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Prognostic indicators for the onset of ischaemic versus haemorrhagic stroke in stable coronary artery disease

Wei-Ting Wang, MD[a,b,c,d], Tao-Cheng Wu, MD, PhD[b,c], Wei-Kung Tseng, MD, PhD[e,f], Yen-Wen Wu, MD, PhD[g], Tsung-Hsien Lin, MD, PhD[h], Hung-I Yeh, MD, PhD[i], Kuan-Cheng Chang, MD, PhD[j,k], Ji-Hung Wang, MD[l], Hsin-Bang Leu, MD, PhD[a,b,c,m], Wei-Hsian Yin, MD, PhD[d,n], Chau-Chung Wu, MD, PhD[o,p], Jaw-Wen Chen, MD[b,c,m,q,*]

Abstract

The incidence of stroke may be increased in patients with coronary artery disease (CAD). We aimed to investigate the specific risk factors for the development of ischaemic and haemorrhagic stroke in stable CAD patients.

Patients with stable CAD were prospectively enrolled for future cardiovascular events in Taiwan. All the patients had received coronary interventions and were stable for least 1 month before enrolment. The incidence of ischaemic stroke was identified and confirmed by telephone and hospital records. Baseline characteristics, including demographic data, lipid profiles, medications, and biomarkers for potential inflammatory and atherosclerosis, were analysed.

In total, 1428 patients (age, 63.07 ± 11.4 years; 1207 males) were under standard medical treatment and regularly followed-up for at least 4 years. Multivariate logistic regression analysis showed that baseline serum myeloperoxidase (MPO) level (hazard ratio [HR]: 1.89, 95% CI: 1.16–3.10, $P = .01$) and statin use (HR: 0.37; 95% CI: 0.17–0.79, $P = .01$) were independently associated with the onset of ischaemic stroke. Age (HR: 1.07, 95% CI: 1.00–1.14, $P = .04$) and angiotensin receptor blocker (ARB) use (HR: 0.37, 95% CI: 0.17–0.79, $P = .01$) were independently associated with future onset of intracranial haemorrhage (ICH), implying the different mechanisms of ischaemic stroke and ICH.

Age and ARB use were related to ICH onset. Baseline MPO level and statin use were independently associated with longer and shorter future ischaemic stroke onset in stable CAD patients, respectively. Further studies are indicated to confirm the potential mechanisms and advance individual risk stratification for the onset of different types of stroke in clinical CAD.

Abbreviations: ARB = Angiotensin receptor blocker, CAD = coronary artery disease, FABP3 = fatty acid-binding protein 3, HDL = high-density lipoprotein, HR = hazard ratio, hsCRP = high-sensitivity C-reactive protein, ICH = intracranial haemorrhage, IL-6 = interleukin-6, LDL = low-density lipoprotein, LpPLa2 = lipoprotein-associated phospholipase A2, MMP-9 = matrix metallopeptidase-

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[a] Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, R.O.C., [b] Cardiovascular Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan, R.O.C., [c] From the Divison of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taiwan, R.O.C., [d] School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, R.O.C., [e] Department of Medical Imaging and Radiological Sciences, I-Shou University, Kaohsiung, Taiwan, R.O.C., [f] Division of Cardiology, Department of Internal Medicine, E-Da Hospital, Kaohsiung, Taiwan, R.O.C., [g] Cardiology Division of Cardiovascular Medical Center and Department of Nuclear Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan, R.O.C, [h] Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital and Kaohsiung Medical University, Taiwan, R.O.C., [i] Mackay Memorial Hospital, Mackay Medical College, New Taipei City, Taiwan, R.O.C., [j] Division of Cardiology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, R.O.C, [k] Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan, R.O.C, [l] Department of Cardiology, Buddhist Tzu-Chi General Hospital, Tzu-Chi University, Hualien, Taiwan, R.O.C., [m] Heath Care and Management Center (H.-B.L., J.-W.C.), Taipei Veterans General Hospital, Taiwan, [n] Division of Cardiology, Heart Center, Cheng-Hsin General Hospital, Taipei, Taiwan, R.O.C, [o] Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan, R.O.C., [p] Department of Primary Care Medicine, College of Medicine, National Taiwan University, Taipei, [q] Institute of Pharmacology, National Yang Ming Chiao Tung University, Taipei, Taiwan, R.O.C.

[*] Correspondence: Jaw-Wen Chen, Healthcare and Services Center, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan, R.O.C. (e-mail: jwchen@vghtpe.gov.tw).

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9, MPO = myeloperoxidase, NGAL = neutrophil gelatinase-associated lipocalin, NT-pro-BNP = N-terminal pro-B-type natriuretic peptide, TG = triglyceride, TNT = treating to new targets.

Keywords: coronary artery disease, haemorrhagic stroke, ischaemic stroke, low-density lipoprotein cholesterol, myeloperoxidase, statins

1. Introduction

Coronary artery disease (CAD) is the leading cause of death in developed countries.[1] Another major cause of mortality, especially in Asians, is stroke, a heterogeneous disease with various aetiologies presenting in the presence or absence of underlying arterial pathologies. While the pathogenesis of these diseases may be different in nature, the incidence of stroke has been shown increased in clinical CAD,[2] and vice versa, the CAD is prevalent in patients with ischemic stroke.[3,4] Atherosclerosis, a systemic inflammatory disease of arterial wall,[5] is believed to play an important role in both diseases.

For the atherosclerosis, pro-inflammatory cells generate and release reactive oxygen species and various cytokines such as C-reactive protein (CRP),[6] myeloperoxidase (MPO),[7] lipoprotein phospholipase A2 (Lp-PLA2),[8] interleukin 6 (IL-6),[9] tumor necrosis factor alpha,[10,11] and fibrinogen[12,13] leading to detrimental effects related to the subsequent onset of cardiovascular and cerebrovascular events.

Previous large-scale cohort studies have suggested the increased risk of new-onset stroke, especially ischaemic stroke, in CAD patients.[14] Nevertheless, few studies to date have systemically explored the specific risk factors of stroke in patients with stable CAD by examining the combination of epidemiologic profiles, laboratory data, and serial inflammatory-associated biomarkers in a longitudinal manner. Given the emerging risk stratification for stroke prevention in CAD patients, this study was conducted to identify the potential predictors for the onset of ischaemic stroke versus intracranial haemorrhage (ICH) in stable CAD patients via a prospective long-term observational Biosignature study in Taiwan.[15] We systemically explored the specific risk factors of stroke in patients with stable CAD by examining the combination of epidemiologic profiles, laboratory data, and serial inflammatory-associated biomarkers in a longitudinal manner.

2. Materials and methods

2.1. Study population

The Biosignature study is a prospective multicenter observational study in Taiwan and detailed protocol was reported in our previously published study.[15] In brief, we initially evaluated patients with history of

1. coronary angiogram showed significant CAD,
2. 12-lead ECG showed myocardial infarction, hospitalisation due to CAD, or
3. angina with ischaemic ECG changes or a positive response to the stress test.

Then, we only enrolled patients with receiving successful percutaneous coronary intervention and stable on medical treatment for at least one month before enrollment, which meets our definition of the patients with stable CAD. The research protocol, including experiments on human and the use of human tissue sample was approved by the independent ethical committees and independent review boards (IRBs) in each hospital, including Taipei Veterans General Hospital, Kaohsiung Medical University, Cheng-Hsin General Hospital, Mackay Memorial Hospital, Far-Eastern Memorial Hospital, China Medical University Hospital, E-Da Hospital, National Taiwan University Hospital and Buddhist Tzu-Chi General Hospital, complying with the Declaration of Helsinki. All of the patients agreed to participate and signed the informed consents.

2.2. Patient and public involvement

We excluded patients who

1. had been hospitalised for acute cardiovascular events, such as unstable angina, acute coronary syndrome, acute MI, acute cerebrovascular event, within 3 months prior enrolment,
2. had schedule of receiving further coronary interventional procedures for other cardiovascular diseases in the next year,
3. had significant malignancy or other major systemic diseases requiring advanced medical or surgical therapy or both in the following year, or
4. 4were unable or unwilling to be followed up regularly have been excluded.

Additionally, patients whose life expectancies less than 6 months (e.g., malignant metastatic neoplasm) and concurrent with immunosuppressive agents were excluded.

We set up a biospecimen bank with identified disease phenotype and related clinical information through the conduct of these multicentre trials. For the current study, we initially sampled 1930 patients with stable CAD who were enrolled between July 2012 and June 2014 to ensure a substantial follow-up duration of at least 4 years. The vascular inflammation-related biomarkers were determined at initial enrolment, resulting to a total of 1428 patients for the analysis. At the end of follow-up on June 30, 2016, 1207 (84.52%) men and 221 (15.48%) women were available for analysis with a median follow-up duration of 5.53 years (interquartile range: 3.52–5.91 years). The patient selection algorithm is shown in Figure 1.

2.3. Laboratory investigations and novel biomarkers measurements

Fasting serum lipid and glucose levels were measured from blood samples stored at–80°C, previously obtained from all patients who underwent overnight fasting for more than 8 hours. Serum levels of creatinine and lipid profiles, including triglycerides (TG), total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, were measured using a Hitachi 7600 autoanalyser (Hitachi Ltd, Tokyo, Japan). Serum levels of MPO, Fatty acid binding protein 3 (FABP3), FABP 4, LIGHT (CD40 Ligand) and Neutrophil gelatinase-associated lipocalin (NGAL) were measured using commercially available EMD Millipore MILLIPLEX MAP Human Cardiovascular

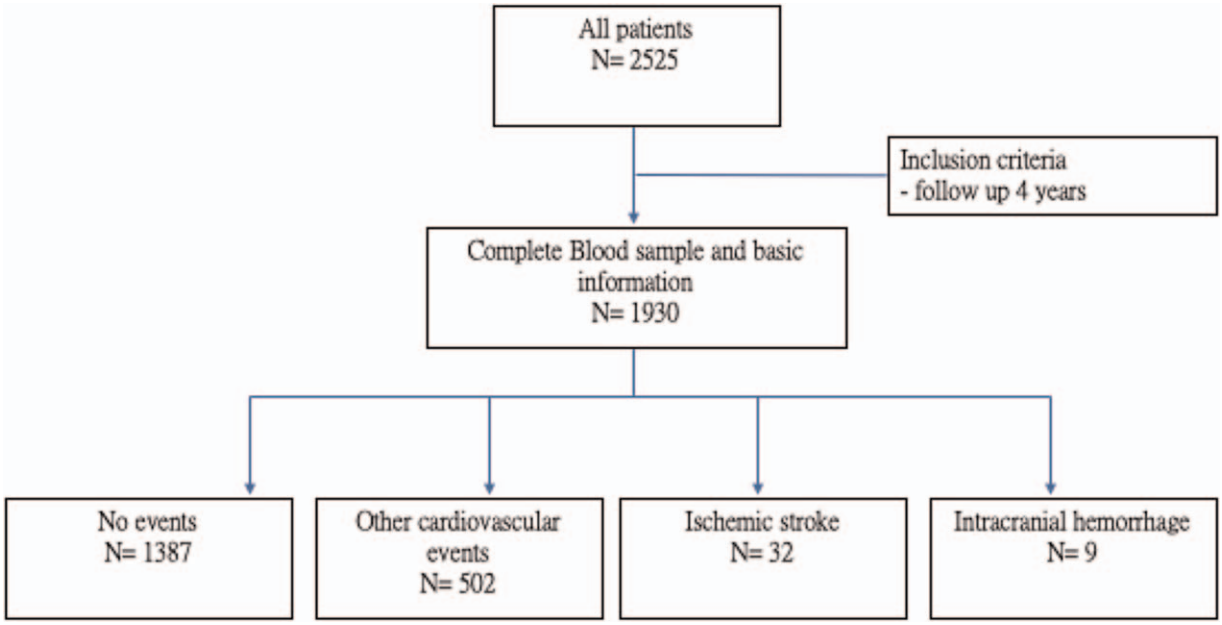

Figure 1. Patient selection algorithm.

diseases Panel 1 Magnetic Bead kit (Millipore, Inc., MO, USA) with the Luminex xMAP platform (Millipore, Inc.).[16,17] Serum N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), hsCRP (high-sensitivity C-reactive protein), CXC chemokine ligand 16, adiponectin, lipoprotein-associated phospholipase A2 (LpPLa2), TNF-α, IL-6, and matrix metallopeptidase (MMP-9) levels were measured using immunoturbidimetric assays.

The serum levels of each biomarker were determined using enzyme immunoassay kits which were established in our laboratories as previously reported.[18] The lowest detection limits and assay ranges were 1.00 ng/mL (1.00–256), 2.86 ng/mL (2.86–400), 0.039 pg/mL (0.039–10), 0.106 pg/mL (0.106–32), and 15.6 pg/mL (15.6–2000) for adiponectin, LpPLa2, IL-6, TNF-α, and MMP-9, respectively.

2.4. Clinical follow-up

The primary outcomes of this study were ischaemic and ICH. Both were defined as the presence of a new neurological deficit lasting at least 24 hours with definite evidence of a cerebrovascular accident verified by either magnetic resonance imaging or computed tomography.

2.5. Statistical analysis

Because of the observational nature of our study, missing data were replaced by mean imputation in the entire cohort. A complete case analysis was used to address the issue given the small amount of missing data across all variables. Data were expressed as the mean ± SD for numeric variables and as the number (percent) for categorical variables. Comparisons of continuous variables between groups were performed by the Student *t* test or one-way analysis of variance (ANOVA) test. Subgroup comparisons of categorical variables were assessed by the Chi-Squared or Fishe exact test.

Survival curves were generated using the Kaplan–Meier method and survival was compared between groups using log-rank test. Significant variables associated with the stroke in univariate analysis were entered into the multivariate regression model. Multivariate logistic regression analysis was performed to identify the independent predictors of stroke. To determine the independent predictors of end points, multivariate Cox regression analysis was performed after adjustment for variables significantly associated with clinical outcomes. Data were analysed using SPSS software (version 20, SPSS, Chicago, IL). A P value $<.05$ was considered to be statistically significant.

3. Results

3.1. Differential baseline characteristics in cad patients with ischaemic versus ICH

The clinical characteristics of the study population, stratified by the events, are summarized in Table 1. Compared to the patients without events, patients with ischaemic stroke were elderly who had lower levels of haemoglobin, used statins less frequently, and had higher serum levels of BNP and MPO. On the other hand, patients with ICH were elderly who had used RAS blockers more frequently and had lower serum levels of total cholesterol, TG, hsCRP, FABP3, FABP4, LIGHT, and NGAL.

After propensity score matching with age, sex, previous stroke, diabetes, hypertension, smoking, and family history of CAD, patients with ischaemic stroke had lower baseline levels of haemoglobulin and eGFR, lower frequency of statin use, and higher baseline serum level of BNP/NT-proBNP. Patients with ICH had higher frequency of RAS blocker use and reduced baseline serum levels of TG, hsCRP, FABP4, LIGHT, and NGAL levels (Table 2).

3.2. Differential predictors for future onset of ischaemic versus ICH in CAD Patients

Figures 2 and 3 show the Kaplan–Meier survival curve stratified by the statistically significant risk factors in ischaemic stroke and

Table 1

Baseline characteristics in different subgroups patients.

	Study population N = 1428	No-event N = 1387	Ischaemic stroke N = 32	Intracranial haemorrhage N = 9	*P* value (no-event vs IS)	*P* value (no-event vs ICH)	*P* value (IS vs ICH)
Epidemiology data							
Age, yrs	63.07 ± 11.44	62.86 ± 11.37	69.44 ± 10.99	73.22 ± 14.11	.001	.007	.398
Male, n (%)	1207 (84.52%)	1172 (84.50%)	27 (84.38%)	8 (88.89%)	.985	.717	.735
BMI, kg/m^2	26.53 ± 3.82	26.55 ± 3.83	26.2 ± 3.58	25.14 ± 2.49	.614	.272	.412
SBP, mm Hg	130.59 ± 17.22	130.53 ± 17.17	134.13 ± 19.98	128.44 ± 16.06	.243	.717	.439
DBP, mm Hg	75.47 ± 11.77	75.49 ± 11.74	76.06 ± 12.72	70.22 ± 13.24	.786	.180	.235
LVEF, %	59.57 ± 13.06	59.6 ± 13.06	54.03 ± 17.01	62.33 ± 10.97	.397	.718	.498
Previous stroke, %	40 (2.80%)	38 (2.74%)	1 (3.13%)	1 (11.11%)	.895	.129	.336
Family history of CAD, n (%)	280 (19.61%)	289 (19.04%)	7 (21.88%)	2 (22.22%)	.686	.840	.982
Diabetes Mellitus, n (%)	502 (35.15%)	513 (33.79%)	13 (40.63%)	5 (55.56%)	.419	.195	.425
Hypertension, n (%)	919 (64.36%)	962 (63.37%)	24 (75.00%)	5 (55.56%)	.176	.591	.257
Smoking, n (%)	772 (54.06%)	787 (51.84%)	20 (62.50%)	7 (77.78%)	.233	.149	.393
Laboratory data							
Hgb, mg/dL	13.79 ± 1.82	13.81 ± 1.82	12.96 ± 1.95	13.26 ± 2.02	.011	.360	.695
Fasting sugar, mg/dL	119.77 ± 41.94	119.39 ± 41.58	135.28 ± 56.61	121.67 ± 28.47	.125	.870	.332
Creatinine, mg/dL	1.19 ± 1.01	1.18 ± 0.99	1.73 ± 1.66	1.12 ± 0.2	.069	.387	.047
eGFR, mL/min/1.73 m2	77.82 ± 28.57	78.24 ± 28.56	61.86 ± 27.62	69.07 ± 14.86	.001	.103	.458
Cholesterol, mg/dL	163.16 ± 36.34	163.77 ± 36.81	162.16 ± 37.86	148.33 ± 17.78	.806	.036	.133
TG, mg/dL	137.19 ± 85.26	137.36 ± 85.84	137.87 ± 100.55	105.44 ± 31.28	.974	.016	.128
HDL-C, mg/dL	42.3 ± 10.82	42.53 ± 11.13	42.15 ± 10.51	41.1 ± 12.28	.852	.738	.801
LDL-C, mg/dL	94.91 ± 29.91	95.43 ± 30.03	88.67 ± 25.61	86.01 ± 17.46	.207	.364	.773
Medications							
Statin use, n (%)	1070 (74.93%)	1143 (75.30%)	18 (56.25%)	7 (77.78%)	.014	.866	.242
RAS blockade, n (%)	939 (65.76%)	908 (65.47%)	22 (68.75%)	9 (100.00%)	.699	.030	.054
ACEI, n (%)	310 (21.71%)	298 (21.49%)	11 (34.38%)	1 (11.11%)	.081	.450	.175
ARB, n (%)	634 (44.40%)	615 (44.34%)	11 (34.38%)	8 (88.89%)	.262	.007	.004
Antiplatelets, n (%)	1329 (93.07%)	1291 (93.08%)	30 (93.75%)	8 (88.89%)	.882	.622	.621
Anticoagulants, n (%)	41 (2.87%)	38 (2.74%)	2 (6.25%)	1 (11.11%)	.236	.129	.621
Beta-blocker, n (%)	955 (66.88%)	930 (67.05%)	21 (65.63%)	4 (44.44%)	.865	.151	.250
Biomarkers							
hsCRP, mg/dL	0.34 ± 0.95	0.34 ± 0.96	0.3 ± 0.53	0.16 ± 0.15	.750	.013	.260
Adiponectin, ng/mL	7572.09 ± 12801.19	7560.88 ± 13055.86	8174.13 ± 6779.52	6688.13 ± 3451.39	.688	.527	.560
LpPLa2, ng/mL	153.04 ± 301.46	146.97 ± 287.41	302 ± 526.46	183.75 ± 408.6	.174	.721	.569
IL6, pg/mL	2.95 ± 4.76	2.95 ± 4.85	3.21 ± 2.71	2.45 ± 1.51	.661	.402	.456
TNF-a, pg/mL	3.71 ± 4.28	3.72 ± 4.36	3.43 ± 2.15	3.48 ± 2.81	.558	.878	.960
MMP-9, pg/mL	573.11 ± 437.28	569.62 ± 439.29	648.73 ± 365.61	619.52 ± 502.48	.394	.750	.861
BNP, pg/mL	78.32 ± 219.47	76.42 ± 219.75	159.01 ± 224.76	85.61 ± 53.93	.036	.638	.100
NT-proBNP, pg/mL	339.95 ± 641.16	333.57 ± 636.16	620.1 ± 833.47	327.16 ± 447.52	.062	.976	.320
CXCL16, pg/mL	387.05 ± 194.94	388.54 ± 195.82	351.81 ± 158.17	283.47 ± 143.57	.293	.108	.251
Myeloperoxidase, ng/mL	758.45 ± 590.52	752.32 ± 584	1064.66 ± 761.48	615.25 ± 679.94	.028	.483	.118
FABP3, pg/mL	3820.48 ± 6612.37	3764.08 ± 6534.85	6488.74 ± 9775.58	3023.89 ± 778.65	.127	.030	.056
FABP4, pg/mL	8232.14 ± 20369.45	8158.4 ± 20431.3	12784.73 ± 20083.51	3409.36 ± 4030.18	.205	.008	.018
LIGHT, pg/mL	291.7 ± 475.94	294.81 ± 480.33	216 ± 300.69	81.62 ± 87.69	.159	<.0001	.033
NGAL, ng/mL	426.31 ± 692.25	422.29 ± 686.5	654.74 ± 955.64	234.44 ± 193.62	.181	.020	.026

Data were means ± SD for skewed variables or proportions for categorical variables.

ACEI = angiotensin- converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = B-type natriuretic peptide, BMI = body mass index, CV = cardiovascular, CAD = coronary artery disease, CXCL16 = CXC chemokine ligand 16, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FABP3 = fatty acid-binding protein 3, FABP4 = fatty acid-binding protein 4, hsCRP = high-sensitivity C-reactive protein, Hgb = hemoglobin, HDL-C = high density lipoprotein cholesterol, IL6 = interleukin-6, IS = indicates ischemic stroke, ICH = intracranial haemorrhage, LDL-C = low-density lipoprotein cholesterol, LpPLa2 = lipoprotein-associated phospholipase A2, LIGHT = CD40 Ligand, LVEF = left ventricular ejection fraction, MMP = matrix metallopeptidase, NT-proBNP = N-terminal pro-brain natriuretic peptide, NGAL = neutrophil gelatinase-associated lipocalin, RAS = renin-angiotensin system, SBP = systolic blood pressure, TNF = tumor necrosis factor, TG = triglyceride.

ICH, respectively. Age <63 years, lower serum level of MPO (<0.589 ng/mL), increased eGFR (>76 mL/min/1.73 m^2), and statin use were associated with lower incidence of ischaemic stroke; while angiotensin receptor blocker (ARB) use was associated with future ICH onset.

3.3. Independent predictors for future ischaemic stroke onset in cad patients

In the multivariate analysis (Table 3), only baseline serum level of MPO and statin use independently predicted future ischaemic stroke onset in the whole population.

3.3.1. Serum myeloperoxidase. The predictive power of MPO (0.6425) for future ischaemic stroke onset was significantly higher than hsCRP (0.4667) (*P* value = .042) (Supplement Digital Content Figure 1, http://links.lww.com/MD/G503). This suggests that MPO, rather than hsCRP, is a specific predictor for ischaemic stroke onset in the presence of CAD.

3.3.2. Statin use. To further clarify the potential association between the use of statins and ischaemic stroke, we divided the study population into different subgroups according to statin use (Supplemental Digital Content Table S1, http://links.lww.com/MD/G503) and their baseline LDL levels (Supplemental Digital Content Table S2, http://links.lww.com/MD/G503). Compared to the non-users, the patients on statins were younger and had higher serum haemoglobulin and LIGHT levels, lower serum creatinine level, and higher frequency of drug use at baseline involving ARB, angiotensin converting enzyme inhibitor, antiplatelet, and beta-blocker. While baseline serum lipid profiles (total cholesterol, HDL, LDL, and TG) were similar in patients with or without statin use, serum inflammatory biomarkers, including LpPLa2, FABP3, and IL-6 levels were lower in statin

Table 2

Baseline characteristics between stroke and non-stroke patients after propensity matched with age, gender, history of stroke, diabetes mellitus, hypertension, smoking family history of coronary artery disease.

	Total N = 608	No CV event N = 576	Ischaemic stroke N = 32	*P* value	Total N = 171	No CV event N = 162	Intracranial haemorrhage N = 9	*P* value
Epidemiologic data								
Age, yrs	67.54 ± 11.83	67.44 ± 11.88	69.44 ± 10.99	.351	64.73 ± 15.73	64.26 ± 15.72	73.22 ± 14.11	.096
Male, n (%)	513 (84.38%)	486 (84.38%)	27 (84.38%)	1.000	152 (88.89%)	144 (88.89%)	8 (88.89%)	1.000
BMI, Kg/m2	26.23 ± 3.84	26.23 ± 3.85	26.2 ± 3.58	.971	26.25 ± 3.93	26.31 ± 3.99	25.14 ± 2.49	.387
SBP, mm Hg	131.24 ± 17.85	131.07 ± 17.73	134.13 ± 19.98	.347	129.22 ± 17.2	129.26 ± 17.31	128.44 ± 16.06	.891
DBP, mmHg	74.2 ± 11.71	74.1 ± 11.65	76.06 ± 12.72	.356	73.92 ± 11.68	74.12 ± 11.6	70.22 ± 13.24	.331
LVEF, %	67.54 ± 11.83	67.44 ± 11.88	69.44 ± 10.99	.351	61.27 ± 14.25	61.2 ± 14.5	62.33 ± 10.97	.895
Previous stroke, %	18 (2.96%)	17 (2.95%)	1 (3.13%)	.955	11 (6.43%)	10 (6.17%)	1 (11.11%)	.557
Family history of CAD, n (%)	132 (21.71%)	125 (21.70%)	7 (21.88%)	.982	35 (20.47%)	33 (20.37%)	2 (22.22%)	.893
Diabetes mellitus, n (%)	234 (38.49%)	221 (38.37%)	13 (40.63%)	.798	65 (38.01%)	60 (37.04%)	5 (55.56%)	.265
Hypertension, n (%)	444 (73.03%)	420 (72.92%)	24 (75.00%)	.796	112 (65.50%)	107 (66.05%)	5 (55.56%)	.519
Smoking, n (%)	359 (59.05%)	339 (58.85%)	20 (62.50%)	.683	108 (63.16%)	101 (62.35%)	7 (77.78%)	.350
Laboratory data								
Hgb, mg/dL	13.64 ± 1.79	13.67 ± 1.77	12.96 ± 1.95	.033	13.38 ± 1.8	13.39 ± 1.79	13.26 ± 2.02	.827
Fasting sugar, mg/dL	120.64 ± 40.94	119.82 ± 39.8	135.28 ± 56.61	.137	118.71 ± 40.1	118.54 ± 40.72	121.67 ± 28.47	.821
Creatinine, mg/dL	1.2 ± 0.85	1.17 ± 0.78	1.73 ± 1.66	.066	1.31 ± 1.43	1.32 ± 1.47	1.12 ± 0.2	.135
eGFR, mL/min/1.73m2	73.68 ± 25.66	74.34 ± 25.41	61.86 ± 27.62	.007	73.9 ± 25.94	74.17 ± 26.43	69.07 ± 14.86	.568
Cholesterol, mg/dL	161.72 ± 35.32	161.7 ± 35.21	162.16 ± 37.86	.943	156.48 ± 32.28	156.94 ± 32.88	148.33 ± 17.78	.438
TG, mg/dL	134.37 ± 80.77	134.18 ± 79.66	137.87 ± 100.55	.842	130.08 ± 75.61	131.46 ± 77.17	105.44 ± 31.28	.049
HDL-C, mg/dL	42.18 ± 10.71	42.18 ± 10.73	42.15 ± 10.51	.987	40.68 ± 9.83	40.66 ± 9.72	41.1 ± 12.28	.897
LDL-C, mg/dL	93.64 ± 29.31	93.92 ± 29.5	88.67 ± 25.61	.324	89.59 ± 29.69	89.79 ± 30.26	86.01 ± 17.46	.711
Medications								
Statin use, n (%)	444 (73.03%)	426 (73.96%)	18 (56.25%)	.028	122 (71.35%)	115 (70.99%)	7 (77.78%)	.661
RAS blockade, n (%)	416 (68.42%)	394 (68.40%)	22 (68.75%)	.967	121 (70.76%)	112 (69.14%)	9 (100.00%)	.048
ACEI, n (%)	133 (21.88%)	122 (21.18%)	11 (34.38%)	.079	35 (20.47%)	34 (20.99%)	1 (11.11%)	.475
ARB, n (%)	286 (47.04%)	275 (47.74%)	11 (34.38%)	.140	87 (50.88%)	79 (48.77%)	8 (88.89%)	.019
Antiplatelets, n (%)	566 (93.09%)	536 (93.06%)	30 (93.75%)	.880	157 (91.81%)	149 (91.98%)	8 (88.89%)	.742
Anticoagulants, n (%)	14 (2.30%)	12 (2.08%)	2 (6.25%)	.126	6 (3.51%)	5 (3.09%)	1 (11.11%)	.203
Beta-blocker, n (%)	395 (64.97%)	374 (64.93%)	21 (65.63%)	.936	108 (63.16%)	104 (64.20%)	4 (44.44%)	.232
Biomarkers								
hsCRP, mg/dL	0.36 ± 1.19	0.37 ± 1.22	0.3 ± 0.53	.627	0.37 ± 0.75	0.4 ± 0.78	0.16 ± 0.15	.031
Adiponectin, ng/mL	8298.03 ± 13806.29	8307.89 ± 14224.07	8174.13 ± 6779.52	.936	9651.5 ± 18398.11	9980.76 ± 19348.29	6688.13 ± 3451.39	.208
LpPLa2, ng/mL	163.19 ± 285.52	152.15 ± 255.34	302 ± 526.46	.189	138.42 ± 242.95	133.39 ± 221.26	183.75 ± 408.6	.741
IL6, pg/mL	3.06 ± 5.03	3.05 ± 5.18	3.21 ± 2.71	.805	3.05 ± 3.03	3.12 ± 3.16	2.45 ± 1.51	.318
TNF-a, pg/mL	3.75 ± 3.98	3.77 ± 4.09	3.43 ± 2.15	.512	3.99 ± 4.36	4.05 ± 4.51	3.48 ± 2.81	.730
MMP-9, pg/mL	575.4 ± 412.21	569.56 ± 415.71	648.73 ± 365.61	.376	572.02 ± 404.64	566.74 ± 396.24	619.52 ± 502.48	.729
BNP, pg/mL	73.78 ± 128.2	69.04 ± 119.17	159.01 ± 224.76	.032	82.88 ± 184.54	82.73 ± 189.25	85.61 ± 53.93	.903
NT-proBNP, pg/mL	326.17 ± 508.26	309.84 ± 479.77	620.1 ± 833.47	.045	333.98 ± 656.38	334.36 ± 667.06	327.16 ± 447.52	.975
CXCL16, pg/mL	377.32 ± 184.6	378.74 ± 185.97	351.81 ± 158.17	.422	400.7 ± 177.19	407.21 ± 176.96	283.47 ± 143.57	.041
Myeloperoxidase, ng/mL	804.6 ± 608.31	790.15 ± 596.15	1064.66 ± 761.48	.053	772.32 ± 578.49	781.05 ± 573.53	615.25 ± 679.94	.404
FABP3, pg/mL	3897.16 ± 5052.61	3753.19 ± 4626.35	6488.74 ± 9775.58	.126	3715.77 ± 4147.81	3754.21 ± 4255.32	3023.89 ± 778.65	.091
FABP4, pg/mL	8862.78 ± 15535.85	8644.89 ± 15236.33	12784.73 ± 20083.51	.259	7194.32 ± 9954.25	7404.6 ± 10147.59	3409.36 ± 4030.18	.022
LIGHT, pg/mL	293.06 ± 508.32	297.34 ± 517.25	216 ± 300.69	.164	255.62 ± 470.8	265.28 ± 481.53	81.62 ± 87.69	.000
NGAL, ng/mL	492.19 ± 806.46	483.16 ± 797.36	654.74 ± 955.64	.242	454.08 ± 819.81	466.28 ± 839.62	234.44 ± 193.62	.017

Data were means ± SD for skewed variables or proportions for categorical variables.

ACEI = angiotensin- converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BNP = B-type natriuretic peptide, CV = indicates cardiovascular, CAD = coronary artery disease, CXCL16 = CXC chemokine ligand, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FABP3 = fatty acid-binding protein 3, FABP4 = fatty acid-binding protein 4, hsCRP = high-sensitivity C-reactive protein, HDL-C = high density lipoprotein cholesterol, Hgb = haemoglobin, LpPLa2 = lipoprotein-associated phospholipase A2, IL6 = interleukin-6, LIGHT = CD40 Ligand, LVEF = left ventricular ejection fraction, LDL-C = low-density lipoprotein cholesterol, MMP = matrix metallopeptidase, NT-proBNP = N-terminal pro-brain natriuretic peptide16, NGAL = neutrophil gelatinase-associated lipocalin, RAS = renin-angiotensin system, SBP = systolic blood pressure, TNF = tumor necrosis factor, TG = triglyceride.

users than in non-users (Supplemental Digital Content Table S1, http://links.lww.com/MD/G503). The anti-inflammatory effects of statins rather than its lipid-lowering role might be related to the potential benefits.

Interestingly, compared to the other subjects, the patients with reduced LDL levels (LDL <70 mg/dL) were older and had more comorbidities (including hypertension and type 2 diabetes) and lower baseline serum total cholesterol, TG, haemoglobulin levels, and higher NT-pro-BNP levels. While statin use was similar across the subgroups at baseline, more medications (including ARB) and healthy foods (including cornmeal) were taken in patients with lower baseline LDL level (LDL <70, 70–100, >100 mg/dL: 86 [30.07%], 167 [28.4%], 120 [22.02%], respectively, *P* value = .014) (Supplemental Digital Content Table S2, http://links.lww.com/MD/G503). In addition to statins, that healthy diet (such as cornmeal) might contribute to serum LDL control in these patients.

3.4. Independent predictors for future ICH onset in CAD patients

Baseline age (HR: 1.07, 95% CI: 1.00–1.14, *P* = .04) and ARB use (HR: 0.37, 95% CI: 0.17–0.79, *P* = .01) were independently associated with the future ICH onset There were no observed associations of baseline blood pressure, glucose level, statin use, and lipid profiles on future ICH onset (Table 3).

4. Discussion

The main findings of our study were that baseline serum level of MPO and statin use are the major predictors for the occurrence of ischaemic stroke, while the age and ARB use were significantly associated with future ICH onset in stable CAD patients. Our findings provided some real-world rationale to the substantially different prognostic factors, including comprehensive serial novel

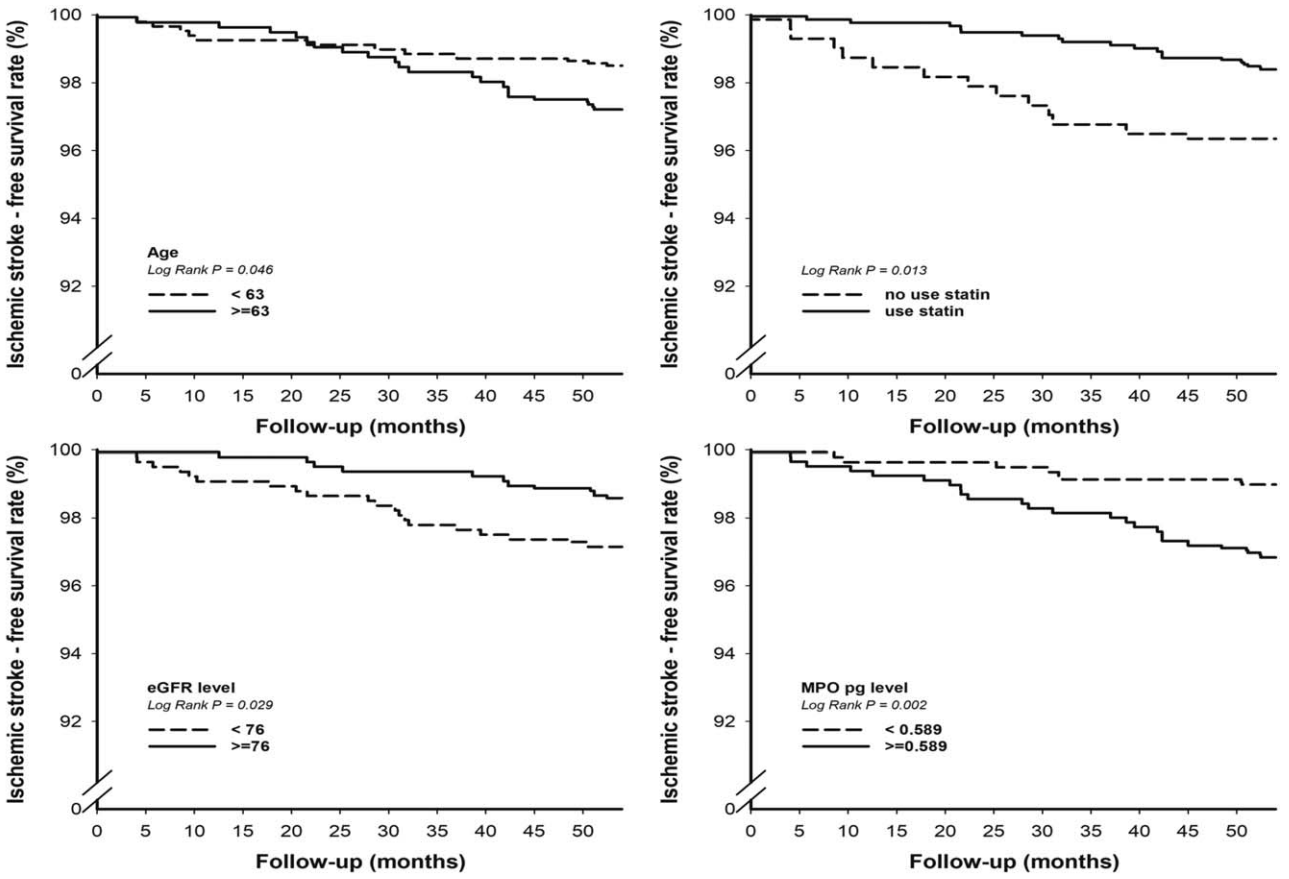

Figure 2. Kaplan–Meier method and survival compared between 5 significant risk predictors and ischaemic stroke by use of the log-rank test.

inflammatory biomarker evaluation and risk stratification for the onset of ischaemic stroke versus ICH. Furthermore, the completely different risk profiles in our study might support the differential pathogenesis for the onset of ischaemic versus ICH in the patients with CAD.

4.1. Statins for ischaemic stroke

It has been well demonstrated that statins are effective in primary and secondary stroke prevention.[19] For example, a prospective randomized trial performed by the Stroke Prevention by Aggressive Reduction in Cholesterol Levels investigators revealed

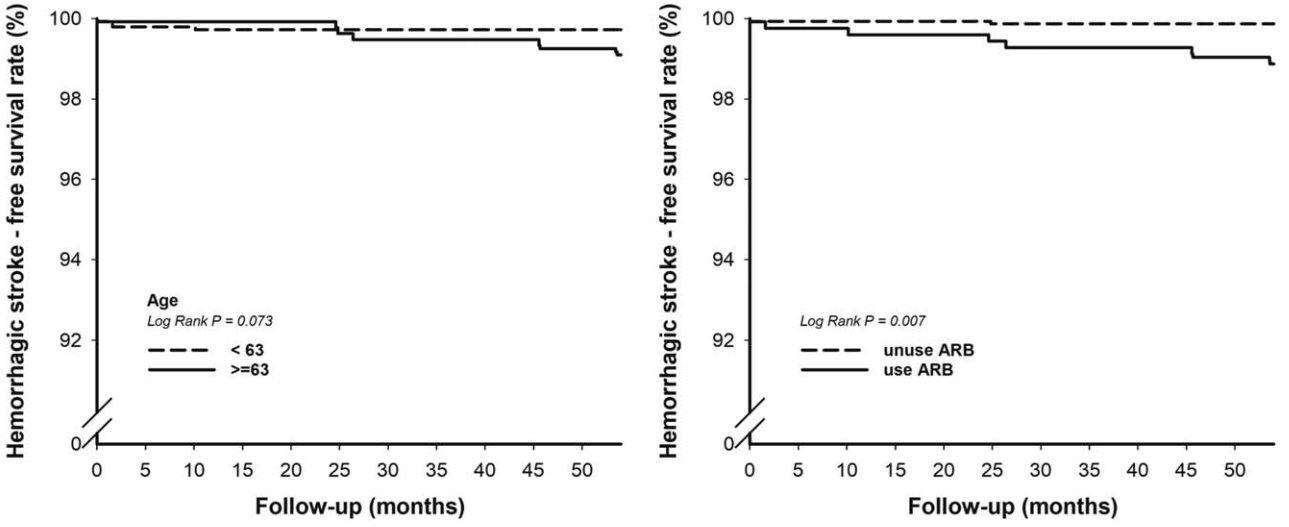

Figure 3. Kaplan–Meier method and survival compared between 2 significant risk predictors and intracranial stroke by use of the log-rank test.

Table 3

Predictors for the ischaemic stroke vs intracranial haemorrhage in coronary artery disease patients in multivariate model.

	Ischaemic stroke						Intracranial haemorrhage					
	Univariate			multivariate			univariate			multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years	1.05	1.02-1.08	.00	1.03	0.99–1.07	0.08	1.09	1.02–1.16	.008	1.07	1.00–1.14	.04
Fasting glucose, mg/dL	1.00	1.00–1.01	.03	1.00	0.99–1.01	0.13						
Creatinine, mg/dL	1.22	0.76–1.21	.01	0.95	0.73–1.25	0.73						
eGFR, mL/min/1.73m^2	0.98	0.96–0.99	.00	0.98	0.96–1.00	0.07						
Hgb, mg/dL	0.79	0.67–0.95	.01	0.99	0.81–1.24	0.99						
ACEI, n (%)	1.89	0.91–3.91	.08	1.92	0.87–4.25	.11						
Statin, n (%)	0.42	0.21–0.85	.01	0.37	0.17–0.79	.01						
BNP, mg/dL	1.00	1.00–1.00	.07	1.03	0.94–1.13	.46						
NT-proBNP, mg/dL	1.00	1.00–1.00	.01	1.02	0.97–1.06	.37						
FABP3, ng/mL	1.00	1.00–1.00	.03	1.00	0.99–1.00	.62						
Myeloperoxidase, ng/mL	3.42	1.48–7.91	.00	1.89	1.16–3.10	.01						
NGAL, ng/mL	1.00	1.00–1.00	.07	1.00	1.00–1.00	.77						
ARB, n (%)							10.03	1.25–80.1	.03	9.11	1.14–72.9	.03
nitrate, n (%)							4.49	0.93–21.6	.06	3.32	0.67–16.4	.14
CXCL16, pg/mL							1.00	.099–1.00	.09	0.05	0.00–4.71	.19

ARB = angiotensin receptor blocker, ACEI = angiotensin- converting enzyme inhibitor, BNP = B-type natriuretic peptide, CI = confident interval, CXCL16 = CXC chemokine ligand 16, eGFR = estimated glomerular filtration rate, FABP3 = fatty acid-binding protein 3, HR = indicates hazard ratio, Hgb = haemoglobin, NT-proBNP = N-terminal pro-brain natriuretic peptide, NGAL = neutrophil gelatinase-associated lipocalin.

that apart from significantly lowering serum LDL levels, statin use reduced 16% of non-fatal or fatal stroke in patients with recent stroke or transient ischaemic attack.[20] Statins may also have pleiotropic effects such as anti-oxidative effect, anti-inflammatory effect, promotion of endothelial NO production, and enhancement of angiogenesis in ischaemic stroke patients.[21–23] In the present study, statin use, but not the baseline lipid profile, could be related to future ischaemic stroke onset in stable CAD patients. Furthermore, baseline inflammatory biomarkers decreased with statin use.

Though the findings may be preliminary, our data did support the specific and potentially direct role of statins on the lipid profiles for the prevention of ischaemic stroke in patients with CAD. On the other hand, there were no association of baseline statin use with future ICH onset, suggesting the safety of statins in stable CAD patients.

4.2. Serum MPO and ischaemic stroke

MPO, an enzyme secreted during inflammation by activated neutrophil, catalyses the formation of oxidative reactants and participates in the promotion and propagation of atherosclerosis by destabilising atherosclerotic plaques with oxidation of HDL.[24] In the current study, baseline MPO level, rather than CRP and lipid profiles, was the only biomarker predicting ischaemic stroke onset in CAD patients. In stable CAD patients, a positive interaction has been suggested to exist between increased inflammatory markers (MPO, hsCRP, TNF-α, and IL-6) and progression of dyslipidaemia and dyslipoproteinaemia, including decreased circulating apoAI, apoAII, and HDL levels.[25] Several studies further indicated that circulating MPO could be increased in patients with acute ischaemic stroke and was associated with worse outcomes and higher mortality rates within 3 months.[26] Khine et al also showed that increased MPO/HDL ratio was associated with the increased risk of cardiovascular events in a general population without initial cardiovascular disease.[24] To our knowledge, our findings are the first to show the association of baseline MPO levels with future ischaemic stroke onset in stable CAD patients during a long follow-up period. Moreover, circulating MPO was an independent prognostic factor even after adjustment for statins, lipid profiles, and serial biomarkers, suggesting the unique role of MPO-related mechanisms for ischaemic stroke onset in CAD patients.

However, the previous substudy of Treating to New Targets (TNT) showed that the plasma levels of neopterin, NT-pro-BNP and soluble receptor for advanced glycation end-products, rather than plasma levels of LDL, hsCRP, MMP-9, and MPO, were significantly associated with the risk of recurrent major cardiovascular events in stable, statin-treated CAD patients. It was also indicated, however, that plasma MPO levels increased with dose of atorvastatin. No such correlation was identified in our study.

The possible explanations for this discrepancy may be

1. while the combination of myocardial infarction, cardiovascular death, and stroke was defined in TNT substudy, only ICH and ischaemic stroke events were explored in our study;
2. while all patients received statin treatment in TNT substudy, only 70% to 80% of our study patients received statins;
3. some biomarkers such as neopterin and soluble receptor for advanced glycation end-products were not examined in the current study.

Future studies may confirm if MPO and related mechanisms also play a role in the onset of cardiovascular events other than ischaemic stroke in CAD patients.

4.3. Age for the onset of ICH

Different from those for ischaemic stroke, both age and ARB use were the main predictors for ICH in stable CAD patients. Advanced age was suggested as a well-known risk factor for ICH although it may be associated with significantly increased risk of multiple pathologies (such as essential hypertension, CAD, atrial fibrillation, and type 2 DM).[27] It may also affect the body via changes in the cardiovascular and central nervous systems.[28] However, in the present study, age rather than other traditional

risk factors and serial biomarkers was independently associated with ICH onset. The exact mechanism and extent of the impact remain to be clarified.

4.4. Potential impact of ARBs on ICH

Knowing the potential effects of some medications on the occurrence of stroke, especially ICH in CAD patients, is interesting and critical. Previous randomized, double-blinded Scandinavian Candesartan Acute Stroke Trial studies reported the association of candesartan with worsening functional outcome in 6 months according to the modified Rankin Scale in the patients with acute ICH and systolic blood pressure >140 mm Hg.[29] However, Sundbøll et al have found that ARB use was associated with reduced 30-day mortality among patients with ischaemic stroke while having neutral effects in patients with ICH or subarachnoid haemorrhage.[30] The LIFE study also showed the beneficial effects of losartan on future cardiovascular events, especially ischaemic stroke in high risk hypertensive patients. Collectively, it seems that ARBs may have a different impact on ICH versus ischaemic stroke.

Here, while no effects on future ischaemic stroke was established, ARB use was significantly associated with increased future ICH events in stable CAD patients, hinting its potential clinical impact. However, the underlying mechanisms were not known, and the study was conducted mainly in ethnic Chinese people in Taiwan. Given the limited number of ICH events in the present study, future large randomized controlled trials may be required to clarify this issue in different ethnicities from different areas. Our findings further support the notion that different risk factors and mechanisms may be identified for the onset of ICH versus ischaemic stroke.[31,32]

There were other potential risk factors accounting for the incidence of the ischemic stroke and intracranial haemorrhage we did not investigate. For example, Chao et al, based on program established by the China Stroke Prevention Project Committee, had found that the motivation and empowerment of individual is also a crucial component of effective primary prevention of stroke in addition to the population screening for stroke risks.[33,34]. Moreover, multi-level community interventions, like the validated and free mobile tool, the Stroke Riskometer app, endorsed by global neurology and heart organizations[35] might also be important for primary stroke prevention recommended by World Stroke Organization.

4.5. Limitations

Some limitations of the present study should be acknowledged. First, while the Biosignature study is a real-world hospital-based multicentre prospective cohort study in Taiwan, selection bias may be unavoidable with the use of clinical data. Moreover, since our cohort was male-dominant, similar to previous population-based studies,[36,37] gender bias may exist although we tried to minimize the bias by statistically adjusting these confounders in our multivariate Cox regression and propensity scoring match analysis. Secondly, in the present study, no atrial fibrillation data were identified, which is a well-known risk factor for ischaemic stroke. The consumption of warfarin was used as the surrogate, while no patient with mechanical valve replacement was enrolled. However, the data may be underdetermined since no data for the use of new oral anticoagulants existed. Thirdly, ischaemic stroke and ICH onsets were identified only by imaging studies and clinical judgement according to the records. The detailed aetiology of each subtype of stroke could not be further defined. However, according to the previous data, intracranial origin was the most common subtype of ischaemic stroke in Asians and Taiwanese.[38–40] Fourth, statin use rather than its detailed dose was recorded in this study. However, moderate potency of statins was usually used for CAD patients in Taiwan according to the national insurance guideline.[41] It might still confound the result since serum MPO level and other inflammatory biomarkers vary with statin use. Finally, the incidence of the clinical outcomes especially ICH in our study was relatively low even though we checked with National Insurance Databank and followed up for at least 4 years. The small event number may also result in the tremendous bias on the proportion of the use of the medications, like ARB, and further confound the potential role of ARB on the stroke. Thus, the current data may not be sufficiently conclusive and further confirmation by future large-scale randomized controlled trials in different geographic and racial cohorts must be performed.

5. Conclusions

Baseline MPO level and statin use were independently associated with longer and shorter future ischaemic stroke onset in stable CAD patients, respectively. Age and ARB use were positively related to ICH onset, suggesting the independent clinical risk stratification and potential involvement of different mechanisms. Further large-scale studies are required to confirm these associations.

Author contributions

Conceptualization: Tao-Cheng Wu, Wei-Kung Tseng, Yen-Wen Wu, Tsung-Hsien Lin, Hung-I Yeh, Kuan-Cheng Chang, Ji-Hung Wang, Hsin-Bang Leu, Wei-Hsian Yin, Chau-Chung Wu, Jaw-Wen Chen, Wei-Ting Wang.
Data curation: Wei-Ting Wang, Wei-Kung Tseng, Yen-Wen Wu, Hung-I Yeh, Kuan-Cheng Chang, Ji-Hung Wang, Hsin-Bang Leu, Wei-Hsian Yin, Chau-Chung Wu, Jaw-Wen Chen.
Formal analysis: Hsin-Bang Leu, Wei-Ting Wang.
Investigation: Tao-Cheng Wu, Wei-Hsian Yin, Chau-Chung Wu.
Methodology: Wei-Ting Wang, Hsin-Bang Leu, Chau-Chung Wu, Jaw-Wen Chen.
Project administration: Wei-Kung Tseng, Yen-Wen Wu, Hung-I Yeh, Kuan-Cheng Chang, Ji-Hung Wang, Hsin-Bang Leu, Wei-Hsian Yin, Chau-Chung Wu, Jaw-Wen Chen.
Supervision: Hung-I Yeh, Kuan-Cheng Chang, Hsin-Bang Leu, Wei-Hsian Yin, Chau-Chung Wu, Jaw-Wen Chen.
Validation: Wei-Ting Wang, Jaw-Wen Chen.
Writing – original draft: Wei-Ting Wang.
Writing – review & editing: Wei-Ting Wang, Jaw-Wen Chen.

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