

Skin Autofluorescence and Clinical Outcomes in Patients with Coronary Artery Disease

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Aim: This study aimed to investigate whether skin autofluorescence (SAF) is associated with clinical outcomes in patients with coronary artery disease. Advanced glycation end products (AGE) play a crucial role in atherosclerosis. Accumulation of AGE can be measured non-invasively by SAF.

Methods: We performed a single-center prospective study of 896 patients with coronary artery disease treated with percutaneous coronary intervention (PCI) between January 2014 and December 2015. SAF was measured before the PCI procedure. The primary endpoint was patient-oriented composite endpoints (POCE) defined as a composite of all-cause death, any myocardial infarction, any stroke, and any revascularization.

Results: Patients were significantly older and suffered higher rates of chronic kidney disease (CKD) in the high SAF group. A higher SAF was associated with an increased risk for POCE (HR 1.43; 95% CI 1.19–1.71, $p < 0.001$) that was mainly driven by any coronary revascularization (HR 1.33; 95% CI 1.08–1.65, $p = 0.01$) including target lesion revascularization (HR 1.41; 95% CI 1.02–1.94, $p = 0.04$). The higher SAF group also experienced worse outcomes in stroke (HR 2.08; 95% CI 1.38–3.15, $p = 0.001$). Multivariate analyses indicated that SAF was an independent predictor of POCE (HR 1.36; 95% CI 1.13–1.63, $p = 0.001$).

Conclusions: SAF as a measure of AGE deposition is independently associated with cardiovascular events amongst patients with coronary artery disease treated with PCI. SAF also predicts the incidence of restenosis and stroke.

Key words: Percutaneous coronary intervention, Advanced glycation end products, Skin autofluorescence

ABBREVIATIONS AND ACRONYMS: CVD=cardiovascular disease, AGE=advanced glycation end products, CKD=chronic kidney disease, SAF=skin autofluorescence, PCI=percutaneous coronary intervention, DES=drug-eluting stent, CABG=coronary artery bypass grafting, POCE=patient-oriented composite endpoints, MI=myocardial infarction, eGFR=estimated glomerular filtration rate, ST=stent thrombosis, TLR=target lesion revascularization, SD=standard deviation, HR=hazard ratio, CI=confidence interval

Introduction

Although the incidence of cardiovascular disease (CVD) has decreased over the last few decades, it remains a leading cause of death¹⁾. Therefore, the identification of high-risk patients is a major priority in the field of public health.

Long-term hyperglycemia promotes cardiovascular mortality among patients with type 1 diabetes mellitus²⁾, and the DCCT/EDIC study demonstrated the importance of the mean HbA1c level on CVD during long-term (mean 27 years) follow-up³⁾. Advanced glycation end products (AGE) are modifications of proteins or lipids that become

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Received: April 7, 2023 Accepted for publication: August 2, 2023

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glycated and oxidized non-enzymatically in a complex biochemical process⁴). Cross-linking of tissue proteins including collagen by AGE modification not only cause an increase of vascular and myocardial stiffness^{5,6}, but also promotes inflammation, thrombosis, and leukocyte recruitment, contributing to the development and progression of CVD⁷). Deposition and accumulation of AGE are elevated in patients with increased cardiovascular risk factors such as diabetes mellitus, chronic kidney disease (CKD), or CVD^{8,9}). Levels of accumulated AGE can be evaluated non-invasively by skin autofluorescence (SAF), which is defined as the average fluorescence over the entire emission spectrum (420-600nm) as a ratio of the average fluorescence over the 300-420nm range. This method has been validated in non-pigmented skin⁹). Previous studies have shown that SAF is higher in patients with type 2 diabetes mellitus compared to healthy individuals^{10,11}), and is associated with future cardiovascular events in these patients¹²⁻¹⁴). Several studies have demonstrated that SAF is associated with an increased risk of cardiovascular events among patients with type 1 or 2 diabetes mellitus^{13,14}). When SAF measurements have been evaluated in the general population, SAF significantly predicted the risk of new-onset type 2 diabetes mellitus, CVD and all-cause mortality¹⁵). These studies support the clinical utility of SAF as a marker of CVD and mortality in the general population irrespective of the presence of diabetes mellitus. Therefore, it is proposed that SAF may be a novel biomarker that reflects long-term hyperglycemia and may also help identify high-risk patients for CVD regardless of the presence of diabetes mellitus.

Percutaneous coronary intervention (PCI) using drug-eluting stents (DES) has dramatically reduced the rate of in-stent restenosis¹⁶), and clinical outcomes have further improved with the advent of newer-generation DES in conjunction with optimal medical therapy. However, around 5% of CVD patients treated with PCI using DES experience target-lesion failure (cardiac death, target vessel myocardial infarction or ischemic-driven target lesion revascularization) at 1-year follow-up. Furthermore, these patients suffer from CVD events at around 1.8% per year, every year (even after the first year) for the duration of their lives¹⁷).

Aim

Because of the promise of SAF as a measure of tissue AGE deposition, the aim of this study was to establish whether SAF is associated with clinical outcomes in patients with coronary artery disease

treated using the current-generation DES irrespective of the presence of diabetes mellitus.

Methods

Study Population

A single-center study prospectively including all consecutive patients who underwent PCI using DES between January 2014 and December 2015 at New Tokyo Hospital, Chiba, Japan. We excluded patients with prior PCI or coronary artery bypass grafting (CABG), acute coronary syndrome, CKD on hemodialysis, or a life expectancy of less than 1 year. Patients with skin phototype V and VI (those with ultraviolet reflectance <10%) were not included due to the inability to obtain dependable, reproducible measurements¹⁸). Dual-antiplatelet therapy was planned for a minimum of 12 months after PCI. Ticagrelor, or glycoprotein IIb/IIIa inhibitors were not available during the inclusion period in Japan. The study protocol was approved by the institutional review board, and informed consent was obtained from all patients.

SAF Measurements

SAF was measured with the AGE Reader (DiagnOptics Technologies BV, Groningen, The Netherlands). The AGE Reader illuminates a skin surface of 4cm² guarded against surrounding light with an excitation light source with a peak excitation of 370nm (ultraviolet A). Emission light (fluorescence in the wavelength of 420-600 nm) and reflected excitation light (with a wavelength of 300-420 nm) from the skin are measured with a spectrometer. SAF is calculated as the ratio between the emission light and reflected excitation light, multiplied by 100 and expressed in arbitrary units (AU). Consecutive measurements were carried out three times before the PCI procedure, taking less than a minute. The mean SAF was calculated from these measurements and used in the analysis.

Study Definitions and Endpoints

The patient-oriented composite endpoints (POCE) were defined as a composite of all-cause death, any myocardial infarction (MI), any stroke, and any revascularization. Death was considered cardiac in origin unless obvious non-cardiac causes were identified. The endpoints were classified according to the Academic Research Consortium (ARC)-2 definitions¹⁹). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula²⁰). The primary endpoint was the rate of

Table 1. Baseline clinical and lesion characteristics

	Low SAF (≤ 2.6) <i>n</i> = 474	High SAF (> 2.6) <i>n</i> = 422	<i>p</i> value
SAF	2.2 $\pm$ 0.3	3.1 $\pm$ 0.4	<0.001
Male	328 (69.2)	310 (73.5)	0.16
Age, years	70.6 $\pm$ 9.8	73.7 $\pm$ 8.6	<0.01
Hypertension	359 (75.7)	318 (75.4)	0.89
Dyslipidemia	284 (59.9)	238 (56.4)	0.29
LDL cholesterol, mg/dl	114 $\pm$ 33	111 $\pm$ 33	0.11
Smoking			
Current smoker	79 (16.7)	79 (18.7)	0.42
Diabetes	175 (36.9)	179 (42.4)	0.09
HbA1c, %	6.3 $\pm$ 1.0	6.5 $\pm$ 1.1	0.03
Chronic kidney disease			
eGFR, ml/min/1.73m ²	64.9 $\pm$ 16.7	59.4 $\pm$ 17.6	<0.001
eGFR < 60 ml/min/1.73m ²	174 (36.7)	216 (51.2)	<0.001
COPD	6 (1.5)	8 (2.1)	0.49
LVEF, %	60.0 $\pm$ 10.2	58.7 $\pm$ 10.9	0.08
LVEF < 30%	20 (4.2)	15 (3.6)	0.6
Target vessel			
Left main disease	43 (9.1)	29 (6.9)	0.23
1VD	306 (64.6)	254 (60.2)	
2VD	116 (24.5)	118 (28.0)	0.18
3VD	52 (11.0)	49 (11.6)	

Data are presented as absolute numbers and percentages or mean $\pm$ standard deviation. SAF = skin autofluorescence; eGFR = estimated glomerular filtration rate; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; VD = vessel diseased.

POCE. The secondary endpoints were each component of POCE, definite or probable stent thrombosis (ST), and target lesion revascularization (TLR).

Statistical Analysis

All data are shown as mean $\pm$ standard deviation (SD) for continuous variables, or as number (%). The patients were divided into two groups by the median SAF value (Low SAF group; SAF ≤ 2.6 , and High SAF group; SAF > 2.6). Continuous variables between groups were compared using an independent Student *t*-test. Categorical data were compared using the chi-square or Fisher's exact test as appropriate. The cumulative events were generated with Kaplan–Meier method, and compared using log-rank test between the groups. The clinical outcomes in the overall cohort were reported as the hazard ratios (HR) and 95% confidence interval (CI) those calculated with Cox regression analysis using continuous SAF variables. The rates of TLR were calculated on the patient basis.

Multivariable Cox regression analysis was performed to identify the independent risk factors of POCE during the follow-up period. The Cox regression analyses were performed to test the

association between each covariate and POCE in order to select variables for multivariate analysis. All variables with values of $p < 0.10$ at univariable analysis and those judged to be clinically important were retained into the final stepwise regression model. Analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). All reported *p* values were 2-sided, and values of $p < 0.05$ regarded as statistically significant.

Results

Baseline Characteristics

During the study period, 2738 patients were treated with PCI in our center. A total of 896 patients were included in the final analysis after excluding individuals who had a history of prior PCI or CABG ($n=1203$), acute coronary syndrome ($n=335$), and in those in whom a SAF measurement was unable to be obtained ($n=247$). All patients were of Asian ethnicity. The median follow-up period was 6.3 (interquartile range 2.9–7.0) years. Patient and lesion characteristics are shown in [Table 1](#). The mean SAF value was 2.6 ± 0.6 in the overall cohort. Patients were significantly older and has a significantly higher prevalence of

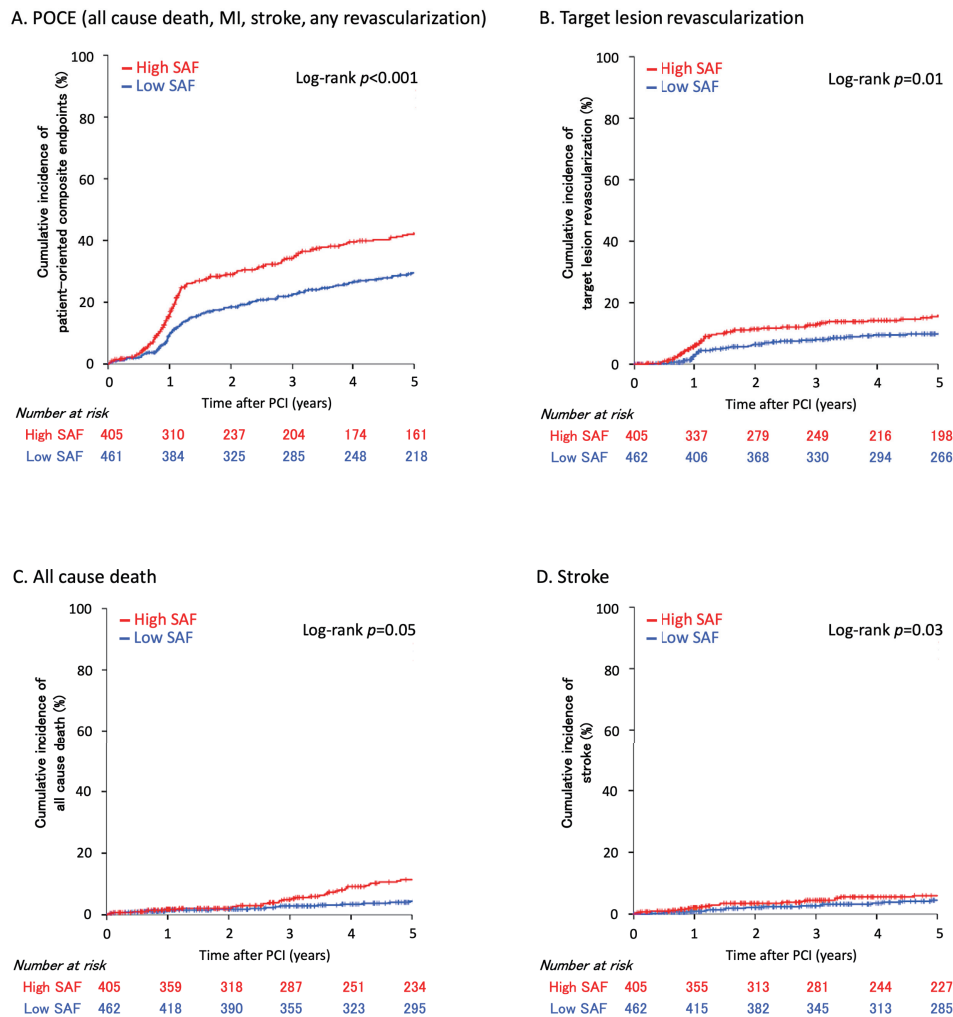


Fig. 1. Clinical outcomes

Kaplan–Meier curves are shown for (A) patient-oriented composite endpoints (POCE), (B) target lesion revascularization, (C) all-cause death, and (D) stroke.

MI = myocardial infarction; PCI = percutaneous coronary intervention.

chronic kidney disease (CKD) in the high SAF group. There was a trend towards a greater prevalence for diabetes but this did not reach statistical significance (diabetes; 36.9% vs. 42.2%, $p = 0.09$), whereas the HbA1c level was significantly higher in the high SAF group (HbA1c; 6.3 ± 1.0 vs. 6.5 ± 1.1 , $p = 0.03$). No differences were observed in the prevalence of left main coronary disease and the number of diseased coronary arteries.

The medical history of study patients at the time of PCI are illustrated in the [Supplementary Table 1](#). When comparing the medications amongst the diabetes patients only, the use of dipeptidyl peptide-4 inhibitors was significantly higher in the high SAF group. There were no differences in the use of antiplatelet, angiotensin receptor blocker, angiotensin-

converting-enzyme inhibitor, and statin irrespective of the presence or absence of diabetes mellitus.

Clinical Outcomes

The clinical outcomes of the two groups are shown in [Fig. 1](#). The cumulative event of POCE was significantly higher in the high SAF group (log-rank $p < 0.001$), that was mainly driven by TLR (log-rank $p = 0.01$) and any revascularization (log-rank $p < 0.01$). The rate of stroke was also significantly higher in the high SAF group (log-rank $p < 0.03$).

Clinical event rates evaluated using continuous SAF variables are summarized in [Table 2](#). The outcomes were consistent with those compared between the low and high SAF groups (POCE; HR 1.43; 95% CI 1.19–1.71, $p < 0.001$, any revascularization;

Table 2. Clinical outcomes

	HR	95% CI	<i>p</i> value
POCE	1.43	1.19-1.71	<0.001
All-cause death	1.44	0.99-2.08	0.06
Cardiac death	1.26	0.72-2.20	0.42
Myocardial infarction	1.23	0.55-2.76	0.62
Definite or probable ST	0.51	0.04-7.39	0.62
TLR	1.41	1.02-1.94	0.04
Any revascularization	1.33	1.08-1.65	0.01
Stroke	2.08	1.38-3.15	0.001

POCE; patient-oriented composite endpoints; ST = stent thrombosis; TLR = target lesion revascularization; HR = hazard ratio; CI = confidence interval.

Table 3. Cox regression analyses for patient-oriented composite endpoints

Covariates	Univariate			Multivariate		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
SAF	1.43	1.19-1.71	<0.001	1.36	1.13-1.63	0.001
Male	1.12	0.88-1.43	0.35			
Age	1.02	1.01-1.03	0.002			
Hypertension	0.97	0.76-1.25	0.81			
Dyslipidemia	0.88	0.71-1.10	0.27			
Diabetes	1.19	0.96-1.48	0.12			
HbA1c, %	1.04	0.95-1.15	0.4			
Current smoking	1.15	0.88-1.51	0.32			
CKD (<60 ml/min/1.73m ²)	1.51	1.22-1.87	<0.001	1.39	1.12-1.73	0.003
eGFR, ml/min/1.73m ²	0.98	0.98-0.99	<0.001			
Left main disease	1.14	0.78-1.66	0.5			
Number of vessel diseased	1.28	1.11-1.48	0.001	1.27	1.10-1.47	0.001
LVEF, %	0.99	0.98-1.00	0.06			

SAF = skin autofluorescence; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; HR = hazard ratio; CI = confidence interval.

HR 1.33; 95% CI 1.08–1.65, $p=0.01$, and TLR; HR 1.41; 95% CI 1.02–1.94, $p=0.04$). The high SAF patients were noted to have worse outcomes with regards to stroke (HR 2.08; 95% CI 1.38–3.15, $p=0.001$).

Predictors of POCE

Univariable analysis revealed that predictors of POCE were SAF (HR 1.43; 95% CI 1.19–1.71, $p<0.001$), age (HR 1.02; 95% CI 1.01–1.03, $p=0.002$), CKD (HR 1.51; 95% CI 1.22–1.87, $p<0.001$), eGFR (HR 0.98; 95% CI 0.98–0.99, $p<0.001$), and the number of diseased coronary arteries (HR 1.28; 95% CI 1.11–1.48, $p=0.001$). Multivariable analyses indicated that SAF, number of diseased coronary arteries, and CKD were independent predictors of POCE [SAF (HR 1.36; 95% CI 1.13–1.63, $p=0.001$); number of diseased coronary arteries (HR 1.27; 95% CI 1.10–1.47, $p=0.001$); CKD (HR 1.39; 95% CI

1.12–1.73, $p=0.003$)] (**Table 3**).

Differences in Patients with and without Diabetes Mellitus

SAF was slightly higher in the diabetes patients compared to the non-diabetes (diabetes 2.7 ± 0.6 vs. non-diabetes 2.6 ± 0.6 , $p=0.04$). Each of the clinical outcomes in patients with and without diabetes mellitus are shown in **Fig. 2**. POCE and stroke rates were high in both patients with and without diabetes mellitus [POCE; diabetes (HR 1.43; 95% CI 1.10–1.86), non-diabetes (HR 1.42; 95% CI 1.11–1.82), stroke; diabetes (HR 2.36; 95% CI 1.30–4.31), non-diabetes (HR 1.90; 95% CI 1.07–3.37)].

Discussion

The present study demonstrated that SAF, as a

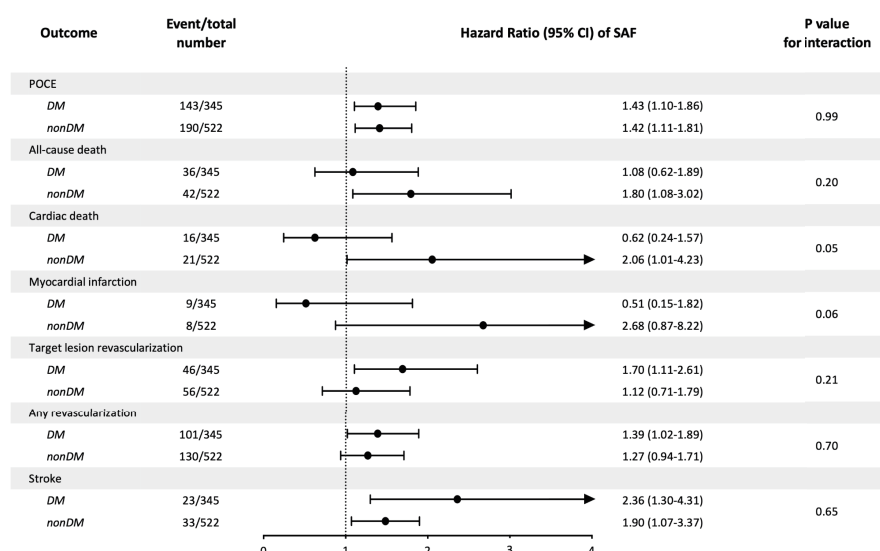


Fig. 2. Forest Plots for the effects of SAF for clinical outcomes stratified by diabetes and non-diabetes

The hazard ratios (HR) were calculated with Cox regression analysis using continuous skin autofluorescence (SAF) variables. POCE = patient-oriented composite endpoints; DM = diabetes mellitus; CI = confidence interval.

measure of AGE deposition, is associated with future cardiovascular events amongst patients with coronary artery disease treated with PCI. SAF was an independent predictor of POCE that was mainly driven by any coronary revascularization. Furthermore, SAF predicts the incidence of restenosis and stroke in this patient group.

The cardiovascular benefits associated with intensive glucose control for patients with type 1 diabetes mellitus during the DCCT/EDIC trial were clear 11 years after the end of active phase of the study. This led to the development in support for the concept of metabolic memory^{21, 22}. This concept is also supported by the long-term outcomes of the UKPDS study for type 2 diabetes mellitus²³. It has been known that the formation and accumulation of AGE are increased in people with diabetes mellitus as a result of hyperglycemia and oxidative stress²⁴. Circulating levels of AGE were previously reported to be associated with cardiovascular events and mortality in high-risk patients for CVD²⁵. However, the lack of standardized methods for quantifying circulating AGE levels have made it difficult to compare the results among studies. Furthermore, it remains unclear which types of AGE are clinically relevant to CVD. The gold standard method for quantifying AGEs is stable isotopic dilution analysis, such as liquid chromatography. However, this method is both time-consuming and costly and cannot be applied to daily clinical practice²⁶. SAF is a non-invasive and

convenient method that can evaluate tissue accumulation levels of AGE. These values correlate with both fluorescent and non-fluorescent AGE levels in the skin^{9, 11}.

Several studies have demonstrated that SAF is associated with an increased risk of cardiovascular events among patients with type 1 or 2 diabetes mellitus^{13, 14}. Furthermore, SAF significantly predicted the risk of CVD and all-cause mortality in the general population¹⁵. These studies support the clinical utility of SAF as a marker of CVD and mortality in the general population irrespective of the presence of diabetes mellitus. There are a few studies that have investigated the association between SAF and clinical outcomes in patients with macrovascular disease. De Vos *et al.* reported SAF was independently associated with all-cause mortality and fatal or nonfatal composite endpoints (myocardial infarction, heart failure, stroke, arterial thrombosis, and sudden cardiac death) amongst patients with peripheral artery disease¹². However, sub-group analyses stratified by diabetes or non-diabetes were not performed in their study. Furthermore, there are no previous reports that have evaluated the impact of SAF amongst patients with coronary artery disease. Our study demonstrates that SAF is an independent predictor for POCE in patients with and without diabetes mellitus. Although the patient demographics are different when compared to their study, it does appear that SAF is a useful marker of future cardiovascular disease in patients

with macrovascular disease irrespective of the presence of diabetes mellitus.

Our study demonstrated for the first time, that SAF predicts the incidence of restenosis following PCI. It should be noted that the follow-up protocol was not standardized and was dependent on the attending physician, especially in terms of patients undergoing routine angiographic follow-up. Amongst the 102 patients with TLR, 79 patients were ischemic-driven and the other 23 patients underwent PCI due to significant stenosis detected at routine angiographic follow-up, that may have resulted in an overestimation of TLR at 1-year follow-up. SAF may also predict other macrovascular events following PCI which may be a marker of the metabolic memory of hyperglycemia, age, or CKD²⁷⁾. Previous studies found that skin concentrations of AGE have been related to coronary calcification, progression of intima-media thickness and left ventricular mass in the DCCT/EDIC study²⁸⁾. AGE play a crucial role in plaque progression and rupture within the biological mechanisms that underly atherosclerosis by stimulation of foam cell formation, plaque angiogenesis, osteogenic differentiation of vascular wall cells and matrix metalloproteinase production²⁹⁾. In addition, the deleterious effect of AGE may directly affect the vascular system³⁰⁾ that might result in restenosis. AGE are recognized by their receptors which could activate nuclear factor kappa B with resultant upregulation of inflammatory pathways in numerous type of cells and tissues^{31, 32)}. These findings may explain the observed relationship of AGE in restenosis following PCI using DES.

Our group previously demonstrated (by optical coherence tomography) that high SAF patients exhibited more vulnerable and advanced coronary artery plaques compared to low SAF subjects³³⁾. The present study did not demonstrate differences in the rates of myocardial infarction possibly due to the low overall event rate. A further larger study that is adequately powered is required to demonstrate the clinical impact of SAF on plaque vulnerability in humans.

SAF measurement is quick and non-invasive, taking less than a minute. Both previous and current studies support the clinical utility of SAF as a first screening method for the prediction of the presence of CVD and for longer-term mortality.

Limitations

The present study had several limitations that should be noted. As this study has been performed in a single center and all patients were of Asian ethnicity,

the results may not be generalized to other populations. Reference values for the Japanese population of SAF have not been reported. Yue *et al.* validated the SAF value in Chinese population and found that these values were similar compared to those in Caucasians³⁴⁾. However, the reference SAF values seem to be different among different ethnicities³⁵⁾, that should be taken into account when evaluating effects of SAF in a multi-ethnic population.

SAF was measured before the PCI procedure in this study. SAF measurements during follow-up were not evaluated. It should also be noted that a significant number of patients could not have a SAF measurement due to the skin pigment or malfunction of the AGE Reader and were thus excluded from the final analysis. Finally, the average duration of diabetes mellitus that may have had an impact upon SAF levels was not available.

Conclusions

SAF as a measure of AGE deposition is independently associated with POCE amongst patients with coronary artery disease treated with PCI. The main driver of POCE was any coronary revascularization including restenosis. SAF also predicts the incidence of restenosis and stroke in this patient group.

Acknowledgements

None.

Financial Disclosures

None.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

Role of the Funding Source

No funding was received related to this manuscript.

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Supplementary Table 1. Medications at the time of PCI

	Low SAF (≤ 2.6)	High SAF (> 2.6)	<i>p</i> value
Overall population	<i>n</i> = 474	<i>n</i> = 422	
Aspirin	472 (99.6)	421 (99.8)	0.54
Prasgrel	40 (8.4)	24 (5.7)	0.11
Clopidogrel	432 (91.1)	394 (93.4)	0.22
ARB or ACE-I	235 (49.6)	220 (52.1)	0.45
Statin	283 (59.7)	233 (55.2)	0.18
Patients with diabetes mellitus	<i>n</i> = 175	<i>n</i> = 179	
Aspirin	175 (100)	179 (100)	NA
Prasgrel	16 (9.1)	11 (6.1)	0.29
Clopidogrel	159 (90.9)	165 (92.2)	0.66
ARB or ACE-I	102 (58.3)	96 (53.6)	0.38
Statin	107 (61.1)	106 (59.2)	0.71
Insulin	27 (15.4)	36 (20.1)	0.25
Biguanide	40 (22.9)	49 (27.4)	0.33
SGLT2-I	2 (1.1)	2 (1.1)	0.68
GLP1 receptor agonist	1 (0.6)	6 (3.4)	0.06
DPP4-I	73 (41.7)	98 (54.7)	0.01
Sulfonylurea	35 (20.0)	52 (29.1)	0.05
Thiazolidinedione	14 (8.0)	17 (9.5)	0.62
Glinide	12 (6.9)	10 (5.6)	0.62
α -glucosidase inhibitor	16 (9.1)	25 (14.0)	0.16

Data are presented as absolute numbers and percentages.

PCI = percutaneous coronary intervention; SAF = skin autofluorescence; ARB = angiotensin receptor blocker; ACE-I = angiotensin converting enzyme inhibitor; SGLT2-I = sodium glucose transporter inhibitor; GLP1 = Glucagon-like peptide-1; DPP4-I = Dipeptidyl peptide-4 inhibitor; NA = not applicable.