



# Association between Variability of Metabolic Risk Factors and Cardiometabolic Outcomes

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Despite strenuous efforts to reduce cardiovascular disease (CVD) risk by improving cardiometabolic risk factors, such as glucose and cholesterol levels, and blood pressure, there is still residual risk even in patients reaching treatment targets. Recently, researchers have begun to focus on the variability of metabolic variables to remove residual risks. Several clinical trials and cohort studies have reported a relationship between the variability of metabolic parameters and CVDs. Herein, we review the literature regarding the effect of metabolic factor variability and CVD risk, and describe possible mechanisms and potential treatment perspectives for reducing cardiometabolic risk factor variability.

**Keywords:** Blood pressure; Body weight; Cholesterol; Gamma-glutamyltransferase; Glucose; Heart rate

## INTRODUCTION

Despite efforts to lower metabolic risk factors for atherosclerotic cardiovascular disease (ASCVD) defined by the Framingham Heart Study, such as dyslipidemia, hypertension (HTN), and diabetes mellitus (DM) [1], residual cardiovascular risk has been reported even in those achieving target goals of risk factors [2-4]. Suspicion regarding the adverse effects of these metabolic risk variabilities has been brought up several decades ago [5-7], but researchers have given attention to it recently, and accumulating evidence has been reported to support it. Not only lowering the mean levels of cardiometabolic risk variables but also preventing fluctuation have become new target treatment goals, and the effect of lowering variability as a treatment option has been actively investigated. In this paper, we review the literature on the effects of metabolic factor variability on cardiovascular disease (CVD) and mortality.

## GLUCOSE VARIABILITY

### Mechanism of adverse effect of glucose variability

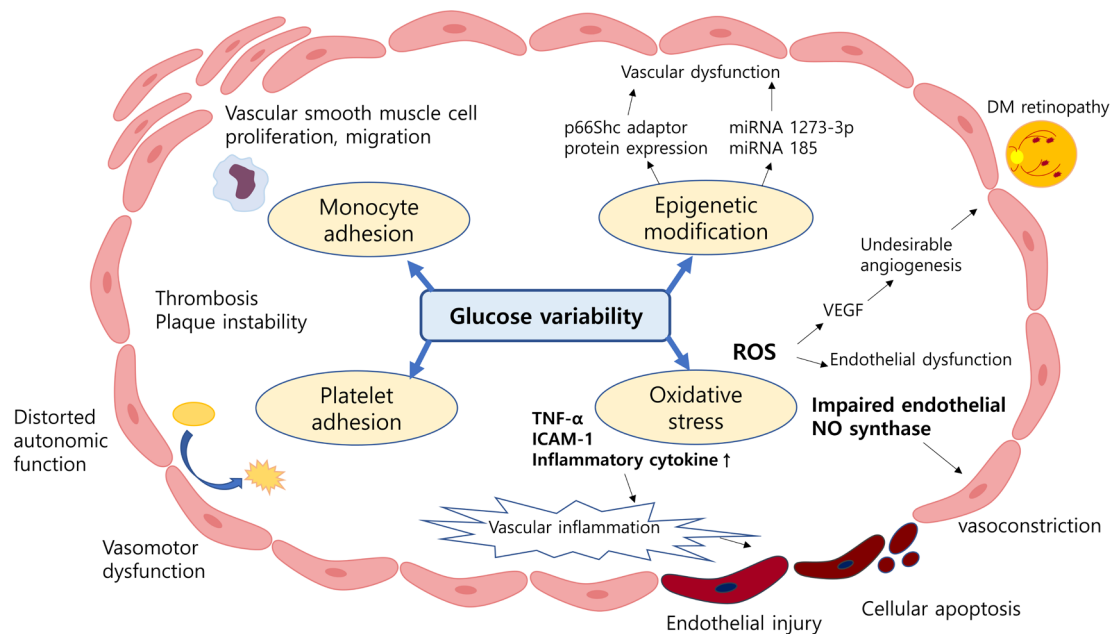
Several *in vivo* and *in vitro* studies have demonstrated the effect of glucose variability (GV) on adverse cardiovascular events (Fig. 1). The primary mechanism is suggested to be the activation of oxidative stress and production of inflammatory cytokines that induce endothelial damage and dysfunction. Research on human coronary artery endothelial cells under fluctuating glucose levels has shown an increase in tumor necrosis factor- $\alpha$ , intercellular adhesion molecule-1, and interleukin-6 [8,9]. Oxidative stress produced by GV leads to apoptosis through the nuclear factor-erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway [10]. Overproduction of reactive oxygen species (ROS) in mitochondria by GV induces vascular endothelial cell growth factor (VEGF) production and triggers undesirable angiogenesis [11]. GV also induces dysfunction of endothelial nitric oxide (NO) synthase, leading to vasoconstriction from decreased NO levels [12].

Costantino et al. [12] reported that epigenetic modification

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**Fig. 1.** Potential pathogenesis of the adverse effects of glucose variability on cardiovascular risk. miRNA, microRNA; DM, diabetes mellitus; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; ICAM-1, intercellular adhesion molecule-1; ROS, reactive oxygen species; VEGF, vascular endothelial cell growth factor.

of p66Shc, the adaptor protein, causes inadequate angiogenesis and vascular damage in type 2 diabetes mellitus (T2DM). Some studies suggested microRNA (miRNA) produced in glucose fluctuating condition influence endothelial dysfunction. Guo et al. [13] indicated miRNA-1273-3p is related to GV-induced autophagy, attenuation of cell proliferation, endothelial dysfunction. La Sala et al. [14] revealed upregulated miRNA-185 in high glucose fluctuation inhibit elevation of glutathione peroxidases-1 which normally suppress ROS damage. Furthermore, glucose fluctuation contributes to activated monocyte and macrophage recruitment, resulting in vascular smooth muscle cell proliferation and migration [15]. In addition, high GV may cause platelet activation, aggregation, and autonomic dysfunction in endothelial cells [16].

### Glucose variability and cardiovascular disease risk

Since the time Monnier et al. [7] demonstrated that not only sustained hyperglycemia but also glucose swing cause oxidative stress and accompanying microvascular and macrovascular complications, numerous studies have published reinforcing evidence (Table 1) [3,17-31] and attempted to find an appropriate index reflecting inter- and intra-day GV. In addition to the traditionally used standard deviation (SD) and coefficient of variation (CV) showing dispersion of data, various

metrics have been reported and applied [32]. The mean of daily difference calculated using the glucose value of 2 consecutive days simultaneously reflects between-day glycemic variation, and Continuous Overlapping Net Glycemic Action (CONGA), measured by the SD of glucose value for the defined period of time, reveals within-day glycemic fluctuation. In addition, indices indicating risk and patient prognosis (lability index) and assessing long-term diabetic complications (time in range) have been used in several studies [16,33].

Early studies were conducted on patients who underwent percutaneous coronary intervention (PCI) or coronary artery bypass graft and measured the periprocedural glucose level of participants [23-25,34-36]. Fluctuating glucose levels are associated with major adverse cardiovascular events (MACEs), atrial fibrillation, and post-procedural complications. However, most of the studies were conducted in an in-hospital setting and used short-term glycemic variability. Subsequent studies performed secondary analysis of randomized clinical trials including T2DM patients, and reported an association between long-term GV and CVD risk [3,26-31]. Hirakawa et al. [3] reported that increased glycosylated hemoglobin (HbA1c) variability was associated with vascular events (hazard ratio, 1.64; 95% confidence interval [CI], 1.05 to 2.55); Zhou et al. [18] reported that high fasting blood glucose (FBG) variability in-

**Table 1.** Studies of the relationship between glycemic variability and cardiovascular outcome

Study	Study design	Population characteristics	GV index	Follow-up, mo	Outcomes	Results
Xia et al. [23]	Prospective observational	864 ACS patients undergoing PCI or CABG China	SD (during peri-intervention hospitalization)	1	MACCE	High GV (SD $\geq 2$ mmol/L) increased incidence of MACCE (OR, 1.97; $P=0.02$ ) and incidence of AF during hospitalization (14.5% vs. 8.9%, $P=0.02$ )
Zhang et al. [24]	Prospective observational	237 ACS patient undergoing PCI China	MAGE (72 hours after PCI)	1	MACE	High GV is related to MACE in DM patient (OR, 2.86; $P=0.025$ ) but not in non-DM patients
Subramaniam et al. [17]	Prospective observational	1,461 Patients undergoing CABG USA	CV (24 hours after surgery)	1	MAE	Higher GV (per quartile) is related to risk for MAE (OR, 1.27; $P=0.02$ )
Gerbaud et al. [25]	Prospective observational	327 ACS patient with DM France	SD	17	MACE	High GV (SD $> 2.70$ mmol/L) in patients with diabetes and ACS is predictive factor of MACE (OR, 2.21; $P<0.001$ )
Hirakawa et al. [3]	Secondary analysis of prospective, randomized (ADVANCE trial)	4,399 T2DM UK	CV, SD, VIM, RSD, ARV	24	Vascular event, all-cause mortality	VVV of HbA1c is related to high vascular event (HR, 1.64; $P=0.01$ ) and mortality (HR, 3.31; $P<0.001$ ) VVV of fasting glucose is associated with increased vascular event (HR, 2.70; $P<0.001$ )
Zinman et al. [26]	Secondary analysis of prospective, randomized (DEVOTE2 trial)	7,586 T2DM	CV	24	MACE, hypoglycemia, all-cause mortality	Day-to-day fasting GV is associated with hypoglycemia (HR, 3.37; $P<0.001$ ) and all-cause mortality (HR, 1.33; $P=0.04$ ) but the association with MACE was not maintained after adjustment for baseline characteristics ( $P=0.08$ )
Zhou et al. [18]	Secondary analysis of prospective randomized (VADT trial)	1,791 T2DM USA	CV, ARV	84	MACCE	Fasting GV is associated with CVD complication (OR, 1.16; $P=0.003$ ) and adverse effect is greatest in patients given intensive glucose control
Sato et al. [19]	Secondary analysis of prospective randomized (EMPATHY trial)	4,532 T2DM Japan	CV	38	MACE	VVV of HbA1c is risk of CVD event (OR, 1.73; $P=0.003$ ) independent of mean-HbA1c Adverse effect of GV is important glycemic indicator especially in those with a mean HbA1c $< 7\%$
Segar et al. [27]	Secondary analysis of prospective, randomized (ACCORD trial)	8,576 T2DM	ARV, CV, SD	77	Incident heart failure (HF)	Higher long-term HbA1c variability is associated with higher risk of HF (HR, 1.34; 95% CI, 1.17–1.54) independent of baseline risk factor
Wan et al. [28]	Population-based prospective cohort study from electronic health records	147,811 T2DM Hong Kong	SD	89	CVD, all-cause mortality	Greater variability of HbA1c is related to CVD (HR, 1.15) and all-cause mortality (HR, 1.32) in patient with DM across all age groups
Critchley et al. [29]	Retrospective matched cohort study	58,832 T2DM UK	CV	49	All-cause mortality, first emergency hospitalization	HbA1c variability is associated with overall mortality and emergency hospitalization and not explained by mean HbA1c and hypoglycemia event
Echouffo-Tcheugui et al. [30]	Secondary analysis of prospective randomized (ALLHAT trial)	4,982 Population with or without DM	SD, CV, VIM, ARV	60	Incident CVD, all-cause mortality	VVV of fasting glucose is associated with increased mortality (HR, 2.22; 95% CI, 1.22–4.04), but not with CVD when adjusting mean blood glucose

(Continued to the next page)

Table 1. Continued

Study	Study design	Population characteristics	GV index	Follow-up, mo	Outcomes	Results
Wang et al. [31]	Prospective cohort	53,607 Population with or without DM, free of previous MI or stroke China	CV	59	CVD, all-cause mortality	Elevated VVV of fasting glucose predicted the risk of CVD (HR, 1.26) and all-cause mortality (HR, 1.46) independent of mean FPG
Kim et al. [22]	Population-based retrospective cohort study from medical records	6,748,773 Population without DM, hypertension, dyslipidemia Korea	CV, SD, VIM	66	MI, stroke, all-cause mortality	High fasting GV is predictor of mortality (HR, 1.20; 95% CI, 1.18–1.23), MI (HR, 1.16; 95% CI, 1.12–1.21), and stroke (HR, 1.13; 95% CI, 1.09–1.17)
Ghouse et al. [21]	Population-based retrospective cohort study	6,756 population without DM, CVD Denmark	SD	76	MACE, all-cause mortality	High HbA1c variability is relate to MACE (HR, 1.08; 95% CI, 1.03–1.15) and all-cause mortality (HR, 1.13; 95% CI, 1.07–1.20) independent of mean HbA1c and CV risk factors
Yu et al. [20]	Population-based retrospective cohort study from medical records	3,211,319 Population without DM, CVD Korea	SD	99	MI, stroke, all-cause mortality	elevated fasting GV is associated with MI (HR, 1.08; 95% CI, 1.04–1.11), stroke (HR, 1.09; 95% CI, 1.06–1.13), and mortality (HR, 1.12; 95% CI, 1.10–1.15)

GV, glucose variability; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; SD, standard deviation; MACCE, major adverse cardiovascular and cerebrovascular event; OR, odds ratio; AF, atrial fibrillation; MAGE, mean amplitude of glycemic excursion; MACE, major adverse cardiovascular event; DM, diabetes mellitus; CV, coefficient of variation; MAE, major adverse event (in-hospital death, MI, reoperation, infection, stroke, renal failure, cardiac tamponade, pneumonia); ADVANCE, Action in Diabetes and Vascular Disease; T2DM, type 2 diabetes mellitus; VIM, variation independent of mean; RSD, residual standard deviation; ARV, average real variability; VVV, visit-to-visit variability; HbA1c, glycosylated hemoglobin; HR, hazard ratio; DEVOTE, Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; VADT, Veterans Affairs Diabetes Trial; CVD, cardiovascular disease; EMPATHY, EMPagliflozin and daPAgliflozin in patients hospitalized for acute decompensated Heart failure; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ALLTHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; MI, myocardial infarct.

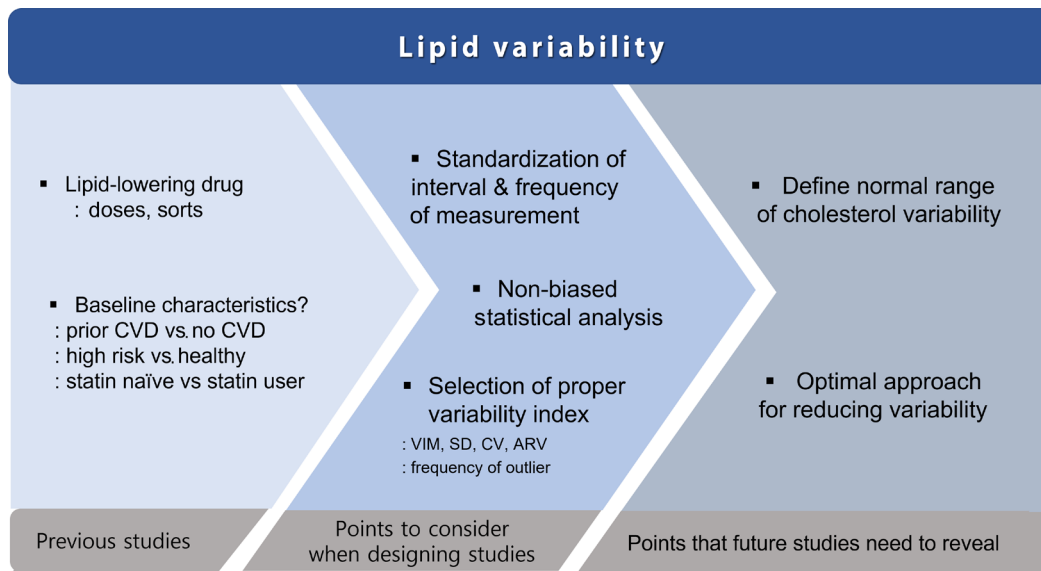
creased CVD risk; and Wan et al. [37] demonstrated this relationship is applied to all age groups regardless of DM duration. The EMPagliflozin and daPAgliflozin in patients hospitalized for acute decompensated Heart failure (EMPATHY) trial recently conducted in Japanese T2DM patients identified that adverse effects of intermittent hyperglycemia were enhanced in patients with HbA1c levels below 7% [19]. These findings indicate the harmfulness of glycemic variation not only in metabolically high-risk patients but also in relatively well-controlled T2DM patients or people whose metabolic risk is low.

Accumulating evidence suggests that glucose fluctuation increases CVD risk in T2DM or patients who undergo coronary artery procedures; however, the possibility of a reverse causality effect must be addressed. Two studies [20,38] demonstrated the relationship between intermittent hyperglycemia and high CVD using data from people without DM and previous CVD from the Korean National Health Insurance. Analysis of data from a Denmark private clinic cohort with non-diabetics also showed that HbA1c variability is a predictor of MACE [21]. In

addition, Kim et al. [39] illustrated that increased FBG variability is predictive of gestational DM.

### Glucose variability depending on medication

In selecting anti-diabetic agents, their effects on GV as well as improving hyperglycemia should be considered. Dipeptidyl peptidase-4 (DPP4) enzyme inhibitors, glucagon-like peptide 1 (GLP1) receptor agonists, and sodium-glucose co-transporter 2 (SGLT2) inhibitors might be desirable oral hypoglycemic agents (OHAs) that reduce GV. Kim et al. [40] reported that sitagliptin reduced GV compared to glimepiride in T2DM patients who used metformin. Bae et al. [41] demonstrated a significant reduction in MACE and SD of glucose in patients treated with teneligliptin compared with placebo. Although several clinical trials have also reported that DPP4 inhibitors blunted glucose fluctuation [42–44], other studies reported that DPP4 inhibitors were unsuccessful in reducing ASCVD risk [45,46]. The Variability of Glucose in Patients with Type 2 Diabetes Treated with Four Different Insulin Combination Regi-



**Fig. 2.** Evidence that previous studies have demonstrated on lipid variability-mediated cardiovascular complications, limitations of previous studies, and suggested directions for future studies. CVD, cardiovascular disease; VIM, variation independent of mean; SD, standard deviation; CV, coefficient of variation; ARV, average real variability.

mens (VARIATION) study illustrated that GLP1 receptor agonists and basal insulin decreased GV and hypoglycemic events, compared to basal and bolus insulin or basal insulin plus OHAs [47]. The FLuctuATion reduction with inSULin and GLP-1 Added together (FLAT SUGAR) trial also demonstrated that adding GLP1 receptor agonist to basal insulin and metformin is better than metformin plus basal/bolus regimen for GV improvement [48]. The superiority of DPP4 inhibitor and GLP1 receptor agonist on GV might be attributable to their intrinsic mechanism of action. While GV aggravation is induced by decline of endogenous insulin and insufficient glucagon suppression, DPP4 inhibitor and GLP1 receptor agonist, which keep incretin level, inhibit postprandial glucagon secretion as well as improve pancreatic-βcell function [49-51]. As for SGLT2 inhibitors, despite limited evidence of the superiority of GV to other OHA, Nomoto et al. [52] showed similar GV between dapagliflozin plus glargine and DPP4 inhibitor plus glargine. In addition, adding dapagliflozin to long-acting insulin and other OHA ameliorated GV in a study including 36 subjects from a Chinese hospital [53]. However, a recently published placebo-controlled, randomized study with 84 Korean patients reported that adding dapagliflozin to basal insulin plus OHA did not show superiority to placebo in terms of GV [54]. Future large-scale studies are needed to demonstrate the effects of SGLT2 inhibitors on GV.

## CHOLESTEROL VARIABILITY

### Mechanism of adverse effects of cholesterol variability

Several theories explain the detrimental effects of lipid variability on CV risk. One hypothesis is that cholesterol variability causes transient hypercholesterolemia and fluctuation of cholesterol plaque composite and structure, inducing endothelial dysfunction and cholesterol plaque instability [55]. Clark et al. [56] demonstrated that high variability of low-density lipoprotein (LDL), non-high-density lipoprotein (HDL) cholesterol, and total cholesterol/HDL (measured by SD) was correlated with percent atheroma volume progression by analyzing nine clinical studies that used intravascular ultrasonography to assess coronary atheroma burden. Second, the existence of cholesterol variability implies general frailty and epiphenomenon of systemic conditions [57]. Another theory is that the adverse effects of lipid variability are linked to statin non-adherence [58,59]. Mann et al. [60] reported that visit-to-visit lipid variability was associated with statin non-adherence after adjusting for mean LDL, age, and sex using pharmacy data. Statin discontinuation induces a rebound phenomenon, and the favorable effect of statin is acutely lost when it is discontinued [58]. Patients who discontinued statin therapy after acute coronary syndrome showed higher mortality than those who did not.

### Studies on cholesterol variability and cardiovascular risk

Since the importance of lipid variability in coronary disease was reported in an observational study on air force officers [5], it took >30 years to shed light on lipid variability. The Framingham study showed that high LDL variability in a population without cardiovascular risk was associated with future CVD risk [61]. In addition, the Treating New Target (TNT) study reported that LDL variability in people with known CVD risk increases coronary and cardiovascular events by 16% and 11%, respectively, regardless of absolute LDL levels [62].

Factors that affect lipid variability have been investigated. The TNT study illustrated that 80 mg of atorvastatin lowered LDL variability than 10 mg of atorvastatin. In contrast, doses and types of statins showed no effect on lipid variability in several other studies [63,64]. Boey et al. [63] reported no significant differences in LDL variability among patients treated with simvastatin (10, 20, and 40 mg). The VOYAGER (an individual patient data meta-analysis Of statin therapy In At risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin) meta-analysis [64] consists of 37 clinical studies using atorvastatin, simvastatin, and rosuvastatin and reported low relevance between lipid variability and types of statins. Discordant results were shown regarding the influence of previous statin use on the harmful effects of lipid variability. Most studies focused on patients with coronary artery disease (CAD) or underwent PCI, and Kim et al. [22] and Zhu et al. [65] excluded people with previous CV events to leave out possible reverse causality. The outcomes were in line with those of previous studies showing the association between lipid variability and CV risk. Furthermore, Kim et al. [58] illustrated that the adverse effect of cholesterol variability was magnified in patients without conventional risk factors and in patients who did not take lipid-lowering medication. However, a Korean nationwide population-based cohort study conducted with statin-naïve healthy young people [66] revealed no significant association between lipid variability and CV risk. Moreover, total cholesterol variability augments the risk of atrial fibrillation [67] and dementia [68] which increases morbidity and mortality in the elderly population.

### Limitations and expected direction of future studies

Future well-designed studies addressing improvements on several points are required (Fig. 2). The intervals and numbers of blood lipid measurements must be standardized. Smith et al. [69] reported that lipid variability tends to increase with longer daily, weekly, and monthly measurement interval. The appro-

priate interval and frequency of cholesterol measurement for optimal variability estimation that reflects CVD risk should be investigated [55]. Controversies on proper statistical methods and variability indices must also be addressed. A large number of previous studies compared the highest quartile (Q4) to the lowest quartile (Q1) or high quartile (Q4) to low quartiles (Q1–3); such approaches might exaggerate the association [70]. In addition, Cox regression is adequate to compare between-group variability but not within-individual variability or correlation across repeated measurements. Multilevel or mixed linear regression models and joint modelling are suggested as proper tools for this type of analysis [70]. Blood lipid level variability was calculated using the following formulas: CV, average successive variability [ $ASV = \sum(X_i - X_{i+1})/n$ ], SD, or variation independent of mean [ $VIM = 100\% \times (SD/\text{mean}\beta)$ , where  $\beta$  is the regression coefficient]. Although VIM is less relevant to the mean than SD and CV, controversy over association with mean value and adequacy for variability estimation still exists [70]. The frequency of deviation outside the designated range or the greatest absolute change is suggested as an alternative index [55]. Future studies are also required to define the normal range of cholesterol variability so that clinicians can pursue an optimal approach to reduce lipid variability. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor which has a long half-life, is expected to maintain a stable cholesterol level. Lipid-lowering agents and treatment strategies that lower not only mean cholesterol levels but also variability are required [37].

## BLOOD PRESSURE VARIABILITY

### Mechanism of adverse effects of blood pressure variability

Blood pressure (BP) fluctuation is necessary to maintain homeostasis and to provide adequate organ perfusion, but consistent blood pressure variability (BPV) reflects dysfunction of regulatory function, leading to pathological problems. Baroreflex dysfunction [71], prolonged sympathetic activation, and increased arterial stiffness cause short-term BP variations [72,73]. Seasonal changes and behavioral factors, such as sleep disturbance or work-related stress, can cause long-term BPV [74,75]. Periodic high BP induced by these factors induces shear stress on the vessel wall and cardiovascular system, which consequently increases intima-media thickness, vascular dysfunction, and atherosclerosis progression [76]. Furthermore, patients' poor adherence to drugs and inappropriate ti-

tration of BP medication lead to visit-to-visit BPV [75]. In addition, Kim et al. [22] suggested that general frailty caused by systemic conditions might play a role in intermittent high BP.

### Studies on blood pressure variability and CVD risk

Parati et al. [75] suggested the classification of BPV according to time frame as very-short-term (beat-to-beat), short-term (day-to-night, hour-to-hour), mid-term (over various days), and long-term (over months, over seasons, over clinic visits). Short-term BP fluctuations from ambulatory BP monitoring is considered to cause target organ damage, particularly left ventricular hypertrophy [77], and predict cardiovascular events and death [78]. Studies on home-monitored BP fluctuation (mid-term) were few, but they proved that BPV was associated with cardiovascular events and mortality [79-82]. Research over 19 years discovered the predictive value of home BPV on cardiovascular events over clinic-based BPV [83]. Several clinical trials and cohort studies identified that visit-to-visit BP fluctuation was predictive of CADs, myocardial infarction (MI), and related mortality, and this association was confirmed in several meta-analyses [22,75,84-87]. Parati et al. [75] indicated that long-term BPV is more strongly associated with CVD than short-term BPV, whereas Meng et al. [84] illustrated that within-visit systolic BPV was inappropriate for CVD prediction. Kim et al. [22] and de Havenon et al. [85] reported that adverse effects of BPV on cardiovascular risk and all-cause mortality were maintained in a general healthy population. However, the predictive value of BPV on CV events was not significant in patients with end-stage renal disease [86].

### Blood pressure variability depending on medications

Several clinical trials have revealed that calcium-channel blockers (CCBs) and non-loop diuretics cause lower BPV than beta-blockers (BBs), angiotensin receptor blockers (ARBs), and angiotensin-converting-enzyme inhibitors (ACEi) [88-90]. A meta-analysis including 398 trials [91] reported that the ratio of variance (VR) increased in the order of CCB, thiazide, ACEi, ARB, and BB (VR=0.81, 0.87, 1.08, 1.16, and 1.17, respectively). The combination of antihypertensive medications has been researched in subsequent studies. Sato et al. [92] reported that adding amlodipine was better than adding thiazide in patients with inadequate BP control with ARB monotherapy in terms of low BP fluctuation. Rakugi et al. [93] demonstrated that the combination of ARB and CCB decreased BPV compared to a combination of ARB and diuretics. Nagai et al. [94]

suggested that CCB plus diuretics are more favorable than ARB plus CCB, which is superior to ARB and diuretics in terms of lowering BPV. Although the mechanism of different effect on BPV among medications is uncertain, decrease of arterial stiffness via vasodilation by CCB and non-loop diuretics is suggested as a possible explanation [88,91,95].

### WEIGHT VARIABILITY

A large proportion of patients succeed in weight reduction but end up regaining lost weight, a phenomenon known as weight cycling. However, Hamm et al. [6] reported that individuals who gain and lose weight have a higher risk of coronary disease mortality compared to weight gain only or no weight change groups. The Framingham cohort study also verified that body weight variability (BWV) increases all-cause mortality and coronary heart disease using biannual body weight data for a mean of 32 years [96]. The association between BWV and all-cause mortality was shown in subsequent cohort studies and meta-analyses [97,98], although few studies reported contradictory results [99]. The adverse effects of weight cycling was independent of traditional CVD risk factors [100] and appeared to be enhanced in the obese population [100,101]. Kim et al. [102] demonstrated that not only BWV, but also waist circumference variability increased all-cause mortality and stroke risk based on a nationwide cohort study in Korea. Two main mechanisms are suggested to explain the harmful effects of weight variability: the repeated overshoot theory and increased visceral energy partitioning theory. The repeated overshoot theory indicates that weight cycling causes fluctuations in renal and cardiovascular risk factors, such as glomerular pressure, glucose, lipids, heart rate, and BP, which place extra burden on the kidneys and heart and lead to vascular injury [103]. Because the fluctuations are not always symmetrical; that is, the period of weight gain overrides that of weight loss, the net effect on the individual is unfavorable. Weight cycling also causes weight loss related to body adaptation in resting energy expenditure, thus reducing basal metabolism even after weight regain [104]. Byrne et al. [105] discovered that the recovery rate of skeletal muscle mass was faster in extremities than in the body trunk, which gives rise to central fat deposition when individuals regain weight. In addition, the relationship between fasting hyperinsulinemia and weight cycling in Japanese subjects might explain this phenomenon [106].

## HEART RATE VARIABILITY

In contrast to other cardiometabolic risk factors, low heart rate variability (HRV) has been proven by Kleiger et al. [107] to increase mortality. They examined patients who survived acute myocardial infarction (AMI) and measured HRV, which showed that the relative risk of mortality was 5.3 in those with HRV <50 ms compared to those with HRV >100 ms. This association is supported by other cohort studies involving patients with recent AMI [108,109] with the predictive value of low HRV being preserved regardless of left ventricular ejection fraction or ventricular arrhythmia [109]. The adverse effect of low HRV is attributable to the reduced ability to antagonize sympathetic activation through the vagal mechanism in patients with AMI [109]. T2DM patients without previous CAD who have low heart rate fluctuation also show increased mortality and sudden cardiac death [110,111]. Cardiac autonomic neuropathy, which is important for adaptation to a given environmental change, might explain these results [110]. Subsequent studies consisting of the general population with or without previous cardiovascular heart disease also illustrated that low heart rate fluctuation increases all-cause mortality [112,113] and CV events [114]. Based on carotid intima-media thickness data, Pereira et al. [115] demonstrated that low HRV is related to subclinical atherosclerosis, and Tsuji et al. [114] suggested that low HRV implies enhanced subclinical cardiac disease risk in the general population. BBs, ACEi, and statins have been shown to increase HRV [116] and the additional use of ivabradine on BB increases HRV in patients with systolic heart failure or stable CAD [117,118].

## GAMMA-GLUTAMYL TRANSFERASE VARIABILITY

The association between high gamma-glutamyl transferase (GGT) levels and cardiovascular events and mortality has been proven in a British prospective cohort study including 7,613 patients [119]. Several cohort studies in different populations and meta-analyses have shown supporting evidence [120-122]. Recently, Chung et al. [123] demonstrated that not only mean GGT levels but also GGT variability predicted MI, stroke, and cardiovascular mortality in the general population from a Korean cohort. Lee et al. [124] illustrated the predictive value of GGT fluctuation on all-cause mortality in T2DM patients without previous CVD or liver disease, and this effect is mag-

nified in a young, male population consuming high alcohol and cigarettes. Subsequent studies showed that variability in GGT increased the hazard ratio of hospitalization for heart failure [125], risk of dementia, and development of end-stage renal disease [126] in the Korean population. The possible mechanism is that GGT has catabolic activity on the antioxidant glutathione, causing a proportional increase in GGT levels with oxidative stress and inflammation [127]. GGT fluctuations reflect the oscillation of oxidative stress and possibly alters the stability of atherosclerotic plaques, manifesting as LDL variability [124,128].

## CONCLUSIONS

In this review, we examined the current literature on the variability of metabolic risk factors for cardiovascular events and mortality. Except for a few discrepancies over subgroups, the variability of glucose, BP, cholesterol, and GGT increased cardiovascular morbidity and mortality, while reduced HRV yielded unfavorable outcomes. The mechanisms underlying the adverse effects of variability are being investigated, but inflammation and oxidative stress caused by metabolic factor variation cause organ damage. Based on the current findings, clinicians should recognize the variability of patients' metabolic factors and prescribe appropriate drugs to minimize this effect. The trend of values should be evaluated at proper intervals and using suitable methods, as well as measuring a single value at the patient's visit. To offer ideal treatment to patients, selecting a treatment regimen that could reduce both the absolute values and variability of metabolic risk factors is important. Therefore, further research should be performed to find better medication regimens that decrease glucose, BP, and cholesterol variability and to find a desirable lifestyle modification method to address fluctuations in weight. In addition, checking whether patient variability arises from inappropriate regimens or inadequate compliance is important. Patients should be educated on the hazardous effects of variability on health outcomes to encourage drug adherence.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.



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