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Future Perspectives for Management of Stage A Heart Failure

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Patients with Stage A heart failure (HF) show no HF symptoms but have related comorbid diseases with a high risk of progressing to HF. Screening for comorbid diseases warrants closer attention because of the growing interest in addressing Stage A HF as the best means of preventing eventual progression to overt HF such as Stages C and D. The identification of individuals of Stage A HF is potentially useful for the implementation of HF-prevention strategies; however, not all Stage A HF patients develop left ventricular (LV) structural heart disease or symptomatic HF, which lead to advanced HF stages. Therefore, Stage A HF requires management with the long-term goal of avoiding HF development; likewise, Stage B HF patients are ideal targets for HF prevention. Although the early detection of subclinical LV dysfunction is, thus, essential for delaying the progression to HF, the assessment of subclinical LV dysfunction can be challenging. Global longitudinal strain (GLS) as assessed by speckle-tracking echocardiography has recently been reported to be a sensitive marker of early subtle LV myocardial abnormalities, helpful for the prediction of the outcomes for various cardiac diseases, and superior to conventional echocardiographic indices. GLS reflects LV longitudinal myocardial systolic function, and can be assessed usually by means of two-dimensional speckle-tracking. This article reviews the importance of the assessment of subclinical LV dysfunction in Stage A HF patients by means of GLS, and its current potential to prevent progression to later stage HF.

Key words: Stage A heart failure, Left ventricular longitudinal myocardial function, Global longitudinal strain

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Introduction

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification describes stages of heart failure (HF) development as Stages A to D based on structural changes and symptoms¹⁻³. Whereas the New York Heart Association (NYHA) classes focuses on exercise capacity and the symptomatic status of the disease, this HF classification emphasizes the development and progression of the disease and can be used to describe individuals and populations. Patients with Stage A HF show no HF symptoms but have related comorbid diseases with high risk of progressing to HF, such as hypertension, diabe-

tes mellitus (DM), obesity, hypercholesterolemia, and metabolic syndrome, in addition to a history of using cardiotoxins, or a family history of cardiomyopathy. The absolute mortality rate for HF remains approximately 50% within 5 years of diagnosis, although survival has improved⁴. A population cohort study reported that 5-year survival rates for Stages A, B, C, and D HF were 97%, 96%, 75%, and 20%, respectively⁵. Screening for comorbid diseases warrants closer attention because of the growing interest in addressing Stage A HF as the best means of preventing eventual progression to overt HF such as Stages C and D. Prospective epidemiologic studies have identified risk factors and risk markers for HF development. In addition, the identification of individuals with Stage A HF is potentially useful for the implementation of HF prevention strategies. It is not clear yet whether all Stage A HF patients or only those at high risk of developing HF should be screened using serial noninvasive assessment for detection of the beginning of left ventricular (LV) dysfunction such as seen in Stage B HF. Therefore, Stage A

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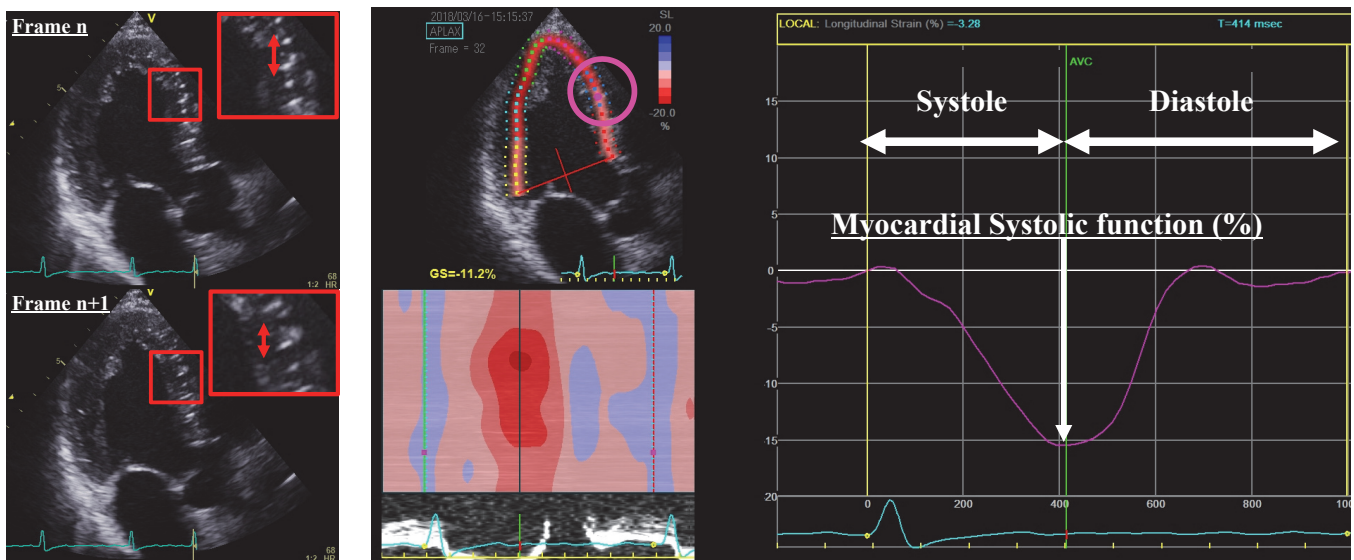


Fig. 1. Diagram of speckle tracking strain derived from two-dimensional long-axis echocardiographic images. Information about myocardial strain is generated by changes in speckles from frame to frame. Strain is calculated as the change in length divided by the original length and expressed as a percentage.

HF requires management with the long-term goal of avoiding HF development; likewise, Stage B HF patients are ideal targets for HF prevention. These individuals with prevalent cardiovascular diseases but without overt symptomatic HF include the majority of patients whose hearts are undergoing progressive maladaptive cardiac remodeling, which leads to HF. These silent abnormalities may lead over time to symptomatic LV dysfunction; however, such progression may be positively affected by early treatment. Although the early detection of subclinical LV dysfunction is, thus, essential for delaying progression to HF, the assessment of subclinical LV dysfunction can be challenging.

This article reviews the importance of the assessment of subclinical LV dysfunction, and LV longitudinal myocardial systolic dysfunction in particular, in Stage A HF patients, its current potential and future perspectives for the management of such patients.

Speckle-Tracking for Assessment of LV Longitudinal Myocardial Systolic Function

Echocardiography plays a pivotal role in the quantification and early detection of LV structural findings. However, global longitudinal strain (GLS) as assessed by speckle-tracking echocardiography has recently been reported to be a sensitive marker of early subtle abnormalities of LV myocardial performance, helpful for the prediction of outcomes for various cardiac diseases, and superior to conventional echocardiographic indices such as LV ejection fraction (LVEF), mitral inflow

E and mitral e' annular velocities ratio (E/e')⁶⁻¹⁰. GLS reflects LV longitudinal myocardial systolic function, and can be assessed usually by means of two-dimensional speckle-tracking, while speckle-tracking is a post-processing computer algorithm that uses routine grayscale digital images⁷. Although several manufacturers have devised various speckle-tracking echocardiographic approaches, the basic approach is similar. Briefly, routine grayscale digital images of the myocardium contain unique speckle patterns. A user-defined region of interest is placed on the myocardial wall, and within this region of interest, the image-processing algorithm automatically subdivides regions into blocks of pixels by tracking stable speckle patterns. Then, subsequent frames are analyzed automatically by searching for new locations of the speckle patterns within each of the blocks by means of correlation criteria and the sum of absolute differences (**Fig. 1**). The shifts in location of these acoustic markers from frame to frame representing tissue movement provide the spatial and temporal data used to calculate velocity vectors. Temporal alterations in these stable speckle patterns are identified as moving farther apart or closer together and create a series of regional strain vectors. Strain information is not dependent on the Doppler angle of incidence, which makes the analysis of longitudinal strain possible. GLS is then determined as the averaged peak longitudinal strain of 18 LV segments from the three standard apical views, and is expressed as an absolute value (**Fig. 2**)¹¹.

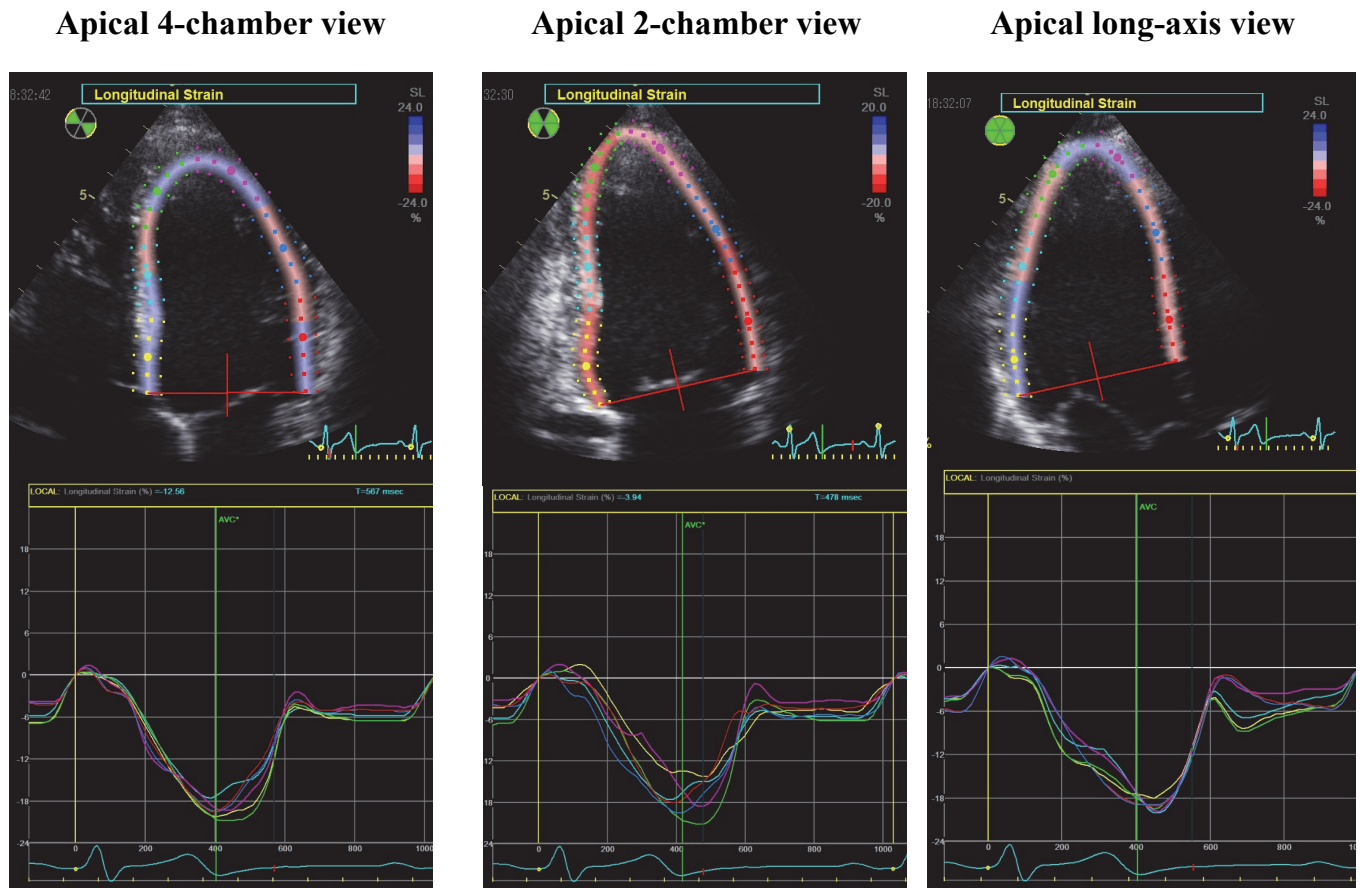


Fig. 2. Example of the assessment of LV longitudinal systolic myocardial function, known as GLS, by means of two-dimensional speckle-tracking imaging, showing color-coded speckle-tracking images and corresponding longitudinal time-strain curves. GLS is determined as the averaged peak longitudinal strain of 18 segments from the three standard apical views, and is expressed as an absolute value.

Utility of the Assessment of LV Longitudinal Myocardial Systolic Dysfunction for the Management of Stage A HF

Recent studies suggest that GLS might be helpful for the prediction of cardiovascular outcomes even for a general population^{6, 12, 13}. The echocardiographic sub-study from the Copenhagen City Heart Study used 1,296 participants from a general population who underwent a health examination, including conventional echocardiography and GLS measurement⁶. During a median follow-up of 11 years, lower GLS was associated with a higher risk of the composite end point of incident HF, acute myocardial infarction, or cardiovascular death, and an association that persisted after multivariable adjustment for age, gender, heart rate, hypertension, systolic blood pressure, LVEF, LV mass index, LV dimension, deceleration time, left atrium dimension, E/e' , and pro B-type natriuretic peptide. In addition, GLS provided incremental prognostic information beyond the

Framingham Risk Score, the Systemic Coronary Evaluation risk chart, and the modified ACCF/AHA Pooled Cohort Equation for the composite outcome and incident HF. LV longitudinal myocardial systolic dysfunction as assessed in terms of low GLS is altered in Stage A HF patients and can be an early marker of LV dysfunction, and, therefore, may point to cardiovascular morbidity and mortality. The next section will deal in more detail with the utility of LV longitudinal myocardial systolic dysfunction for individual comorbidity in Stage A HF patients.

1. LV Longitudinal Myocardial Systolic Dysfunction and Hypertension

With a proven population attributable risk of 39% for men and 59% for women, hypertension is the most common risk factor for HF¹⁴. Moreover, men with hypertension have a higher lifetime risk of developing HF than normotensive men¹⁵. Over 30% of Stage A HF patients during the surveyed period had blood pres-

sure above the target blood pressure, despite being diagnosed with hypertension¹⁶). Previous studies have reported a prevalence of low GLS values, ranging from 15% to 42%, for patients with hypertension, depending on the severity and control of hypertension¹⁷⁻²⁰. Bendiab *et al.* found that 46% of patients showed low GLS values (<17%), and low GLS was associated with long-lasting hypertension and uncontrolled blood pressure for 200 outpatients with hypertension with preserved LVEF without overt HF. Moreover, Chen *et al.* reported that patients with uncontrolled blood pressure ($\geq 140/90$ mmHg) were associated with low GLS regardless of LV hypertrophy for 276 patients with treated hypertension²⁰.

2. LV Longitudinal Myocardial Systolic Dysfunction and DM

DM is another well-known risk factor for HF, and as important a comorbid disease of Stage A HF as hypertension. Lack of DM control is an important predictor of the new onset of HF, with every 1% increase in HbA1c correlating to an 8%–19% increase in HF incidence^{21, 22}. The presence of LV longitudinal myocardial systolic dysfunction has been identified in DM patients with preserved LVEF without overt coronary artery disease or HF²³⁻³². Nakai *et al.* reported that GLS in DM patients was significantly lower than that in age-matched normal subjects in spite of similar LVEF, and that 43% of DM patients showed LV longitudinal myocardial systolic dysfunction defined as GLS <17.2%²³, while Ernande *et al.* showed that 23% of DM patients with preserved LVEF had LV longitudinal myocardial systolic dysfunction defined as GLS <18%²⁶. In addition, Holland *et al.* investigated the association of subclinical LV dysfunction as detected by GLS with long-term, 10-year outcomes in 230 asymptomatic patients with type 2 DM and preserved LVEF³³. They found that patients with GLS <18.9% had significantly worse outcome than those with a higher percentage, and concluded that GLS was independently associated with the primary endpoint.

DM is also a major cause of HF with preserved LVEF (HFpEF) as well as hypertension, with HFpEF usually presenting as LV diastolic dysfunction. Some investigators have maintained that LV longitudinal myocardial systolic dysfunction, rather than LV diastolic dysfunction, should be considered the first marker of a preclinical form of DM-related cardiac dysfunction in DM patients with preserved LVEF without overt HF^{27, 34}. Ernande *et al.* showed that LV longitudinal myocardial systolic dysfunction detected as GLS <18% was present even in DM patients with preserved LVEF and normal LV diastolic function²⁷. Thus, it has been suggested that the progression of uncontrolled DM

leads to LV myocardial systolic dysfunction as well as LV diastolic dysfunction, that GLS is associated with LV diastolic function, and that reduced GLS can coexist with LV diastolic dysfunction in DM patients with preserved LVEF, leading to HFpEF.

3. LV Longitudinal Myocardial Systolic Dysfunction and Obesity

Healthy lifestyle habits, including the maintenance of normal body weight at body mass index (BMI) <25 kg/m², are associated with lower lifetime risk of HF¹⁵. Compared to those with normal BMI, obese subjects were found to have twice the risk of developing HF, with a graded relationship between BMI and HF incidence, including for those in the overweight category³⁵. Ho *et al.* observed that higher BMI was associated with low GLS in 6,231 participants³⁶. They showed that higher circulating leptin concentrations were associated with low GLS, suggesting potential involvement of circulating adipokines in obesity-related LV damage. Suto *et al.* recently reported that GLS of overweight patients (BMI ≥ 25 kg/m²) was significantly lower than that of non-overweight patients, and multiple regression analysis revealed that BMI was the independent determinant parameter for GLS as well as LV mass index in 145 asymptomatic type 2 DM patients with preserved LVEF without coronary artery disease³⁷. Furthermore, Leung *et al.* have detected an association of weight loss with an increase in GLS in obese patients. They showed that in eight obese patients with type 2 DM with BMI of 44 ± 9 kg/m² who underwent sleeve gastrectomy, GLS improved from $13.2 \pm 3.7\%$ to $19.7 \pm 2.2\%$ after surgery³⁸.

4. LV Longitudinal Myocardial Systolic Dysfunction and Hypercholesterolemia

Hypercholesterolemia has become well known as an extremely strong risk factor for coronary artery disease; however, its direct effect on LV myocardial function remains unclear. Liu *et al.* used 28 experimental rabbit models to investigate the effect of hypercholesterolemia on LV myocardial function in an attempt to elucidate such an effect³⁹. They showed that GLS in an atherogenic diet group was significantly lower than that in a normal chow group even though the two groups had similar blood pressure, heart rate, and LVEF. Furthermore, a significant inverse correlation was observed between GLS and low-density lipoprotein cholesterol (LDL-C). In addition, Di Salvo *et al.* showed that GLS in 45 children with heterozygous familial hypercholesterolemia was significantly lower than that in 45 age-, gender-, and LVEF-matched control healthy children, and a significant linear correlation was observed between LDL-C and GLS⁴⁰. Since arterioscle-

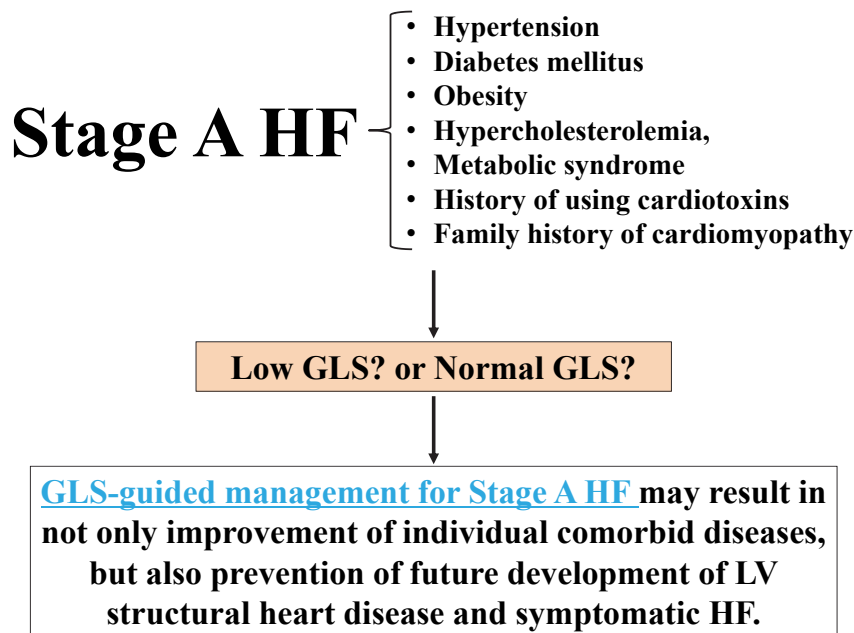


Fig. 3. Schema of the potential future perspectives or using global longitudinal strain for the management of Stage A HF.

rotic disease due to hypercholesterolemia can lead to an increase risk for HF, early intervention for hypercholesterolemia would be necessary to prevent eventual progression to overt HF.

5. LV Longitudinal Myocardial Systolic Dysfunction and Patients with History of Cardiotoxin Use

Patients without HF symptoms or LV structural abnormalities, but with a history of using cardiotoxins such as doxorubicin and trastuzumab, are included in Stage A HF. These cardiotoxins are used as anticancer drugs in chemotherapy treatment and have resulted in a recent decrease in the mortality rate for patients with various types of cancer. However, cancer therapeutics-related cardiac dysfunction (CTRCD) has become a leading cause of morbidity and mortality for cancer survivors^{41, 42}, and the mortality rate for patients with CTRCD is reportedly as high as 60% by 2 years after treatment⁴³. This is caused by the irreversible LV myocardial changes due to anticancer drugs, such as myocyte loss, interstitial fibrosis leading to diminished LV contractility, reduced LV wall thickness, and progressive LV dilation. Anthracycline is an effective antineoplastic agent used for a wide spectrum of hematologic malignancies and solid tumors; however, the most serious adverse effect of anthracycline chemotherapy is progressive dose-dependent LV dysfunction followed by congestive HF, even years after the treatment has been completed. For this reason, there has been a growing interest in early detection of CTRCD by means of

GLS, because it is a more sensitive and robust parameter for detecting subclinical LV myocardial dysfunction than other conventional LV functional parameters such as LVEF⁴⁴⁻⁴⁷. A systematic review of 1,504 patients during or after cancer chemotherapy showed that early changes in GLS appear to be the best measure for predicting cardiotoxicity⁴⁶. Specifically, a drop in LVEF or occurrence of HF, reflected in a 10% to 15% early reduction in GLS during chemotherapy, appears to be the most useful parameter for the prediction of cardiotoxicity.

Future Perspectives for the Assessment of GLS for the Management of Stage A HF

The current ACCF/AHA guidelines recommend counseling, risk factor reduction, and control of concurrent diseases for Stage A HF¹⁻³. Although the identification of individuals with Stage A HF is potentially useful for the implementation of HF-prevention strategies, not all Stage A HF patients develop LV structural heart disease or symptomatic HF, which can lead to advanced HF stages. This review article indicates that LV longitudinal myocardial systolic dysfunction as assessed in terms of low GLS can first appear in Stage A HF, which suggests the importance of the assessment of GLS for detecting subclinical LV dysfunction in this sub-clinical stage. Thus, GLS-guided management such as strict control of hypertension, DM, hypercholesterolemia and obesity may result in not only the

improvement of individual comorbid diseases, but also the prevention of future development of LV structural heart disease and symptomatic HF. However, more research is needed to further understand the efficacy of GLS-guided therapy using cardioprotective drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β -blockers, and mineralocorticoid receptor antagonists for Stage A HF patients. Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of diabetic medications currently indicated only for the treatment of type 2 DM. In addition to reducing glycated hemoglobin levels in patients with type 2 DM, SGLT2 inhibitors are associated with weight loss and reductions in blood pressure which are important comorbid diseases for Stage A HF⁴⁸⁻⁵⁰. Thus, SGLT2 inhibitors may have potential for a new therapeutic strategy for Stage A HF⁵¹.

The Measurement of GLS has certain limitations, however; among known sources of variety, the primary determinant is post-processing. The most important limitation is that different vendors have reported significantly different measurements of GLS^{52, 53}. However, this issue has been minimized since Strain Standardization Taskforce intervention⁵⁴. Furthermore, the difference among vendors in GLS measurements is at most equivalent to or even smaller than that in LVEF measurements⁵³, and the reproducibility of GLS measurements was found to be as good as, and in many cases superior to that of conventional echocardiographic measurements⁵³.

Conclusion

HF is a worldwide healthcare epidemic, known as "The HF Pandemic." HF is likely to be more serious in the near future with the epidemiological transition and the accompanying aging of the population. In addition, there is a high prevalence of patients with Stage A HF, many of whom are not being appropriately or adequately treated for their risk factors. Thus, GLS-guided management for patients with Stage A HF may have the potential of preventing progression to later stage HF (**Fig. 3**).

References

- 1) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ and Wilkoff BL: 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*, 2013; 128: 1810-1852
- 2) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C: 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*, 2017; 136: e137-e161
- 3) Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C: 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*, 2016; 134: e282-293
- 4) Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP and Jacobsen SJ: Trends in heart failure incidence and survival in a community-based population. *Jama*, 2004; 292: 344-350
- 5) Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Jr. and Rodeheffer RJ: Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation*, 2007; 115: 1563-1570
- 6) Biering-Sorensen T, Biering-Sorensen SR, Olsen FJ, Sengelov M, Jorgensen PG, Mogelvang R, Shah AM and Jensen JS: Global Longitudinal Strain by Echocardiography Predicts Long-Term Risk of Cardiovascular Morbidity and Mortality in a Low-Risk General Population: The Copenhagen City Heart Study. *Circulation Cardiovascular imaging*, 2017; 10:
- 7) Gorcsan J, 3rd and Tanaka H: Echocardiographic assessment of myocardial strain. *J Am Coll Cardiol*, 2011; 58: 1401-1413
- 8) Stanton T, Leano R and Marwick TH: Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circulation Cardiovascular imaging*, 2009; 2: 356-364
- 9) Kalam K, Otahal P and Marwick TH: Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart*, 2014; 100: 1673-1680
- 10) Mignot A, Donal E, Zaroui A, Reant P, Salem A, Hamon C, Monzy S, Roudaut R, Habib G and Lafitte S: Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: a multicenter study. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2010; 23: 1019-1024
- 11) Lang RM, Badano LP, Mor-Avi V, Afzal J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA,

- Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W and Voigt JU: Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2015; 28: 1-39 e14
- 12) Russo C, Jin Z, Elkind MS, Rundek T, Homma S, Sacco RL and Di Tullio MR: Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. *Eur J Heart Fail*, 2014; 16: 1301-1309
- 13) Cheng S, McCabe EL, Larson MG, Merz AA, Osypiuk E, Lehman BT, Stantchev P, Aragam J, Solomon SD, Benjamin EJ and Vasan RS: Distinct Aspects of Left Ventricular Mechanical Function Are Differentially Associated With Cardiovascular Outcomes and All-Cause Mortality in the Community. *J Am Heart Assoc*, 2015; 4: e002071
- 14) Levy D, Larson MG, Vasan RS, Kannel WB and Ho KK: The progression from hypertension to congestive heart failure. *Jama*, 1996; 275: 1557-1562
- 15) Djousse L, Driver JA and Gaziano JM: Relation between modifiable lifestyle factors and lifetime risk of heart failure. *Jama*, 2009; 302: 394-400
- 16) National Cholesterol Education Program Expert Panel on Detection E and Treatment of High Blood Cholesterol in A: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*, 2002; 106: 3143-3421
- 17) Soufi Taleb Bendib N, Meziane-Tani A, Ouabdesslam S, Methia N, Latreche S, Henaoui L, Monsuez JJ and Benkhedda S: Factors associated with global longitudinal strain decline in hypertensive patients with normal left ventricular ejection fraction. *Eur J Prev Cardiol*, 2017; 24: 1463-1472
- 18) Kosmala W, Plaksej R, Strotmann JM, Weigel C, Herrmann S, Niemann M, Mende H, Stork S, Angermann CE, Wagner JA and Weidemann F: Progression of left ventricular functional abnormalities in hypertensive patients with heart failure: an ultrasonic two-dimensional speckle tracking study. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2008; 21: 1309-1317
- 19) Imbalzano E, Zito C, Carerj S, Oretto G, Mandraffino G, Cusma-Piccione M, Di Bella G, Saitta C and Saitta A: Left ventricular function in hypertension: new insight by speckle tracking echocardiography. *Echocardiography (Mount Kisco, NY)*, 2011; 28: 649-657
- 20) Chen XJ, Sun XL, Zhang Q, Gao XL, Liang YJ, Jiang J, Kang Y, Chen YC, Zeng Z and Yu CM: Uncontrolled blood pressure as an independent risk factor of early impaired left ventricular systolic function in treated hypertension. *Echocardiography (Mount Kisco, NY)*, 2016; 33: 1488-1494
- 21) Vaur L, Gueret P, Lievre M, Chabaud S, Passa P and study DSG: Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril) study. *Diabetes Care*, 2003; 26: 855-860
- 22) Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S and Selby JV: Glycemic control and heart failure among adult patients with diabetes. *Circulation*, 2001; 103: 2668-2673
- 23) Nakai H, Takeuchi M, Nishikage T, Lang RM and Otsuji Y: Subclinical left ventricular dysfunction in asymptomatic diabetic patients assessed by two-dimensional speckle tracking echocardiography: correlation with diabetic duration. *European journal of echocardiography: the journal of the Working Group on Echocardiography of the European Society of Cardiology*, 2009; 10: 926-932
- 24) Ng AC, Delgado V, Bertini M, van der Meer RW, Rijzewijk LJ, Shanks M, Nucifora G, Smit JW, Diamant M, Romijn JA, de Roos A, Leung DY, Lamb HJ and Bax JJ: Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus. *Am J Cardiol*, 2009; 104: 1398-1401
- 25) Zoroufian A, Razmi T, Taghavi-Shavazi M, Lotfi-Tokaldany M and Jalali A: Evaluation of subclinical left ventricular dysfunction in diabetic patients: longitudinal strain velocities and left ventricular dyssynchrony by two-dimensional speckle tracking echocardiography study. *Echocardiography (Mount Kisco, NY)*, 2014; 31: 456-463
- 26) Ernande L, Bergerot C, Girerd N, Thibault H, Davidsen ES, Gautier Pignon-Blanc P, Amaz C, Croisille P, De Buyzere ML, Rietzschel ER, Gillebert TC, Moulin P, Altman M and Derumeaux G: Longitudinal myocardial strain alteration is associated with left ventricular remodeling in asymptomatic patients with type 2 diabetes mellitus. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2014; 27: 479-488
- 27) Ernande L, Bergerot C, Rietzschel ER, De Buyzere ML, Thibault H, Pignonblanc PG, Croisille P, Ovize M, Groisne L, Moulin P, Gillebert TC and Derumeaux G: Diastolic dysfunction in patients with type 2 diabetes mellitus: is it really the first marker of diabetic cardiomyopathy? *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2011; 24: 1268-1275 e1261
- 28) Ernande L, Rietzschel ER, Bergerot C, De Buyzere ML, Schnell F, Groisne L, Ovize M, Croisille P, Moulin P, Gillebert TC and Derumeaux G: Impaired myocardial radial function in asymptomatic patients with type 2 diabetes mellitus: a speckle-tracking imaging study. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2010; 23: 1266-1272
- 29) Tadic M, Ilic S, Cuspidi C, Stojcevski B, Ivanovic B, Bukarica L, Jozika L and Celic V: Left Ventricular Mechanics in Untreated Normotensive Patients with Type 2 Diabetes Mellitus: A Two- and Three-dimensional Speckle Tracking Study. *Echocardiography (Mount Kisco, NY)*, 2014;
- 30) Mochizuki Y, Tanaka H, Matsumoto K, Sano H, Toki H, Shimoura H, Ooka J, Sawa T, Motoji Y, Ryo K, Hirota Y, Ogawa W and Hirata KI: Clinical features of subclinical left ventricular systolic dysfunction in patients with diabetes mellitus. *Cardiovasc Diabetol*, 2015; 14: 37

- 31) Mochizuki Y, Tanaka H, Matsumoto K, Sano H, Toki H, Shimoura H, Ooka J, Sawa T, Motoji Y, Ryo K, Hirota Y, Ogawa W and Hirata KI: Association of peripheral nerve conduction in diabetic neuropathy with subclinical left ventricular systolic dysfunction. *Cardiovasc Diabetol*, 2015; 14: 47
- 32) Mochizuki Y, Tanaka H, Tatsumi K, Matsumoto K, Imanishi J, Yoshida A, Yokoyama M, Kawai H and Hirata K: Easy-to-use comprehensive speckle-tracking approach for cardiac resynchronization therapy. *Circulation journal: official journal of the Japanese Circulation Society*, 2014; 78: 2250-2258
- 33) Holland DJ, Marwick TH, Haluska BA, Leano R, Hordern MD, Hare JL, Fang ZY, Prins JB and Stanton T: Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart*, 2015;
- 34) Cognet T, Vervueren PL, Dercle L, Bastie D, Richaud R, Berry M, Marchal P, Gautier M, Fouilloux A, Galinier M, Carrie D, Massabuau P, Berry I and Lairez O: New concept of myocardial longitudinal strain reserve assessed by a dipyridamole infusion using 2D-strain echocardiography: the impact of diabetes and age, and the prognostic value. *Cardiovascular diabetology*, 2013; 12: 84
- 35) Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB and Vasan RS: Obesity and the risk of heart failure. *N Engl J Med*, 2002; 347: 305-313
- 36) Ho JE, McCabe EL, Wang TJ, Larson MG, Levy D, Tsao C, Aragam J, Mitchell GF, Benjamin EJ, Vasan RS and Cheng S: Cardiometabolic Traits and Systolic Mechanics in the Community. *Circ Heart Fail*, 2017; 10:
- 37) Suto M, Tanaka H, Mochizuki Y, Mukai J, Takada H, Soga F, Dokuni K, Hatani Y, Hatazawa K, Matsuzoe H, Sano H, Shimoura H, Ooka J, Matsumoto K, Hirota Y, Ogawa W and Hirata KI: Impact of overweight on left ventricular function in type 2 diabetes mellitus. *Cardiovasc Diabetol*, 2017; 16: 145
- 38) Leung M, Xie M, Durmush E, Leung DY and Wong VW: Weight Loss with Sleeve Gastrectomy in Obese Type 2 Diabetes Mellitus: Impact on Cardiac Function. *Obes Surg*, 2016; 26: 321-326
- 39) Liu L, Mu Y, Han W and Wang C: Association of hypercholesterolemia and cardiac function evaluated by speckle tracking echocardiography in a rabbit model. *Lipids Health Dis*, 2014; 13: 128
- 40) Di Salvo G, D'Aiello AF, Castaldi B, Fadel B, Limongelli G, D'Andrea A, Pergola V, Pacileo G, Del Giudice EM, Perrone L, Calabro R and Russo MG: Early left ventricular abnormalities in children with heterozygous familial hypercholesterolemia. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2012; 25: 1075-1082
- 41) Hoening MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, Taylor CW and van Leeuwen FE: Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*, 2007; 99: 365-375
- 42) Doyle JJ, Neugut AI, Jacobson JS, Grann VR and Hershtman DL: Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. *J Clin Oncol*, 2005; 23: 8597-8605
- 43) Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL and Kasper EK: Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*, 2000; 342: 1077-1084
- 44) Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC and Marwick TH: Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. *European heart journal cardiovascular Imaging*, 2014; 15: 324-331
- 45) Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC and Marwick TH: Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2013; 26: 493-498
- 46) Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A and Marwick TH: Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*, 2014; 63: 2751-2768
- 47) Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR and Lancellotti P: Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2014; 27: 911-939
- 48) Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE and Investigators E-RO: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*, 2015; 373: 2117-2128
- 49) Haring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ, Broedl UC and Investigators E-RMT: Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*, 2013; 36: 3396-3404
- 50) Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, Broedl UC and Investigators E-RMT: Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care*, 2014; 37: 1815-1823
- 51) Tanaka H and Hirata KI: Potential impact of SGLT2 inhibitors on left ventricular diastolic function in patients with diabetes mellitus. *Heart Fail Rev*, 2018;
- 52) Takigiku K, Takeuchi M, Izumi C, Yuda S, Sakata K, Ohte N, Tanabe K, Nakatani S and investigators J: Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. *Circulation journal: official journal of*

- the Japanese Circulation Society, 2012; 76: 2623-2632
- 53) Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP and Voigt JU: Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2015; 28: 1171-1181, e1172
- 54) Yang H, Marwick TH, Fukuda N, Oe H, Saito M, Thomas JD and Negishi K: Improvement in Strain Concordance between Two Major Vendors after the Strain Standardization Initiative. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 2015; 28: 642-648 e647