Introduction

Coronary artery disease (CAD) is regarded as the leading cause of left ventricular (LV) dysfunction and subsequent development of heart failure in the western world [1]. The subgroup of patients with stable CAD is heterogenic,

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including stabilized patients after an acute coronary syndrome, often treated with coronary revascularization. Although long-term prognosis in stable CAD has gradually improved over the last decades as a result of more cost-effective medical treatment, the prevalence is increasing due to an aging population, increased prevalence of risk factors and more sensitive diagnostic tools [2].

A resting transthoracic echocardiogram is recommended in all patients with suspected stable CAD for evaluation of cardiac structure and function [2]. LV dysfunction, most commonly quantified by measurement of LV ejection fraction (EF), is the most important predictor of outcome in these patients. Whereas EF is closely linked to mortality in patients with moderate and severe LV dysfunction, no such association is applicable for normal or mild impairment of LV function [3]. Although most patients with stable CAD have normal EF, the risk of de novo heart failure development is not negligible, despite standard medical therapy [4]. In this respect, improved identification of stable CAD patients with increased risk of adverse outcomes is of clinical importance.

Myocardial strain by two-dimensional speckle tracking echocardiography (2D-STE) has emerged as a validated tool for evaluation of LV function [5, 6]. Global longitudinal strain (GLS) is established as a robust parameter for early identification of LV dysfunction [7], and is superior to EF in the prediction of adverse outcomes in diverse cardiac disorders [8]. In patients with clinically suspected stable angina pectoris, GLS improves the diagnostic performance and identification of high-risk patients [9].

LV mechanical dispersion (MD) is a novel application of 2D-STE that quantifies the contraction heterogeneity in 16 LV segments [10]. Increased MD is associated with malignant arrhythmias in patients with ischemic heart disease and hypertrophic cardiomyopathy [11]. Furthermore, MD has incremental diagnostic value to GLS when identifying patients with significant CAD [12]. Thus, we hypothesized that MD might be a promising marker of subtle myocardial dysfunction and long-term prognosis in patients with stable CAD.

Methods

Study design and population

This prospective study was conducted between 2008 and 2009 in a single tertiary coronary care center and includes 160 patients referred to a follow-up echocardiography approximately 1 year after successful coronary revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) [13]. Exclusion criteria were valvular disease, ongoing atrial fibrillation, left bundle branch block, ventricular paced rhythm and recurrent angina or cardiovascular events between revascularization and study inclusion.

Echocardiographic studies

Echocardiographic examinations were performed with a Vivid 7 scanner (GE Ultrasound, Horten, Norway) and analyzed off-line using EchoPAC version 12 (GE Ultrasound). Images from three apical planes (four-chamber, two-chamber and long-axis) were obtained and used for strain analyses. The median frame rate was 63 (interquartile range [IQR] 59–71) frames per second. EF was assessed by the Simpson biplane method [6], and body surface area (BSA) was calculated using the Mosteller equation [14]. All patients underwent coronary angiography by Judkins technique 346 (IQR 281–376) days prior to follow-up, 73% due to non-ST elevation acute coronary syndrome and 27% due to stable angina pectoris.

Longitudinal strain was measured using a 16-segment LV model, and GLS was obtained by averaging all peak systolic strain values [15]. Peak strain was defined as the maximum absolute value of peak negative strain during systole, including post-systolic shortening, if present. End of systole was defined by the aortic valve closure in apical long-axis view. The operator manually adjusted segments that failed to track, and segments that subsequently failed to track were excluded. Patients were excluded from strain analyses if more than two segments failed to track in a single view [6]. Contraction duration was calculated as the time from ECG onset of the Q/R-wave to peak strain in all 16 LV segments, and MD was defined as the standard deviation of the contraction durations in the same 16 LV segments (Fig. 1) [10, 16]. Assessment of GLS and MD was performed by a single observer (B.K) and blinded to other patient data during the reevaluation of the echocardiographic examinations in conjunction with the current study.

Feasibility and variability analysis

Measurement of GLS and MD was repeated in 10 randomly selected patient records, and showed intra-observer intra-class correlation coefficients of 0.84 (95% confidence interval [CI] 0.27–0.96; $P < 0.001$) and 0.88 (95% CI 0.50–0.97; $P < 0.001$). Inter-observer analyses were performed in 10 randomly selected patient records by a second observer (E.N.A), and intra-class correlation coefficients of 0.90 (95% CI 0.43–0.98; $P < 0.001$) and 0.93 (95% CI 0.73–0.98; $P < 0.001$) were found for GLS and MD, respectively.

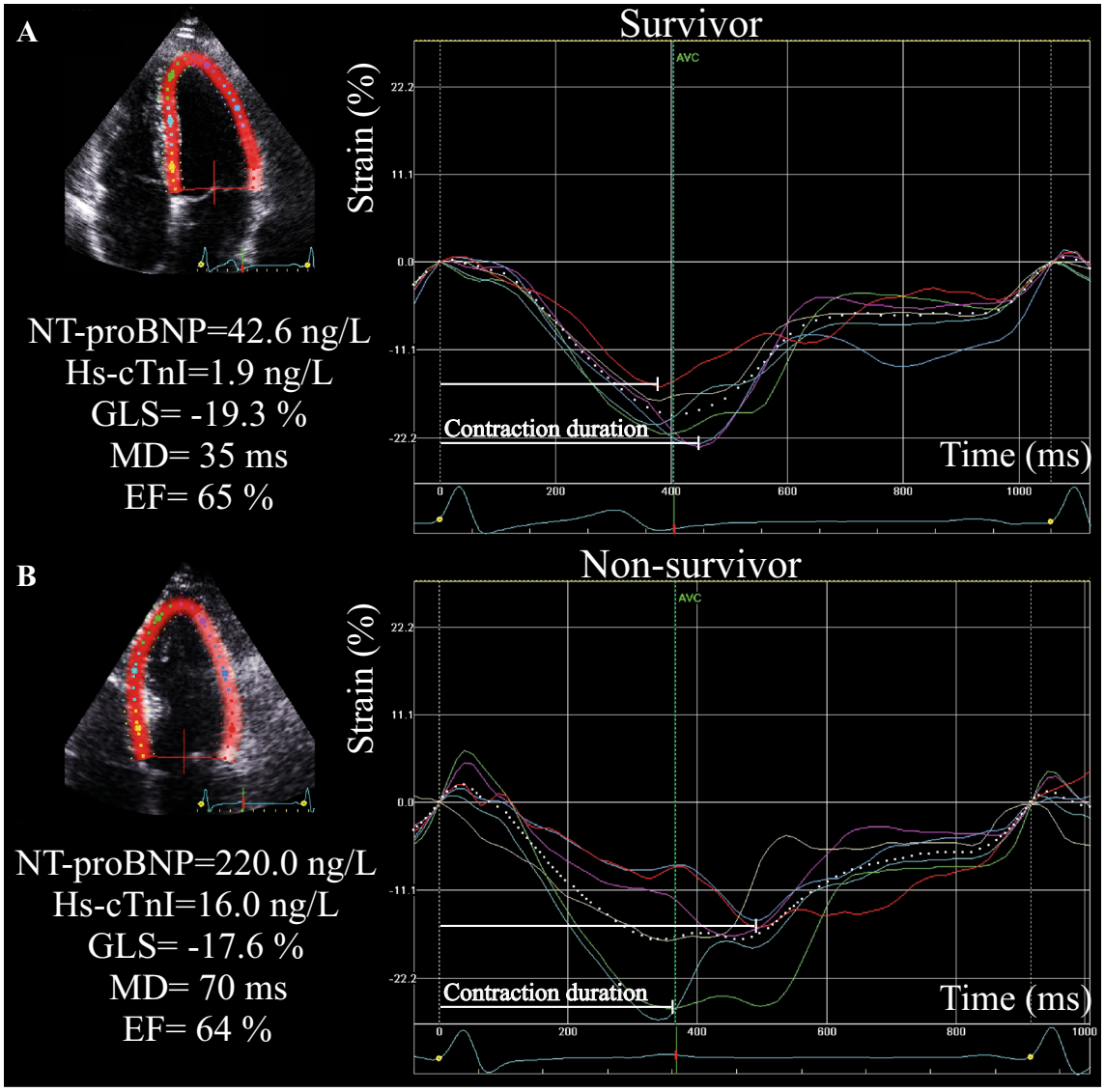

Fig. 1 Biochemical markers and deformation parameters in representative patients. White horizontal lines indicate contraction duration, defined as the time from ECG onset of Q/R to peak negative strain. MD was defined as the standard deviation of contraction duration in 16 LV segments. Despite normal EF in both patients, the patient from the survivor group displays normal biochemical markers and deformation parameters (**a**), while the patient from the non-survivor group displays pathological deformation parameters and increased biochemical markers (**b**). *ECG* electrocardiogram, *LV* left ventricular, *Hs-cTnI* high-sensitivity cardiac troponin I, *NT-proBNP* amino-terminal pro-B-type natriuretic peptide, *GLS* global longitudinal strain, *MD* mechanical dispersion, *EF* ejection fraction

Biochemical analysis

Peripheral venous blood was collected the same day as the echocardiographic recordings, and serum aliquots were stored at − 70 °C until analysis. The Roche amino-terminal pro-B-type natriuretic peptide (NT-proBNP) assay was analyzed on a Modular E170 platform using the Elecsys reagents, with a limit of detection (LoD) of 5 ng/L, and a 97.5th percentile cutoff of 263 ng/L. The inter-assay CV was 3.1% at a concentration of 46 ng/L and 2.7% at a concentration of 125 ng/L. The Abbott hs-cTnI assay was measured on ARCHITECT STAT and had a LoD of 1.9 ng/L, a 99th percentile in healthy individuals of 26 ng/L, and a 10% CV at 4.7 ng/L [17]. Renal function was evaluated by the estimated glomerular filtration rate (eGFR) [18]. The investigational assays were commercially available and supplied by the respective manufacturers, which had no role in the preparation of the manuscript.

Study outcomes

The primary endpoint was all-cause mortality, defined as time to death irrespective of the cause. The secondary endpoint was defined as the composite of all-cause mortality and hospitalization for recurrent acute myocardial infarction or new-onset heart failure. Follow-up was obtained by review of the patient's hospital charts or telephone interviews with the patients or relatives, and no patients were lost to follow-up.

Statistical analysis

The data are presented as medians and IQR. Categorical and discrete variables are presented as counts and percentages. Groups were compared with the Mann–Whitney U test or χ^2-tests where appropriate. The correlations between echocardiographic findings and log-transformed biomarker levels were estimated by the Pearson method. Variables associated with either GLS or MD were examined by first order linear regression analysis and are presented if $P < 0.1$. The unadjusted prognostic accuracy of the respective echocardiographic methods in the prediction of both endpoints was determined by the area under the ROC curve (AUCs). In the survival models, the echocardiographic parameters were evaluated both as continuous and dichotomous variables. EF, GLS and MD were dichotomized at 53%, − 18% and 64 ms, respectively, using previously defined reference levels [6, 16, 19, 20]. Cox proportional hazards regression models were generated to test the relationship between levels of echocardiographic markers and time to events. Kaplan–Meier survival curves were generated and associations between the respective echocardiographic parameters and endpoints were compared by the log-rank test. AUCs were compared by the DeLong test [21]. The incremental value of adding MD to the respective echocardiographic and biochemical parameters was investigated using continuous net reclassification improvement (NRI) and integrated discrimination index [22]. All statistical tests were 2-sided, and a significance level of 0.05 was used. All statistical analyses were performed using either SPSS version 25 (SPSS Inc.), MedCalc Statistical Software version 18.2.1 or R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

The authors are solely responsible for study design, all analyses, and drafting and editing of the manuscript.

Results

Patient characteristics

Baseline characteristics for all 160 patients are presented in Table 1. The study included 118 males (74%) and all patients

Table 1 Baseline characteristics

Characteristics	All patients (n = 160)
Age, years	59 (52–67)
Male sex	118 (73.8)
Risk factors	
Prior myocardial infarction	29 (18)
Current smoking	46 (29)
Diabetes	14 (8.8)
Hypertension	65 (41)
Clinical findings	
BMI, kg/m^2	27 (25–29)
BSA, m^2	2.0 (1.9–2.1)
Systolic blood pressure, mm Hg	144 (127–160)
Diastolic blood pressure, mm Hg	81 (71–90)
Heart rate, beats/min	61 (53–69)
Echocardiographic data	
EF, %	63 (56–68)
GLS, %	− 17.7 (− 19.3 to − 16.5)
MD, ms	46 (37–54)
EDV, mL	106 (89–127)
ESV, mL	40 (30–52)
Laboratory data	
Hs-cTnI, ng/L	3.2 (1.7–5.0)
NT-proBNP, ng/L	74 (34–205)
eGFR, mL min^{-1} (1.73 m^2)$^{-1}$	88 (72–99)
Medical therapy	
ACEI/ARB	48 (30)
Beta-blockers	129 (81)
Lipid-lowering drug	147 (92)
Aspirin or other antiplatelet medication	157 (98)
ECG data	
QRS duration, ms	94 (87–100)
QTc interval, ms	417 (398–439)
T wave changes, %	58 (36)
Q waves, %	13 (8.1)
Procedural data*	
PCI	126 (79)
CABG	34 (21)
One vessel disease	84 (53)
Two or more vessel disease	76 (48)
Total vessel occlusion	26 (16)

Values are median (IQR) and n (%)

BMI body mass index, *BSA* body surface area, *EF* ejection fraction, *GLS* global longitudinal strain, *MD* mechanical dispersion, *EDV* end-diastolic volume, *ESV* end-systolic volume, *hs-cTnI* high-sensitivity cardiac troponin I, *NT-proBNP* amino-terminal pro-B-type natriuretic peptide, *eGFR* estimated glomerular filtration rate, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft

*Approximately 1 year prior to the main examination

had asymptomatic stable CAD at the time of inclusion. Most patients were on medical therapy including antiplatelet medication, lipid-lowering drugs and beta blockers. Either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) were used by 48 patients (30%). The study included 15 (9.4%) patients with renal dysfunction, defined as eGFR < 60 mL min^{-1} 1.73 m^{-2}.

Echocardiographic evaluation and markers of LV dysfunction

The main echocardiographic findings are presented in Table 1. In total, 153 (96%) patients had technically adequate echocardiograms for speckle tracking analysis and 97% of the myocardial segments could be analyzed. Overall, the majority of the cohort displayed a normal EF, with 130 (81%) of the patients with levels above 53%. GLS was slightly reduced, with 69 patients (44%) within the normal range below − 18%. For MD, 138 patients (86%) were within the normal range below 64 ms. In univariate analysis, MD was significantly associated with age, heart rate, and kidney function, while GLS was associated with male sex, diabetes, current smoking and BSA (Supplementary Table 1). The correlation coefficient between GLS and MD was 0.254 ($P = 0.002$). Both deformation parameters were associated with prior CABG.

Levels above the detection limit of hs-cTnI and NT-proBNP were observed in 112 patients (70%) and 159 patients (99%), respectively. The proportion of patients with hs-cTnI levels above the 99th percentile was 1.9%, while 17% of the patients had levels of NT-proBNP above the 97.5th percentile. As opposed to EF, both GLS and MD were associated with increasing hs-cTnI and NT-proBNP levels (Table 2; Fig. 2). Only MD remained significantly associated with rising biomarker levels after adjustment for other echocardiographic parameters (Table 2). Collinearity was not observed.

Prediction of long-term prognosis

The median follow-up period was 8.4 (IQR 8.2–8.8) years. There were 14 deaths, 12 hospitalizations for recurrent AMIs and 3 hospitalizations for new-onset heart failure during the follow-up period. Non-survivors were older, had a higher prevalence of diabetes, lower levels of eGFR and higher BMI. Speckle tracking echocardiography showed a trend towards more pronounced MD in non-survivors vs. survivors (median 54 [IQR 45–72] ms vs. median 45 [IQR 37–53] ms; $P = 0.012$) and in patients with composite endpoint vs. no composite endpoint (median 52 [IQR 42–64] ms vs. median 45 [IQR 36–53] ms; $P < 0.01$). No such differences were found for EF and GLS. MD remained associated with adverse outcomes after adjusting for all ECG parameters. Both hs-cTnI and NT-proBNP were significantly elevated among non-survivors and patients in the composite endpoint group ($P < 0.01$; Fig. 3).

The unadjusted prognostic accuracies for the echocardiographic and biochemical parameters are presented in Table 3. Only NT-proBNP was superior to MD in the prediction of all-cause mortality, while MD, hs-cTnI and NT-proBNP showed similar abilities in the prediction of the composite endpoint. Adding MD to EF, GLS, and hs-cTnI provided significant improvements in risk stratification, but not when MD was added to NT-proBNP (Table 4). Among the echocardiographic parameters, only MD was associated with all-cause mortality and the composite endpoint (Table 5). MD remained a significant predictor for both endpoints when adjusting for both EF and GLS. Kaplan–Meier curves depicting the cumulative incidence of all-cause mortality and the composite endpoint are shown in Fig. 4. A MD > 64 ms identified individuals with a poor prognosis, both for all-cause mortality (log-rank $P < 0.01$), as well as the composite endpoint (log-rank $P = 0.014$).

Table 2 Relationships with hs-cTnI and NT-proBNP

	Multiple linear regression		Final model*	
	B (95% CI)	*P* value	B (95% CI)	*P* value
Abbott hs-cTnI				
EF, per 5% decrease	0.03 (− 0.01 to 0.06)	0.154		
GLS, per 1% increase	0.05 (0.03–0.08)	< 0.001		
MD, per 10 ms increase	0.13 (0.09–0.17)	< 0.001	0.13 (0.09–0.18)	< 0.001
Roche NT-proBNP				
EF, per 5% decrease	0.02 (− 0.03 to 0.07)	0.420		
GLS, per 1% increase	0.04 (0.02–0.18)	0.016		
MD, per 10 ms increase	0.15 (0.10–0.21)	< 0.001	0.16 (0.10–0.22)	< 0.001

The values of hs-cTnI and NT-proBNP are log-transformed. Abbreviations as in Table 1

*Adjusted for all other covariates in the table using forward regression

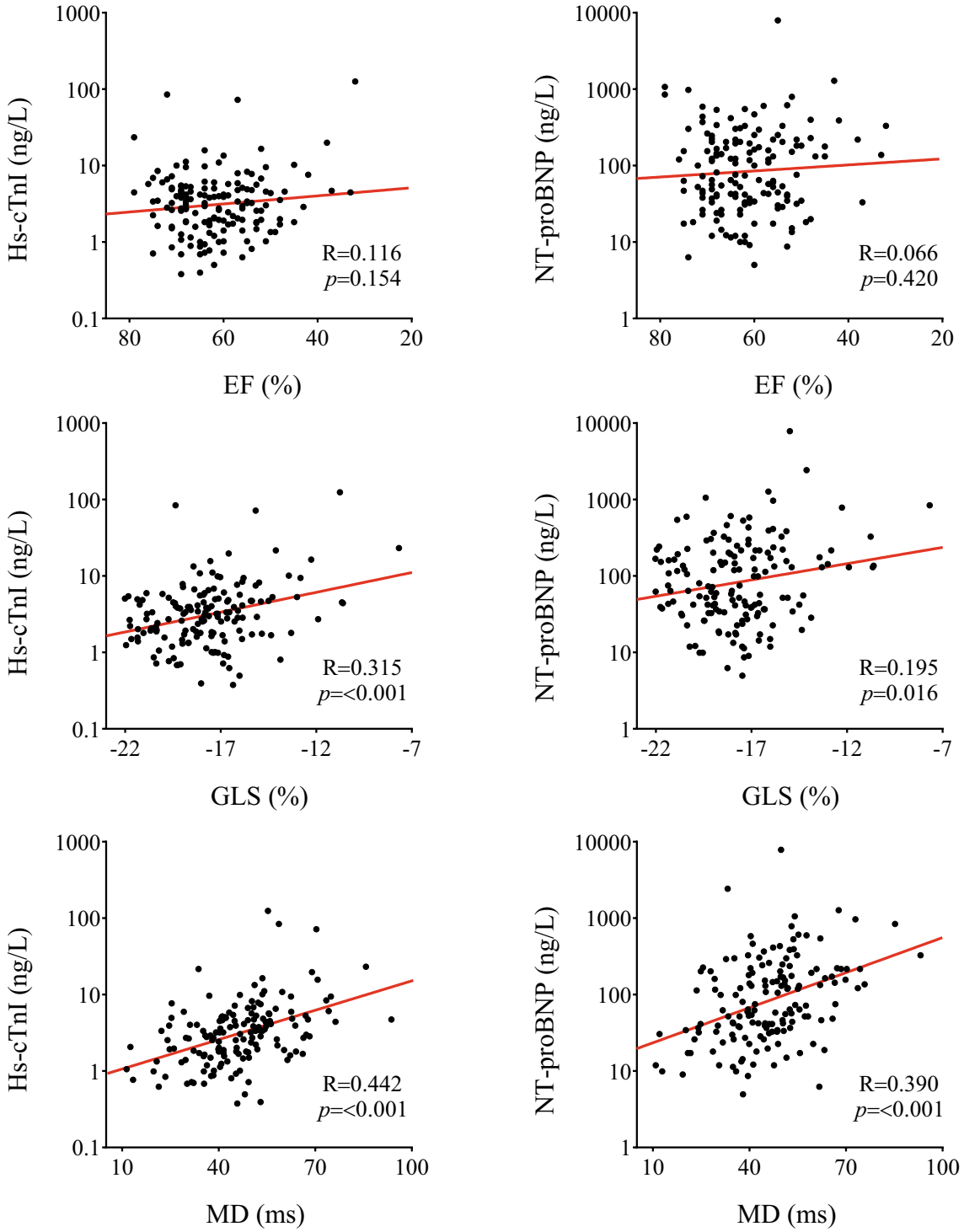

Fig. 2 Relationships between biochemical markers and echocardiographic parameters. Biomarker levels were log-transformed and correlations were estimated by the Pearson method. Abbreviations as in Fig. 1

Discussion

The present study demonstrates that novel deformation parameters obtained by 2D-STE are superior to EF for determining LV function and long-term prognosis in patients with stable CAD. Although both GLS and MD were related to serum markers of LV dysfunction, the association was most prominent for MD. In addition, MD was

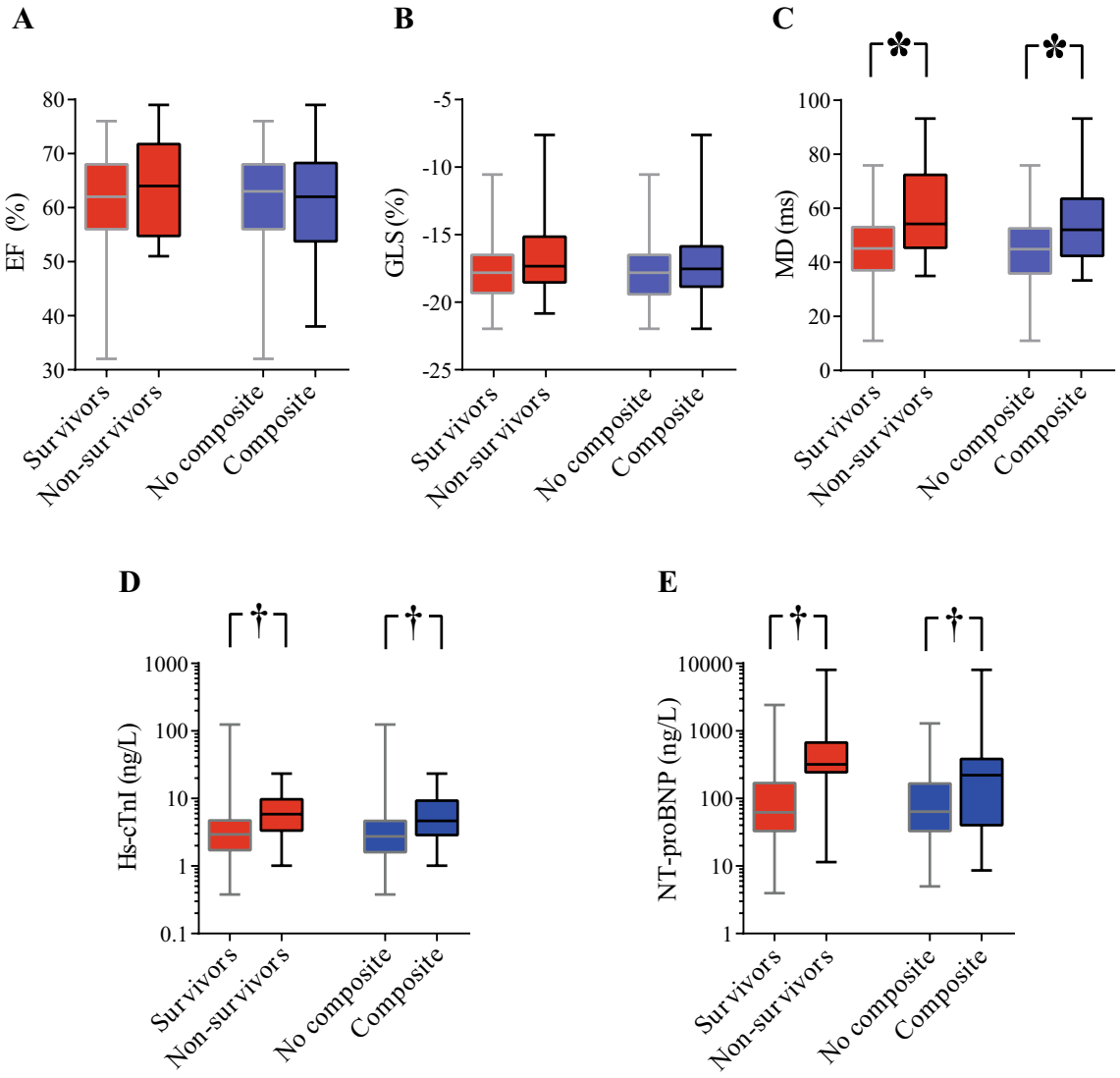

Fig. 3 Range of biochemical markers and echocardiographic parameters depending on clinical outcome. Range of EF (**a**), GLS (**b**), MD (**c**), hs-cTnI (**d**) and NT-proBNP (**e**) depending on clinical outcome. *$P = 0.05$. †$P < 0.01$. Abbreviations as in Fig. 1

the only echocardiographic parameter that provided significant prognostic information in this study. NT-proBNP was superior to all other markers in the prediction of all-cause mortality.

Traditionally, EF has been the established echocardiographic parameter for quantification of cardiac function and prognostic evaluation. However, the association between EF and mortality is most prominent for EF below 45% [3]. As most patients with stable CAD have a normal or subnormal EF and an overall good prognosis, other parameters should be used for prognostic evaluation in this patient group. A systematic review of 16 studies including 5721 patients concluded that GLS provided superior prognostic information to that of EF, in patients with mild LV dysfunction of diverse etiologies [9].

A recent study demonstrated how EF could be maintained in the left ventricle with increased wall thickness or reduced diameter, despite reductions in global strain parameters [23]. A significant reduction in GLS could be compensated by a small increase of global circumferential strain, resulting in an unaltered EF. This may be the fundamental basis for the observed superiority of GLS to EF in the evaluation of LV function in patients with preserved EF [24].

MD is a novel deformation parameter that reflects contraction heterogeneity, with a promising potential for prediction of ventricular arrhythmias in patients with ischemic heart disease, independently of EF and QRS interval [25]. Increased MD may also reflect myocardial scarring and interstitial collagen depositions, which in turn could give rise to local electromechanical delays [19, 20]. As an index

Table 3 Prediction of long-term prognosis

	AUC	95% CI	*P* value	*P* value versus MD
All-cause mortality				
EF, %	0.56	0.38–0.74	0.493	0.384
GLS, %	0.59	0.43–0.75	0.263	0.285
MD, ms	0.71	0.55–0.87	0.009	NA
Hs-cTnI, ng/L	0.72	0.56–0.88	0.007	0.375
NT-proBNP, ng/L	0.86	0.73–0.99	< 0.001	0.049
Composite endpoint				
EF, %	0.52	0.39–0.65	0.742	0.023
GLS, %	0.55	0.44–0.67	0.370	0.036
MD, ms	0.69	0.58–0.79	< 0.001	NA
Hs-cTnI, ng/L	0.67	0.55–0.78	0.005	0.750
NT-proBNP, ng/L	0.67	0.54–0.79	0.012	0.622

AUC area under the receiver operating characteristic curve; other abbreviations as in Table 1

Table 4 Incremental prognostic value of MD

	Continuous NRI	IDI
All-cause mortality		
EF, %	0.613 (0.062–1.164)*	0.109 (0.002–0.215)*
GLS, %	0.574 (0.022–1.125)*	0.087 (0.003–0.171)*
Hs-cTnI, ng/L	0.608 (0.057–1.159)*	0.107 (0.006–0.208)*
NT-proBNP, ng/L	0.352 (−0.211 to 0.914)	0.098 (−0.003 to 0.198)
Composite endpoint		
EF, %	0.447 (0.018–0.876)*	0.100 (0.030–0.171)†
GLS, %	0.593 (0.193–0.992)†	0.080 (0.023–0.137)†
Hs-cTnI, ng/L	0.495 (0.084–0.905)*	0.092 (0.028–0.157)†
NT-proBNP, ng/L	0.333 (−0.078 to 0.745)	0.060 (0.004–0.116)*

Abbreviations as in Table 1

NRI net reclassification improvement, *IDI* integrated discrimination index

*$P < 0.05$, †$P < 0.01$

Table 5 Multivariate analysis; effects of LV EF, GLS and MD on long-term prognosis

	Hazard ratio (95% CI)	
	Unadjusted	Final model*
All-cause mortality		
EF, per 5% decrease	0.81 (0.58–1.14)	
GLS, per 1% increase	1.19 (0.97–1.45)	
MD, per 10 ms increase	1.93 (1.33–2.79)†	1.91 (1.32–2.76)†
Composite endpoint		
EF, per 5% decrease	1.00 (0.80–1.23)	
GLS, per 1% increase	1.08 (0.94–1.25)	
MD, per 10 ms increase	1.62 (1.25–2.09)†	1.68 (1.29–2.20)†

Abbreviations as in Table 1

*Adjusted for all covariates in the table using forward conditional regression

†$P < 0.01$

of contraction discordance of the respective LV segments, MD could potentially give additive information of subtle LV dysfunction at an early stage [26].

While the limit for increased MD is still being debated, current guidelines recommend decision limits for EF and GLS at 53% and − 18%, respectively [6]. In our study, a cutoff limit at − 18% implies LV dysfunction in 55% of the patients. GLS was associated with diabetes, smoking and increased BSA, which are associated with the extent of coronary artery disease [27]. This could explain the large portion of patients with subnormal GLS values. Although earlier studies have suggested a limit for increased MD at 70 ms [16], recent data from healthy volunteers suggest that 64 ms might be a more precise limit in an elderly patient cohort [20]. In our population with stable CAD patients, the latter decision limit seems to provide prognostic information. In univariate analyses, MD was associated with increasing age and reduced kidney function, both factors which are associated with adverse outcome in CAD patients [28]. As only 9% of the patients displayed MD above 64 ms and MD at this cutoff level was superior to GLS in the prediction of long-term prognosis, MD may be a more specific prognostic parameter than GLS.

Although not yet included in the guidelines, the incremental prognostic value of cardiac biomarkers in CAD patients is well documented. Increased levels of both NT-proBNP and cardiac troponins, measured with high-sensitivity assays, are significantly associated with impaired LV function and clinical outcomes in patients with stable CAD and in the general population [29, 30]. Interestingly, prognostic discrimination for these biomarkers can be observed even within the normal range. NT-proBNP levels correlate with both age and other traditional risk factors of CV disease and provide prognostic information beyond that of established risk markers. Further, increased levels of NT-proBNP are associated with a history of myocardial infarction, 3-vessel disease and signs of impaired systolic function in patients with stable CAD. Hence, the prognostic value of NT-proBNP might be related to risk factors associated with asymptomatic LV dysfunction [31].

Chronic elevation of hs-cTn and NT-proBNP levels are considered as markers of increased myocardial stress which in turn could develop into diffuse myocardial fibrosis, hypertrophy and ventricular dysfunction [32]. These processes are strongly associated with the risk of heart failure, ventricular arrhythmias and adverse outcomes. Interestingly, our results indicate that MD display similar characteristics as

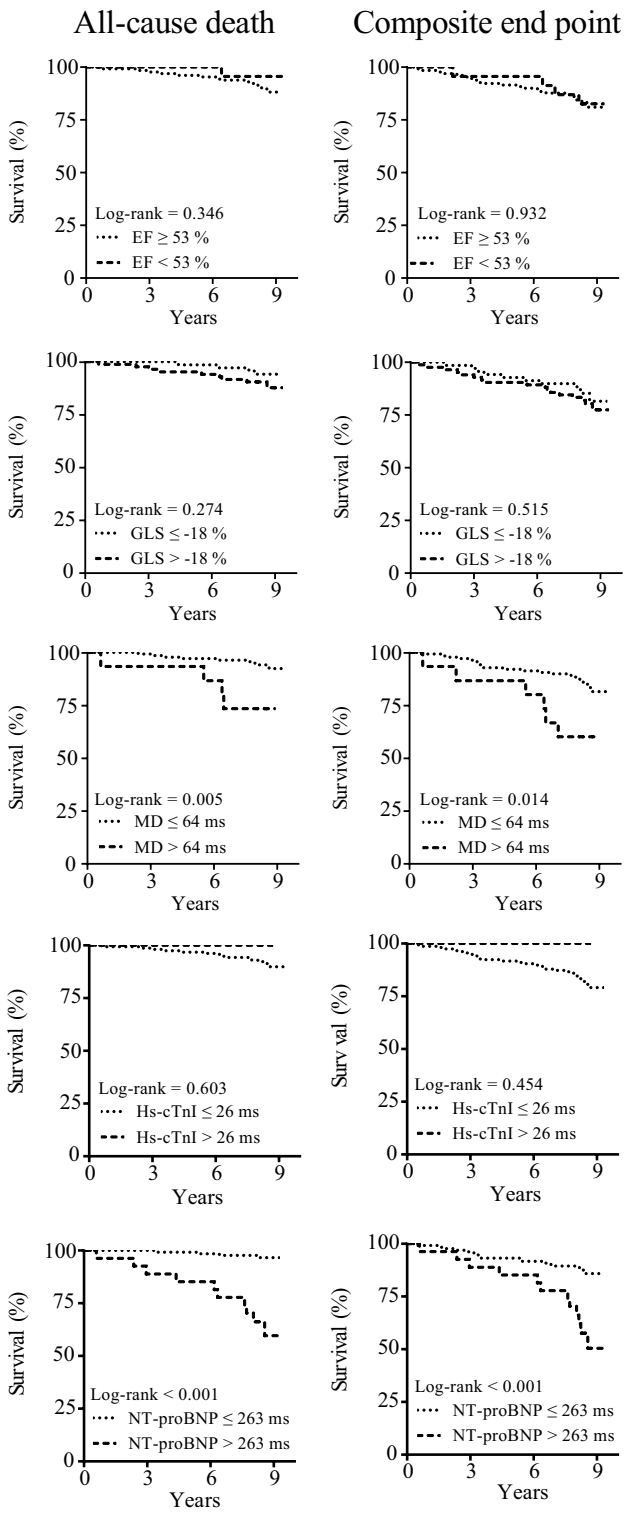

Fig. 4 Prediction of adverse outcomes. Kaplan–Meier curves demonstrating the cumulative incidence of all-cause mortality and the composite endpoint in the total patient cohort, according to dichotomized levels of the different biochemical and echocardiographic parameters. EF, GLS and MD are dichotomized at 53%, − 18% and 64 ms, while hs-cTnI and NT-proBNP are dichotomized at 26 ng/L and 263 ng/L, respectively. Abbreviations as in Fig. 1

NT-proBNP and hs-cTnI, as opposed to EF. Several factors influence a stable CAD population, which may explain the modest correlations found between biomarkers and deformation parameters. However, our findings are in line with previous studies [33, 34]. Similar to NT-proBNP, age and reduced kidney function seem to be important determinants of MD. The fact that they share these important determinants could partly explain why MD did not add prognostic information to NT-proBNP. A recent study of a healthy population showed that aging leads to a progressive rise in MD [20]. Nevertheless, both GLS and MD correlate with myocardial fibrosis [19, 35].

Clinical implications

Although MD provides superior prognostic information to EF and GLS, and GLS is the more sensitive marker of LV dysfunction, the incremental value of cardiac biomarkers should be emphasized. Elevated levels of both NT-proBNP and hs-cTn provide additive prognostic information in patients with stable CAD. Recently, NT-proBNP and hs-cTnT together with several clinical parameters have been incorporated in a novel risk score, in order to improve risk stratification in stable CAD patients [36]. In our study, NT-proBNP was superior to all echocardiographic parameters for prognostic evaluation. To our best knowledge, no previous studies have either compared the diagnostic and prognostic value between biochemical markers and echocardiographic parameters in patients with stable CAD. The use of deformation parameters in a multimarker approach should be examined in future studies with larger sample sizes.

There is evidence supporting the beneficial effects of ACE-inhibitors in subgroups of stable CAD patients, despite preserved EF [37]. Patients with subclinical LV dysfunction in combination with elevated cardiac biomarkers may be tentative candidates to benefit from statins, ACE-inhibitors or other preventive strategies. Current guidelines recommend transthoracic echocardiography to assess EF and wall motion abnormalities, while cardiac troponins and natriuretic peptides are still not a part of standard follow-up in these patients [2]. Although GLS is mentioned as a useful tool in the assessment of stable CAD patients, our results indicate that MD could also be assessed when performing deformation analyses.

Study limitations

This is an observational study and may be prone to inherent bias. The current study performed echocardiographic examinations and obtained blood samples one year after successful coronary revascularization, and is consequently applicable only to this patient group. It is a heterogenic cohort of patients, including new onset angina and previous

myocardial infarctions. Nevertheless, we believe that our cohort reflects common clinical practice. Due to the relatively small sample size and few endpoints, we consider our study to be exploratory, and the results should be confirmed in larger cohorts. All myocardial indexes analyzed in this study have limitations in the detection of LV dysfunction, making risk stratification in this cohort challenging. The study population is at low risk for malignant arrhythmias, and the study was not designed to evaluate arrhythmic events. Finally, strain measurements, as all echocardiographic measurements, are dependent on good image quality and operator experience.

Conclusions

NT-proBNP is the superior marker for prognostic evaluation in patients with stable CAD. MD correlates with established markers of subtle LV dysfunction and give incremental prognostic information to other echocardiographic markers. Further studies are needed to evaluate the role of MD in a multiparameter approach.

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Compliance with ethical standards

Conflict of interest JG has received lecture fees from Abbott Laboratories.

Ethical standards The Regional Ethics Committee approved the study, and all subjects provided written informed consent.

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Mechanical Dispersion as Marker of Left Ventricular Dysfunction and Prognosis in Stable Coronary Artery Disease

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Supplementary Table 1: Determinants of deformation parameters

	Mechanical dispersion		Global longitudinal strain	
	B (95% CI)	***P* value**	**B (95% CI)**	***P* value**
Age, yrs	0.49 (0.27-0.72)	<0.001	0.02 (-0.02-0.06)	0.409
Male sex	0.23 (-4.95-5.41)	0.929	1.27 (0.36-2.17)	0.006
Prior CABG	6.85 (1.40-12.29)	0.014	1.57 (0.62-2.53)	0.001
Current smoking	-0.10 (-5.12-4.92)	0.969	0.92 (0.04-1.81)	0.042
Diabetes	3.12 (-5.27-11.50)	0.464	1.70 (0.23-3.18)	0.024
BSA, kg/m^2	5.84 (-7.61-19.29)	0.392	2.70 (0.40-5.00)	0.022
Heartrate, beats/minute	-0.32 (-0.54 to -0.10)	0.004	0.03 (-0.01-0.07)	0.089
EF, %	-0.15 (-0.41 to -0.11)	0.251	-0.10 (-0.15 to -0.06)	<0.001
Abbott hs-cTnI, ng/L	6.61 (4.44-8.79)	<0.001	0.83 (0.43-1.24)	<0.001
Roche NT-proBNP, ng/L	4.33 (2.69-5.97)	<0.001	0.39 (0.07-0.70)	0.016
eGFR, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	-0.23 (-0.36 to -0.11)	0.001	-0.01 (-0.03-0.01)	0.411

Values of hs-cTnI and NT-proBNP are log-transformed.

B, unstandardized coefficients; CI, confidence interval; CABG, coronary artery bypass grafting; BSA, body surface area; EF, ejection fraction; hs-cTnI, high-sensitivity troponin I; NT-proBNP, amino-terminal pro B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.