Review Article

Echocardiographic feature of diabetic cardiomyopathy: where are we now?

Kazuaki Negishi[1,2]

[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia; [2]Royal Hobart Hospital, Hobart, Australia

Correspondence to: Kazuaki Negishi, MD, PhD, FACC, FESC, FASE, FAHA. Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool St, Hobart, TAS 7000, Australia. Email: Kazuaki.Negishi@utas.edu.au.

Abstract: We are now entering the very exciting era of treatment and management of diabetes mellitus (DM) with the emergence of new therapeutic agents, including sodium-glucose cotransporter 2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP-4i). From a cardiology and echocardiography perspective, the existence of diabetic cardiomyopathy has been proven through over four decades of discussion. DM is highly prevalent in patients with heart failure (HF). Independent associations are found after adjusting for hypertension (HTN) and coronary artery disease (CAD). In patients with both DM and HF, the prognosis is extremely dismal. In this review, the main focus is on both diabetic cardiomyopathy *per se* and its typical features (including myocardial additive insult related to DM), diagnosis, and management.

Keywords: Diabetes mellitus (DM); diabetic cardiomyopathy; echocardiography; myocardial strain; sodium-glucose cotransporter 2 inhibitors (SGLT2i)

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Introduction

The concept of diabetic cardiomyopathy was first described in 1972 by Rubler *et al.* in their manuscript titled "*New type of cardiomyopathy associated with diabetic glomerulosclerosis*" (1). They found that 15% of postmortem cases with diabetic glomerulosclerosis had no hypertension (HTN) and no significant coronary artery disease (CAD) but left ventricular hypertrophy (LVH), cardiomegaly and congestive heart failure (HF). Their histopathologic study revealed diffuse fibrosis, myofibrillar hypertrophy, microvascular disease and deposition of acid mucopolysaccharide material. Their speculation on the pathophysiological mechanism remains valid in the current understanding: "*Probably secondary to diabetic microangiopathy although the direct effects of the abnormal myocardial metabolism in diabetes mellitus (DM) could not be excluded.*" Diabetic cardiomyopathy has subsequently been widely reported and used by epidemiologists and clinicians worldwide.

DM as an independent risk factor for HF

There has been a long debate whether DM causes cardiomyopathy or not (2), because some argue that CM in patients with DM could be due to confounders, such as CAD disease, concomitant HTN, and so on (*Figure 1*). Indeed, DM dramatically increases the risk of HF. Data from Framingham population demonstrated a 2- to 5-fold excess risk for developing new HF in individuals with DM (3). The risk is even higher (4- to 8-fold) in young patients. An almost linear increase in risk is observed: each 1% elevation in hemoglobin A1C (HbA1C) leads to an 8% increase in the frequency of HF. The independent association between DM and HTN is supported by several large sets of clinical data (*Table 1*).

Effect of DM on HF prognosis

When a patient with DM develops HF, the prognosis generally remains dismal. Data were collected from the US Medicare which include >150,000 patients with DM and aged >65 years. Patients with DM and HF had a hazard ratio (HR) for mortality of >10 with very narrow confidence interval (CI) (HR =10.6; 95% CI: 10.4–10.9), compared

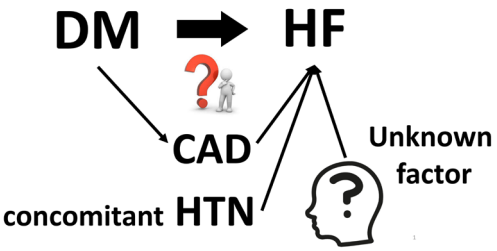

Figure 1 DM and HF. There has been a long period of discussion on the association between DM and HF, if it is an independent association or confounded by concomitant risk factors, like CAD, HTN or unknown factors. CAD, coronary artery diseases; DM, diabetes mellitus; HF, heart failure; HTN, hypertension

Table 1 Association between DM and HF

Study	Journal/year	Heart failure with DM
Framingham (4)	*Am J Cardio* 1974	<65 years—HR =4 in men, 8 in women; overall—2.4 in men, 5.1 in women
CV Health study (5)	*J Am Coll Cardiol* 2000	HR =1.74 (1.38–2.19)
UKPDS (6)	*BMJ* 2000	HF risk related to HbA1c
Kaiser Permanente (7)	*Diabetes Care* 2001	45–54 years—33 cases per 1,000; 55–64 years—68 cases per 1,000; 65–74 years—135 cases per 1,000
ALLHAT (8)	*Circulation* 2006	RR =1.95 for HF hospitalization/death

HF, heart failure; HR, hazard ratio; RR, risk ratio; DM, diabetes mellitus; HbA1c, hemoglobin A1C.

with DM without HF (9). The finding is corroborated by several large clinical trials such as LIFE (HR for mortality was 5.98; 95% CI: 3.90–9.17; P<0.0001) and RENAAL (HR =3.99; 95% CI: 3.02–5.25; P<0.0001) (10).

Current understanding

Based on these data, ACCF/AHA Guidelines for HF determined diabetes as an independent risk factor for HF (11). From this revision of the Guidelines, they categorized HF into four stages (stages A to D). Stage A is at high risk for HF without structural changes or symptoms. They clearly mention that DM itself is a significant independent risk for HF. The definition of diabetic cardiomyopathy has been slightly modified from the initial definition by Rubler *et al.* "ventricular dysfunction that occurs independently of CAD and HTN" to "diabetes-associated structural and functional myocardial dysfunction not related to other confounding traditional factors such as CAD, HTN, congenital or valvular heart diseases" (12-14). In addition, diabetic cardiomyopathy is classified into two types: restrictive [similar to HF with preserved ejection fraction (EF) >50%] and dilated (HF with reduced EF <50%) (15).

The restrictive type is mainly characterized by coronary microvascular endothelial dysfunction and metabolic rearrangements (hyperglycemia, lipotoxicity, and obesity), whereas the dilated counterpart is characterized by cardiomyocyte cell death and autoimmune disorder [e.g., type 1 diabetes mellitus (T1DM)]. They also share common features, such as coronary microvascular rarefaction and advanced glycogen end product (AGE) deposition. Concerning further detailed mechanism, insulin resistance and hyperinsulinemia play a key role (16). They increase systemic metabolic disorders and activate the sympathetic nerve system (autonomic dysfunction); then activate renin-angiotensin-aldosterone system; prompt oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress; and impair calcium homeostasis. These effects result in cardiac fibrosis, hypertrophy, cardiomyocyte death, dysfunction of the coronary microcirculation, and eventually HF. Furthermore, these pathophysiological changes in cardiomyocytes underlie the risk factors for insulin resistance and hyperinsulinemia, which can result in a potentially vicious cycle, which prompt the following question: does HF cause DM?

Does HF cause DM?

Data from the Bezafibrate Infarction Prevention trial, which included >2,600 patients who had myocardial infarction without diabetes at baseline, showed that those with New York Heart Association (NYHA) class III symptoms had a significant increase in subsequent DM with a 1.7-fold (95% CI: 1.1–2.6) increase, but those with NYHA class II did not (HR =1.0; 95% CI: 0.8–1.3) over the 7.7 years of follow-up (17). The main underlying mechanism is insulin resistance (18). A new HF medication, sacubitril/valsartan, has greater glycemic control than angiotensin converting enzyme inhibitor (19).

Who should be screened and how?

Thus far, the brief history of diabetic cardiomyopathy and

HF risk and vicious cycle has been reviewed. The next logical questions are who to be screened and how. Our meta-analysis identified four key independent risk factors: history of CAD, age (every 5 years), poor glycemic control markers (i.e., insulin use, high fasting glucose, and HbA1c of >9.0%), and HTN (20). As routine clinical practice, the screening should comprise history (above four criteria) and physical examination (including blood pressure assessment), blood tests (for glycemic control), and electrocardiography (ECG) (for CAD and LVH).

The screening should include medical encounter for medical history (age, CAD, etc.), symptoms (dyspnea, etc.), and physical examination, including blood pressure measurement, followed by blood tests for glycemic control and ECG for CAD or LVH. As screening is mostly performed in asymptomatic subjects with risks (stage A HF), cardiac imaging plays an important role. The majority of data in the literature are from echocardiography, which will be discussed in the following section.

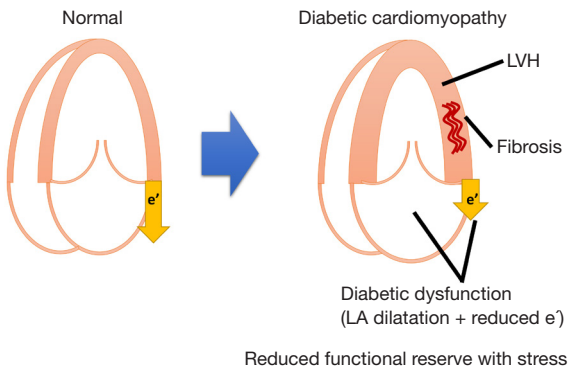

Figure 2 Schematic illustration of diabetic cardiomyopathy. LVH, left ventricular hypertrophy; LA, left atrial.

Echocardiographic assessment of diabetic cardiomyopathy

LVH and myocardial fibrosis (morphological alteration assessed by echocardiography): the main finding of diabetic cardiomyopathy was LVH in the initial autopsy study (1), where histopathologic study revealed diffuse fibrosis and myocyte hypertrophy (*Figure 2*). Using echocardiography, numerous studies, including population-based studies (21-28) (*Table 2*), confirmed LVH in a population with diabetes and in prediabetes stage, for example, impaired glucose tolerance (IGT) (21,22,25,27). In the Strong Heart Study population, Ilercil *et al.* identified independent associations of IGT with higher left ventricular (LV) relative wall thicknesses and LV mass/height$^{2.7}$ (25). Collectively, DM, even from the prediabetes stage, is independently associated with LVH.

The main underlying histopathologic alteration in diabetic cardiomyopathy is fibrosis (29). Integrated backscatter (IB) is a technique used to assess echocardiographic tissue characteristic using the reflectivity of tissue to ultrasound, developed in the 1980s (30,31). From the early 1990s, the IB has been performed in patients with diabetes (32,33) (*Table 3*). Their primary findings are greater IB (indicating greater fibrosis) and lower cyclic variation of IB in the diabetic myocardium.

Diastolic dysfunction: the primary and early functional consequence of these morphological alterations is LV

Table 2 Diabetes mellitus and left ventricular hypertrophy

Year	First author	Study cohort	DM or IGT	Main findings
1991	Galderisi (21)	FHS	DM or IGT	Increase in LVM in women
1997	Lee (22)	CV Health Study	DM or IGT	Increase in LVM in both sexes
2000	Devereux (23)	Strong Heart Study	DM	Increase in LVM
2001	Palmeri (24)	HyperGEN Study	DM + HTN	Increase in LVM and RWT
2001	Ilerci (25)	Strong Heart Study	IGT	Increase of LVM and RWT
2001	Bella (26)	Strong Heart Study	DM ± HTN	Progressive increase of LVM in both DM ± HTN
2003	Rutter (27)	FHS	DM or IGT	Progressive increase in LVM, RWT, and LA

CV, cardiovascular; DM, diabetes mellitus; FHS, Framingham Heart Study; IGT, impaired glucose tolerance; HTN, hypertension; LA, left atrial; LVM, left ventricular mass; RWT, relative wall thickness.

Table 3 Diabetes mellitus and fibrosis

Year	First author	Journal	Main findings
1992	Perez (32)	*J Am Coll Cardiol*	Lower cyclic variation of IB in insulin dependent DM and further reduced in patients with insulin DM with neuropathy
1995	Di Bello (33)	*J Am Coll Cardiol*	Increased echodensity by IB in insulin DM
2003	Fang (34)	*J Am Coll Cardiol*	Greater calibrated IB in DM than in normal controls
2008	van Heerebeek (29)	*Circulation*	Determinants for diastolic stiffness are fibrosis, AGEs, and myocyte resting tension using biopsy specimen

AGEs, advanced glycogen end products; IB, integrated backscatter; DM, diabetes mellitus.

Table 4 Diabetes mellitus and diastolic dysfunction

Year	First author	Journal	Main findings
1988	Zarich (35)	*J Am Coll Cardiol*	Lower E/A ratio and higher A-wave velocity in T1DM than control subjects
1995	Celentano (36)	*Am J Cardio*	Lower E/A ratios in patients with T2DM or IGT than in normoglycemic subjects
2001	Liu (37)	*J Am Coll Cardiol*	Progressive reduction of E/A ratio and prolongation of DT in DM ± HTN
2002	Hansen (38)	*Diabetes*	Lower e' in T1DM than in normal controls
2005	Fang (39)	*Diabetologia*	Subclinical LV diastolic dysfunction is associated with poor diabetic control, advancing age, hypertension, and metformin treatment; ACE inhibitor and insulin therapies appear to be protective
2006	Bajraktari (40)	*Int J Cardio*	Insulin resistance is associated with diastolic dysfunction
2006	Moir (41)	*Heart*	Higher E/E' in T2DM than in controls
2009	From (42)	*Am J Cardio*	DM of >4 years is correlated with significant LV diastolic dysfunction; LV diastolic dysfunction is predictive of all-cause mortality in patients with DM independent of HTN and CAD
2010	From (43)	*J Am Coll Cardiol*	E/E'_{sept} of >15 in patients with DM is associated with the subsequent development of HF and increased mortality independent of HTN, CAD, or other echocardiographic parameters
2010	Sacre (44)	*JACC Cardiovasc Imaging*	Diastolic dysfunction in DM is associated with cardiac autonomic neuropathy assessed by MIBG
2011	Falcão-Pires (45)	*Circulation*	DM further worsens diastolic function in severe aortic stenosis, via greater fibrosis, AGE accumulation, and stiffened myocytes
2013	Poulsen (46)	*J Am Coll Cardiol*	Increased LAVI was an independent and incremental predictor of CV morbidity and mortality in patients with T2DM with no history of CVD

AGE, advanced glycogen end product; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; HTN, hypertension; LV, left ventricular; MIBG, iodine 123-metaiodobenzylguanidine; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance; DM, diabetes mellitus; HF, heart failure; ACE, angiotensin-converting enzyme; DT, deceleration time; LAVI, left atrial volume index.

diastolic dysfunction (16) (*Table 4*). Early reports showed lower transmitral E/A ratios among patients with DM (35-37), followed by lower mitral annular early diastolic velocity assessment (38), greater E/E' (41,43), and larger left atrial (LA) volume (46). Subclinical LV diastolic dysfunction is associated with poor diabetic control, advancing age, HTN, metformin treatment (39), and cardiac autonomic neuropathy (44). Diastolic dysfunction in diabetes indicates worse prognosis (42,43,46). E/E'_{sept} of >15 in patients with DM is associated with subsequent HF and

Table 5 Diabetes mellitus and functional reserve

Year	First author	Journal	Main findings
2003	Vinereanu (51)	*Clin Sci (Lond)*	T2DM has impaired functional reserve in s' during DSE
2003	Fang (52)	*J Am Coll Cardiol*	During DSE, e' in patients with DM was lower than controls at baseline, low, pre-peak, and peak dose
2006	Palmieri (53)	*J Am Soc Echocardiogr*	LV circumferential contractility and longitudinal systolic function reserves correlated with stroke index reserve during low-dose dobutamine stress
2007	Ha (54)	*Heart*	Exercise stress echocardiography demonstrated that both systolic and diastolic reserves in longitudinal function are reduced in DM, compared with age- and sex-matched controls
2010	Mizuno (55)	*J Card Fail*	Patients with DM have exercise-induced delayed onset of LV relaxation and impaired coronary microcirculatory function without coexistent heart disease
2017	Cortigiani (56)	*J Am Soc Echocardiogr*	Dual-imaging stress echocardiography dipyridamole stress echocardiography [conventional wall motion analysis and Doppler-derived coronary flow velocity reserve (CFVR) of the left anterior descending coronary artery] has independent prognostic value in patients with DM

DM, diabetes mellitus; LV, left ventricular; T2DM, type 2 diabetes mellitus; DSE, dobutamine stress echocardiography.

increased mortality independent of HTN, CAD, or other echocardiographic parameters (43).

Valvular heart diseases: there have been significant increases in the prevalence of DM and valvular heart diseases (47,48). DM accelerates progression of calcific aortic stenosis (49) and worsens LV diastolic function via altering myocardial structure and cardiomyocyte stiffness (45). A small study showed the possibility that DM may accelerate aortic stenosis progression with enhanced inflammation (50). In patients with mitral regurgitation (MR), prevalence of MR is as high as 32%, mainly due to both mitral valve and myocardial abnormalities (48). As a result, patients with even mild MR have a 3.3-fold increased risk of all-cause mortality, whereas those with moderate-to-severe MR have a 5.1-fold increased risk (48).

Myocardial reserve assessed by stress echocardiography

Pharmacological and exercise stress echocardiography have provided intriguing insights into diabetic cardiomyopathy (*Table 5*). Patients with DM have impaired longitudinal functional reserve in both systolic (51) and diastolic functions (34). Furthermore, LV circumferential contractility and longitudinal systolic function reserves are correlated with stroke index reserve during low-dose dobutamine stress (53). Exercise stress echocardiography confirmed diminished systolic and diastolic functional reserve in this population (54,55).

Although the negative predictive value of exercise stress echocardiography for exclusion of underlying myocardial ischemia in type 2 diabetes mellitus (T2DM) is reduced compared with the nondiabetic population (57), recent data provided a favorable finding, where dual-imaging dipyridamole stress echocardiography [conventional wall motion analysis and Doppler-derived coronary flow velocity reserve (CFVR) of the left anterior descending coronary artery] has independent prognostic value in patients with DM (56). This result is in line with previous findings on reduced myocardial flow (38) and flow reserve (41) in this population. Among patients with diabetes, hypoglycemia can be fatal. As acute hypoglycemia decreases myocardial blood flow reserve in both healthy humans and patients with T1DM (58), this could be one of the underlying mechanisms.

Myocardial strain

Myocardial strain analysis brought further intriguing insights (*Table 6*). Others and we reported that patients with DM have impaired systolic and diastolic longitudinal strains irrespective of concomitant HTN in tissue Doppler-derived and speckle-tracking strain methods (41,52,61,62). This deteriorated longitudinal function has been demonstrated using more largely available technique, like tissue Doppler and atrioventricular plane displacement by M-mode (64).

Table 6 Diabetes mellitus and tissue Doppler/myocardial strain

Year	First author	Journal	Main findings
2003	Fang (34)	*J Am Coll Cardiol*	Both patients with DM only and DM + HTN showed significant decreases in peak strain as well as peak strain rate compared with controls
2004	Fonseca (59)	*Am J Cardiol*	MRI tagging strain data: peak systolic strains and diastolic rates of relaxation are lower in patients who have T2DM and normal LVEF
2006	Chung (60)	*J Am Coll Cardiol*	MRI tagging strain data showed that paradoxical increase in myocardial torsion (3.5±0.9 *vs.* 2.7±0.4 °/cm; P<0.01) and torsion rate (0.013±0.003 *vs.* 0.010±0.002 °/cm/s; P=0.01) in patients with T1DM
2006	Moir (41)	*Heart*	Impaired strain and strain rate confirmed in T2DM but not associated with abnormal transmural flow
2009	Ng (61)	*Am J Cardiol*	The LV longitudinal systolic and diastolic functions were impaired, but the circumferential and radial functions were preserved in patients with uncomplicated T2DM
2016	Yang (62)	*Open Heart*	Patients with DM had impaired GLS and diastolic function
2016	Leung (63)	*Circ Cardiovasc Imaging*	Reversibility in diabetic cardiomyopathy with intensive treatment including optimization of treatment for blood glucose, blood pressure, and cholesterol

DM, diabetes mellitus; HTN, hypertension; MRI, magnetic resonance imaging; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; LV, left ventricular; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.

Studies using magnetic resonance imaging (MRI) tagging strain reported similar findings (59,60). Not only peak systolic circumferential and longitudinal strains and principal 3-D shortening strain were smaller in the T2DM group but also peak diastolic rate of relaxation of these strains were lower in patients with DM with normal EF (P<0.001 for each) (59). Furthermore, patients with DM have paradoxical increase in myocardial torsion (60). They had a higher resting HR (77.0±12.4 *vs.* 59.0±5.6 beats/min; P<0.01), higher maximal torsion by 23% (3.5±0.9 *vs.* 2.7±0.4 °/cm; P<0.01), and higher maximal systolic torsion rate by 25% (0.013±0.003 *vs.* 0.010±0.002 °/cm/s; P<0.01). Torsion did not significantly change with chronotropic stimulation by atropine injection (P=0.30).

Recently, Leung *et al.* reported possible reversibility in systolic and diastolic functions among patients with DM treated intensively (63). Subjects with T2DM and poor glycemic control received optimization of treatment for blood glucose, blood pressure, and cholesterol to recommended targets for 12 months. The improvement in HbA1c, from 10.3%±2.4% to 8.3%±2.0%, was associated with significant relative improvement in global longitudinal strain (GLS) of 21% and septal e' of 24%. A progressively greater improvement was observed in GLS as patients achieved a lower final HbA1c. Patients achieving an HbA1c of <7.0% had the highest improvement, whereas patients whose HbA1c worsened experienced a decline in GLS. Patients who improved their HbA1c by ≥1.0% had a significantly higher relative improvement in e' than those who did not (32% *vs.* 8%; P=0.003). These encouraging results lead us to the final section on treatment options.

Treatment options

Glycemic control agents: although good glycemic control is the main goal in the management of DM, a meta-analysis demonstrated that intensive glycemic control does not prevent HF (65). Metformin has been previously contraindicated, but recent data showed beneficial protective effects of the drug (66,67). A meta-analysis demonstrated that metformin was associated with reduced mortality [adjusted risk ratio 0.80 (0.74–0.87); P<0.001] (68). No increased risks were observed in those with reduced left ventricular ejection fraction (LVEF) or chronic kidney disease (CKD). Of note, no increased risk of lactic acidosis was found. Insulin has neutral effect on CVD outcome (69). Peroxisome proliferator-activated receptor (PPAR)-γ agonists increase the cardiovascular (CV) risk (70-74). Among the newer generation agents, including dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 receptor agonist (GLP-1 RA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i), to date, DPP-4 inhibitor has demonstrated CV safety

only without clear CV benefit (75). CV benefit has been shown in some of SGLT2i, such as empagliflozin (76) and canagliflozin (77), and GLP-1 RA, such as liraglutide (78) and semaglutide (79). Results from ongoing clinical trials are also underway: CREDENCE (ClinicalTrials.gov identifier: NCT02065791) and DECLARE-TIMI58 (ClinicalTrials.gov identifier: NCT01730534).

Of note, several cardioprotective agents have demonstrated their effectiveness among patients with DM. The effectiveness of angiotensin-converting enzyme (ACE) inhibitor in a population with DM has been confirmed in a meta-analysis (80). A discrepancy has been found among beta-blockers. Favorable effect of carvedilol has been confirmed in this population (81), but metoprolol has a neutral effect so far (82). Accordingly, ACCF/AHA Guidelines on HF recommend ACE inhibitors and beta-blockers for patients with DM, even without HF symptoms (stage A) (11).

Conclusions

Currently, diabetic cardiomyopathy is recognized as a real disease entity and is not a myth anymore. The underlying pathophysiological mechanism includes insulin resistance and cascades of metabolic disorders and autonomic disturbances, which result in clinical phenotype of LVH, diastolic dysfunction, fibrosis, and limited cardiac functional reserve. Recent reports suggest novel links between DM and valvular heart diseases, where mild degree of valvular disease may be associated with adverse prognosis. Myocardial strain analysis also demonstrated subclinical systolic dysfunction on top of diastolic dysfunction and possible reversibility. Collectively, careful cardiac imaging assessments including advanced techniques are crucial in the clinical management of patients with DM. Novel therapeutic agents, such as SGLT2i and DPP4i, are expected to improve these functions as a part of mechanisms explaining favorable prognostic effect on this population.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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