ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3748–3759
Published online 15 July 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13513

ORIGINAL RESEARCH ARTICLE

WBC count predicts heart failure in diabetes and coronary artery disease patients: a retrospective cohort study

Atsuhiko Kawabe[1], Takanori Yasu[1]*, Takeshi Morimoto[2], Akihiro Tokushige[3], Shin-ichi Momomura[4], Kenichi Sakakura[4], Koichi Node[5], Taku Inoue[6], Shinichiro Ueda[7] and The CHD Collaborative Investigators[8]

[1]*Department of Cardiovascular Medicine and Nephrology, Dokkyo Medical University Nikko Medical Center, Nikko, Japan;* [2]*Department of Clinical Epidemiology, Hyogo Medical College, Nishinomiya, Japan;* [3]*Department of Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan;* [4]*Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Japan;* [5]*Department of Cardiology and Renal Medicine, Saga University School of Medicine, Saga, Japan;* [6]*Department of Cardiology, Yuaikai Nanbu Hospital, Itoman, Okinawa, Japan;* [7]*Department of Clinical Pharmacology and Therapeutics, University of the Ryukyus, Nishihara, Okinawa, Japan; and* [8]*The CHD Collaborative Investigators are mentioned in the appendix*

Abstract

Aims White blood cell (WBC) count in healthy people is associated with the risk of coronary artery disease (CAD) and mortality. This study aimed to determine whether WBC count predicts heart failure (HF) requiring hospitalization as well as all-cause death, acute myocardial infarction (AMI) and stroke in patients with Type 2 diabetes mellitus and established CAD.

Methods We conducted this retrospective registry study that enrolled consecutive patients with Type 2 diabetes mellitus and CAD based on coronary arteriography records and medical charts at 70 teaching hospitals in Japan from 2005 to 2015. A total of 7608 participants (28.2% women, mean age 68 ± 10 years) were eligible. In the cohort, the median (interquartile range) and mean follow-up durations were 39 (16.5–66.1 months) and 44.3 ± 32.7 months, respectively. The primary outcome was HF requiring hospitalization. The secondary outcomes were AMI, stroke, all-cause death, 3-point major adverse cardiovascular events (MACE) (AMI/stroke/death) and 4-point MACE (AMI/stroke/death/HF requiring hospitalization). Outcomes were reported as cumulative incidences (proportion of patients experiencing an event) and incidence rates (events/100 person-years). The primary and secondary outcomes were assessed using the Kaplan–Meier method and were compared using the log-rank test stratified by the baseline WBC count. The association between the WBC count at baseline and each MACE was assessed using the Cox proportional hazard model and expressed as the hazard ratio (HR) and 95% confidence interval (CI) after adjusting for other well-known risk factors for MACE.

Results During the follow-up, 880 patients were hospitalized owing to HF. The WBC Quartile 4 (≥7700 cells/μL) had significantly lower HF event-free survival rate (log-rank test, $P < 0.001$). The HRs for HF events requiring hospitalization with each WBC quartile compared with the lowest in the first WBC quartile were 1 for Quartile 1 (WBC < 5300 cells/μL), 1.20 (95% CI, 0.96–1.5; $P = 0.1$) for Quartile 2 (5300 ≤ WBC < 6400), 1.34 (95% CI, 1.08–1.67; $P = 0.009$) for Quartile 3 (6400 ≤ WBC < 7700) and 1.62 (95% CI, 1.31–2.00; $P < 0.001$) for Quartile 4 after adjusting for covariates. Similar findings were observed for the risk of AMI and death; however, no significant difference was found for stroke. WBC Quartile 4 patients had a significantly lower 3- or 4-point MACE-free survival rate (log-rank test, $P < 0.0001$).

Conclusions A higher WBC count is a predictor of hospitalization for HF, all-cause death and AMI but not for stroke in patients with concurrent Type 2 diabetes mellitus and established CAD.

Keywords Coronary heart disease; Diabetes mellitus; Heart failure; Major adverse cardiovascular event; Stroke; White blood cell count

Received: 21 November 2020; Revised: 14 May 2021; Accepted: 4 July 2021
**Correspondence to: Takanori Yasu, Department of Cardiovascular Medicine and Nephrology, Dokkyo Medical University Nikko Medical Center, 632 Takatoku, Nikko, Tochigi 321-2593 Japan. Tel: 81-288-76-1515; Fax: 81-288-76-1030. Email: tyasu@dokkyomed.ac.jp*

Introduction

Accumulated experimental data and clinical evidence support the role of chronic inflammation in atherosclerosis and its complications.[1–4] Recent randomized controlled studies[4,5] evaluating the effect of anti-inflammatory medications on cardiovascular outcomes may suggest additional therapeutic strategies. In the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), inhibition of interleukin-1β using injectable monoclonal antibody—canakinumab—resulted in a 15% reduction in cardiovascular events and a 31% reduction in all-cause death as compared with the use of placebo, if the C-reactive protein (CRP) concentration fell below the median in response to the first treatment with canakinumab.[5] The Colchicine Cardiovascular Outcomes Trial (COLCOT) revealed that in patients with recent myocardial infarction, inhibition of inflammation by low-dose colchicine significantly reduced the risk of recurrent cardiovascular events compared with placebo.[6] White blood cell (WBC)-derived inflammatory cytokines such as tumour necrosis factor alpha[1,2] and interleukin 6[7] also have been reported to contribute to the development of heart failure (HF) and coronary artery disease (CAD).

The number of WBCs is a cellular marker of systemic inflammation.[4,8] Higher WBC counts and an increased risk of CAD, stroke and all-cause mortality have been reported in a population of apparently healthy middle-aged women.[9] An increased number of WBCs are also an independent predictor of major adverse cardiovascular event (MACE) after percutaneous coronary intervention (PCI) in a cohort study in the United States and Europe.[10] In addition, WBC counts have been associated with the risk of HF in an occidental population-based study.[11,12] HF is becoming a global epidemic in the ageing population.

However, whether the WBC count is associated with adverse outcomes in a high-risk population of Type 2 diabetes patients with CAD is unknown. The aim of this study was to investigate the prospective association of WBC count with HF requiring hospitalization as well as all-cause death, acute myocardial infarction (AMI) and stroke in consecutively registered patients with Type 2 diabetes and established CAD using a prospective large cohort database in Japan.

Methods

Study design and patients

We conducted a retrospective registry study that enrolled consecutive patients, aged 20 years or older, with concurrent Type 2 diabetes mellitus and CAD based on the coronary arteriography records and medical charts at 70 teaching hospitals in Japan from 2005 to 2015. They were followed through December 2016. CAD in patients with Type 2 diabetes was defined as stenosis of 75% or greater, based on the American Heart Association classification, in at least one major coronary artery by coronary arteriography since January 2005 or a history of PCI, coronary artery bypass grafting (CABG) or acute coronary syndrome (ACS). The diagnosis of Type 2 diabetes was determined based on the criteria of the Japanese Diabetes Society, which are consistent with European Society of Cardiology/European Association for the Study of Diabetes criteria. Patients with CAD who were receiving anti-diabetic treatment were also included. Patients who had an active malignant tumour with a disease-free survival of less than 3 years were excluded. Patients in the acute phase, such as those with ACS or infection, were registered at least 3 months after the onset, at which point the WBC counts were analysed.

Data collection

Patients with concurrent Type 2 diabetes and CAD were defined by investigators and/or trained clinical research coordinators of research sharing facilities. Clinical research coordinators visited shared research facilities and collected experimental data every 6 months. All records of the patients' coronary arteriography that had been performed since January 2005 were screened. At registration and during follow-up, relevant data such as demographic information, smoking status, medical history, results from laboratory tests and drug treatments were collected from the medical records.

Ethics approval

The cohort study was conducted in accordance with the Declaration of Helsinki guidelines and the ethics guidelines for clinical research from the Ministry of Health, Labour and Welfare (Tokyo, Japan). Informed consent was obtained in the form of opt-out in each institute; those who rejected were excluded. The protocol was reviewed and accepted by the ethics committee of the University of the Ryukyus (104 Nishihara, Japan) as the central ethics committee and by each ethics committee where the study was conducted, including Dokkyo Medical University (Nikko 30005).

Outcome measures

The primary outcome was HF requiring hospitalization. The secondary outcomes were AMI, stroke, all-cause death, 3-point MACE (AMI/stroke/death) and 4-point MACE (AMI/stroke/death/HF requiring hospitalization). Information regarding outcomes was derived from medical records by clinical research coordinators. The diagnosis was confirmed

by physicians in charge or investigators. Hospitalization due to HF was defined as hospitalization for worsening HF requiring intravenous treatment. In our study, HF was principally diagnosed according to the diagnostic criteria of the Framingham Heart Study[13] and based on the information in the medical records (i.e. responses to treatments with diuretics and vasodilators). Events were judged by cardiologists and/or general physicians who were not in charge of patients. All events were reported to the study office and subsequently adjudicated by the event evaluation committee.

Statistical analysis

The analysis of each outcome was categorized into quartiles, based on the baseline WBC count. A statistical significance of a potential association between the WBC quartiles and risk factors was appropriately compared using analysis of variance or the Kruskal–Wallis test for continuous variables and using the chi-square test for categorical variables. Outcomes were reported as cumulative incidences (proportion of patients experiencing an event) and incidence rates (events/100 person-years). The primary and secondary outcomes were assessed using the Kaplan–Meier method and compared using the log-rank test stratified by the baseline WBC count. The association of the WBC count at baseline and each MACE was estimated using the Cox proportional hazard model and expressed as the hazard ratio (HR) and 95% confidence interval (CI). Adjusters for multivariate analysis were age; sex; body mass index; ejection fraction at the time of registration; estimated glomerular filtration rate; end-stage renal failure on maintenance dialysis; smoking habit; medical history of PCI, CABG, cardiac infarction, stroke; the use of statins, metformin, aspirin, beta blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers; Hb A1c; low-density lipoprotein cholesterol level; and systolic blood pressure. Patients with missing values were excluded from all multivariable analyses. Data were statistically analysed using JMP 14.0J software (SAS Institute, Cary, NC, USA) and R (Version 4.0.2; The R Foundation for Statistical Computing, Vienna, Austria). Two-tailed $P < 0.05$ was considered significant.

Results

Among 7785 CAD cohort participants, 7608 had their WBC count measured at baseline and were eligible for this analysis. We excluded patients with missing WBC count data at the time of enrolment (n = 177). The demographic characteristics of the participants based on the WBC quartile are shown in *Table 1*. The median WBC count, top 25th percentile of WBC count and 75th percentile of WBC count were 6400, 5300 and 7700 cells/μL, respectively. Differences among the WBC quartiles were significant ($P < 0.05$) for age, sex, body mass index, left ventricular ejection fraction, current smoker, history of hypertension, history of malignancy, history of PCI, duration of diabetes mellitus, baseline triglyceride, baseline high-density lipoprotein cholesterol, baseline low-density lipoprotein cholesterol, baseline HbA1c, use of insulin, medication of metformin, medication of angiotensin-converting enzyme inhibitors and medication of diuretics. Current smoker status, mean values of low-density lipoprotein cholesterol and haemoglobin A1c and use of insulin and metformin were the highest in the fourth WBC quartile (≥7700 cells/μL). In contrast, age, history of malignancy, post-PCI and high-density lipoprotein cholesterol level were the lowest in the fourth WBC quartile.

In the cohort, the median (interquartile range) and mean follow-up were 39 (16.5–66.1 months) and 44.3 ± 32.7 months, respectively. During the follow-up, 880 patients were hospitalized owing to HF. A comparison of baseline characteristics between patients with or without HF requiring hospitalization is shown in *Table S1*. Age, WBC count, duration of diabetes, low-density lipoprotein cholesterol, haemoglobin A1c and estimated glomerular filtration rate were significantly higher in the HF group. Conversely, body mass index, left ventricular ejection fraction and high-density lipoprotein cholesterol were significantly lower in the HF group. Male sex, history of hypertension, stroke, AMI, malignancy, CABG and end-stage renal failure on maintenance dialysis were more common in the HF group. The use of statins was less common in the HF group, whereas the use of insulin, beta blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and diuretics was more common.

A graphical distribution of WBC did not show normal distribution owing to outliers (WBC > mean + 2SD) according to Lilliefors test ($P < 0.01$) (*Figure S1*). First, we showed HR and the corresponding P-value for WBC as the continuous variables (for an increment of +500 cells/μL) in the subgroup (n = 7277) excluding patients who showed baseline WBC > 10 600 (mean+2SD) (*Table S2*). HR increased by 1.04 (95% CI: 1.02–1.06; $P < 0.001$) for every 500-cell/μL increase in the WBC count. Considering the above data and the results of Cochran–Armitage trend test (*Table S3*), the WBC count with its continuous variables emerged as a significant predictor of HF requiring hospitalization. Of note, patients with the highest values in the fourth WBC quartile had a significantly lower HF event-free survival rate (*Figure 1A*, log-rank test, $P < 0.001$). The adjusted HRs for HF events requiring hospitalization with each WBC quartile compared with the lowest in the fourth WBC quartile (WBC < 5300 cells/μL) were 1 for Quartile 1 (WBC < 5300 cells/μL), 1.20 (95% CI, 0.96–1.5; P = 0.1) for Quartile 2 (5300 ≤ WBC < 6400), 1.34 (95% CI, 0.90–2.16; P = 0.14) for Quartile 3 (6400 ≤ WBC < 7700) and 1.62 (95% CI, 1.04–2.44; $P < 0.034$) for Quartile 4 (WBC ≥ 7700 cells/μL) after adjusting for covariates (*Figure 1B* and *Table 2A*). The incidence rate of HF hospitalization

Table 1 Clinical characteristics of the study participants based on the white blood cell count quartile

	All patients (n = 7608)	WBC < 5300 (n = 1821)	WBC 5300–6399 (n = 1979)	WBC 6400–7699 (n = 1830)	WBC ≥ 7700 (n = 1978)	P-value
Age, y	68 ± 10	69 ± 9	68 ± 10	68 ± 10	66 ± 11	<0.001
Male, n (%)	5466 (71.8)	1246 (68.4)	1448 (73.2)	1330 (72.7)	1442 (72.9)	0.003
BMI, kg/m^2	25.3 ± 4	24.6 ± 3.7	25.3 ± 3.7	25.6 ± 4.1	25.5 ± 4.1	<0.001
LVEF, %	59.9 ± 13.6	60.6 ± 13.1	60.8 ± 13.3	60.0 ± 13.2	58.2 ± 14.6	<0.001
Current smoker, %	1,635 (21.5)	212 (11.6)	365 (18.4)	438 (23.9)	620 (31.3)	<0.001
Ex-smoker, %	2,126 (27.9)	515 (28.3)	546 (27.6)	541 (29.6)	524 (26.5)	0.197
Never smoker, %	3847 (50.6)	1094 (60.1)	1068 (54.0)	851 (46.5)	834 (42.2)	<0.001
WBC count, cells/μL	6704 ± 2065	4477 ± 603	5821 ± 310	6956 ± 371	9405 ± 1772	<0.001
History of hypertension, n (%)	6281 (82.6)	1453 (79.8)	1652 (83.5)	1514 (82.7)	1662 (84)	0.003
History of stroke, n (%)	1277 (16.8)	324 (17.8)	329 (16.6)	284 (15.5)	340 (17.2)	0.3
History of myocardial infarction, n (%)	2670 (35.1)	623 (34.2)	721 (36.4)	640 (35)	686 (34.7)	0.51
History of malignancy, n (%)	360 (4.7)	107 (5.9)	95 (4.8)	87 (4.8)	71 (3.6)	0.01
History of PCI, n (%)	3413 (44.9)	904 (49.6)	898 (45.4)	791 (43.2)	820 (41.5)	<0.001
History of CABG, n (%)	858 (11.3)	228 (12.5)	227 (11.5)	199 (10.9)	204 (10.3)	0.17
Duration of diabetes, median (IQR), y	8 (2–16)	9 (2–17)	8 (2–16)	7 (2–15)	7 (2–15)	<0.001
Triglycerides, median (IQR), mg/dL	131 (91–193)	114 (79–165)	132 (93–193)	142 (97–208)	138 (97–207)	<0.001
HDL-C, mg/dL	47.2 ± 13.1	49.8 ± 14.4	47.4 ± 12.3	46.4 ± 12.5	45.1 ± 12.9	<0.001
LDL-C, mg/dL	103.7 ± 33.0	100.2 ± 31.8	103.5 ± 32.1	103.3 ± 32.1	107.6 ± 35.3	<0.001
Systolic blood pressure, mmHg	134 ± 20	133 ± 19	134 ± 21	135 ± 20	134 ± 21	0.24
Haemoglobin A1c, %	7.3 ± 1.3	7 ± 1.3	7.2 ± 1.3	7.3 ± 1.4	7.4 ± 1.4	<0.001
eGFR, mL/min/1.73 m^2	59.3 ± 26.6	58.6 ± 26.3	60.4 ± 24.9	59.5 ± 26.3	58.6 ± 28.6	0.12
End-stage renal failure on maintenance dialysis, n (%)	774 (10.2)	217 (11.9)	174 (8.8)	170 (9.3)	213 (10.8)	0.0058
Medication of statin, n (%)	4850 (63.7)	1127 (61.9)	1290 (65.2)	1188 (64.9)	1245 (62.9)	0.11
Insulin, n (%)	1510 (19.8)	306 (16.8)	365 (18.4)	386 (21.1)	453 (22.9)	<0.001
Metformin, n (%)	1251 (16.4)	251 (13.8)	309 (15.6)	319 (17.4)	372 (18.8)	<0.001
Aspirin, n (%)	6716 (88.3)	1602 (88)	1775 (89.7)	1612 (88.1)	1727 (87.3)	0.12
Beta blocker, n (%)	2918 (38.4)	680 (37.3)	763 (38.6)	692 (37.8)	783 (39.6)	0.51
ARB, n (%)	3329 (43.8)	772 (42.4)	894 (45.2)	808 (44.2)	855 (43.2)	0.34
ACEi, n (%)	1748 (23.0)	385 (21.1)	442 (22.3)	431 (23.6)	490 (24.8)	0.049
Diuretics, n (%)	2110 (27.7)	428 (23.5)	498 (25.2)	527 (28.8)	657 (33.2)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; WBC, white blood cell; WBCQG, white blood cell quartile group.
WBCQG1 < 5300, 5300 ≤ WBCQ4G2 < 6400, 6400 ≤ WBCQ4G3 < 7700, WBCQ4G4 ≥ 7700

Figure 1 (A) Kaplan–Meier curves for heart failure hospitalization event-free survival rate stratified by the baseline white blood cell (WBC) count. Patients in the WBC Quartile 4 (WBC ≥ 7700 cells/μL) had a significantly lower cumulative survival rate without heart failure hospitalization events, compared with patients in the WBC Quartile 1 (WBC < 5300 cells/μL, $P < 0.0001$). (B) Relative hazard ratio of heart failure hospitalization event during the follow-up period adjusted for confounders in a multivariate Cox-regression model, compared with the lowest quartile WBC count of <5300 cells/μL. WBCQG = white blood cell quartile group. WBCQG1 = (WBC counts < 5300 cells/μL), WBCQG2 = (5300 ≤ WBC < 6400), WBCQG3 = (6400 ≤ WBC < 7700), WBCQG4 = (≥7700 cells/μL).

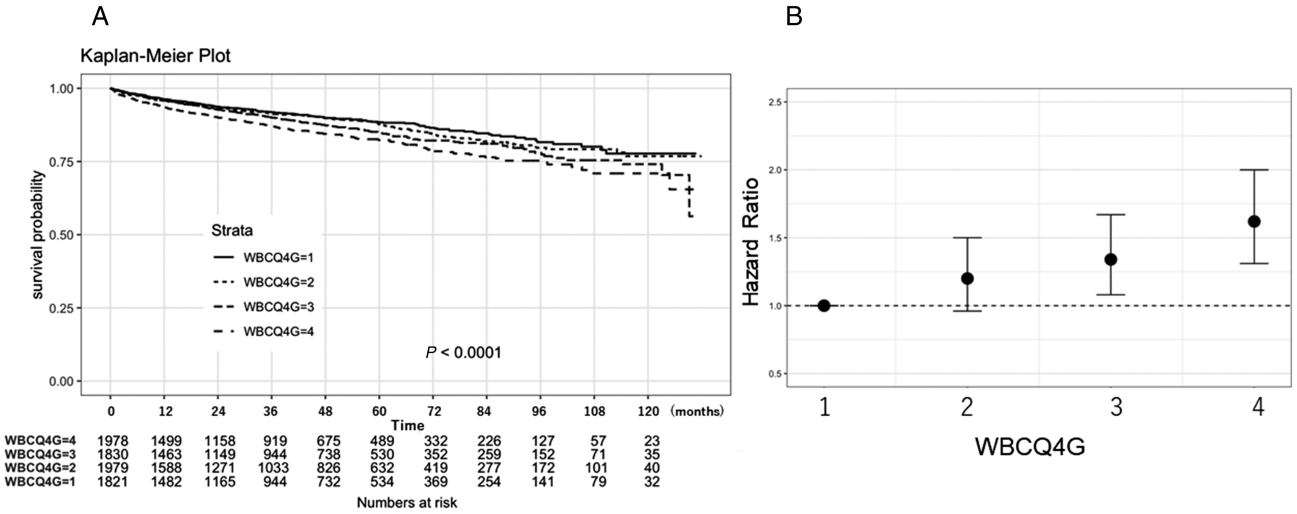


Table 2A Relative hazard of heart failure event requiring hospitalization, adjusted for confounders in a multivariate Cox-regression model, compared with the lowest quartile white blood cell count of <5300 cells/μL

Variables	HR	95% confidence interval		*P*-value
		Lower	Upper	
5300 ≤ WBC < 6400	1.2	0.96	1.5	0.1
6400 ≤ WBC < 7700	1.34	1.08	1.67	0.009
7700 ≤ WBC	1.62	1.31	2	<0.001
Age ≥ 65	1.5	1.26	1.79	<0.001
Male	0.79	0.66	0.94	0.007
BMI ≤ 25	1.18	1.02	1.37	0.027
EF ≥ 40	0.32	0.26	0.38	<0.001
eGFR ≥ 60	0.47	0.4	0.55	<0.001
End-stage renal failure on maintenance dialysis	1.36	1.07	1.72	0.011
Current smoker	1.1	0.89	1.35	0.38
Ex-smoker	1.2	1.01	1.43	0.043
History of malignancy	1.21	0.9	1.62	0.21
History of stroke	1.36	1.14	1.62	<0.001
History of AMI	1.13	0.96	1.34	0.15
History of PCI	0.92	0.78	1.08	0.31
History of CABG	1.53	1.26	1.85	<0.001
Medication of ACEi	1.37	1.15	1.63	<0.001
ARB	1.21	1.04	1.42	0.015
β-Blocker	1.2	1.03	1.39	0.018
Biguanide	1.18	0.97	1.43	0.1
Aspirin	0.78	0.64	0.96	0.017
Statin	0.68	0.59	0.79	<0.001
HbA1c ≥ 7.0	1.29	1.11	1.5	<0.001
LDL-C ≥ 100	0.91	0.79	1.06	0.23
SBP ≥ 140	1.03	0.88	1.19	0.75

ACEi, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; WBC, white blood cell.

DOI: 10.1002/ehf2.13513

was 3.28/100 person-years overall with 2.63/100 person-years in WBC Quartile 1 patients, 2.89/100 person-years in WBC Quartile 2 patients, 3.35/100 person-years in WBC Quartile 3 patients and 4.27/100 person-years in WBC Quartile 4 patients (*Table 3A*). A sensitivity analysis of the association between WBC counts and HF requiring hospitalization in a subgroup (n = 6834) that excluded maintenance dialysis patients (*Figure S2* and *Table S4*) showed consistent findings. The incidence rate of HF (100 person-years) in patients with a clear history regarding HF was similar to that of the overall cohort (*Tables 2B* and *3B*).

During follow-up, 232 patients had a new AMI episode, which included 182 patients with non-fatal AMI. Kaplan–Meier curves of AMI-free survival in relation to quartiles of WBC count are shown in *Figure 2A*. WBC Quartile 4 patients had a significantly lower AMI-free survival rate (log-rank test, P = 0.023). The adjusted HR for AMI with each WBC quartile, compared with the WBC Quartile 1, was 1.35 (95% CI, 0.87–2.07; P = 0.18) for WBC Quartile 2, 1.39 (95% CI, 0.90–2.06; P = 0.14) for WBC Quartile 3 and 1.59 (95% CI, 1.04–2.44; P = 0.034) for WBC Quartile 4 after adjusting for covariates (*Figure 3A* and *Table S5a*). The incidence rate of

Table 2B Relative hazard of heart failure events requiring hospitalization, adjusted for confounders in a multivariate Cox-regression model, compared with the lowest quartile white blood cell count of <5300 cells/μL in the subgroup with a clear history of heart failure (n = 4908)

Variables	HR	95% confidence interval		P-value
		Lower	Upper	
5300 ≤ WBC < 6400	1.17	0.91	1.51	0.21
6400 ≤ WBC < 7700	1.45	1.13	1.85	0.003
7700 ≤ WBC	1.54	1.21	1.95	<0.001
Age ≥ 65	1.55	1.27	1.89	<0.001
Male	0.81	0.67	0.98	0.03
BMI ≤ 25	1.22	1.04	1.44	0.016
EF ≥ 40	0.40	0.32	0.50	<0.001
eGFR ≥ 60	0.50	0.42	0.61	<0.001
HD	1.28	0.98	1.68	0.07
Current smoker	1.26	1.00	1.60	0.053
Past smoker	1.15	0.95	1.40	0.15
History of malignancy	1.23	0.90	1.70	0.20
History of stroke	1.40	1.16	1.69	<0.001
History of AMI	1.13	0.93	1.37	0.23
History of PCI	0.96	0.80	1.15	0.67
History of CABG	1.52	1.23	1.89	<0.001
ACEi	1.19	0.98	1.44	0.08
ARB	1.29	1.09	1.54	0.004
β-Blocker	1.07	0.90	1.27	0.45
Biguanide	1.17	0.94	1.45	0.15
Aspirin	0.82	0.65	1.04	0.10
Statin	0.70	0.59	0.83	<0.001
HbA1c ≥ 7.0	1.20	1.01	1.41	0.04
LDL ≥ 100	0.94	0.80	1.11	0.47
SBP ≥ 140	1.05	0.89	1.24	0.58
HF History	2.45	2.02	2.97	<0.001

ACE, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin-II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HD, haemodialysis; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; WBC, white blood cell.

Table 3A Incidence rate of each cardiovascular adverse event (100 person-years) and event number

	All	WBC < 5300	5300 ≤ WBC < 6400	6400 ≤ WBC < 7700	7700 ≤ WBC
	n = 7608	n = 1821	n = 1979	n = 1830	n = 1978
Incidence rate of hospitalization for HF	3.28 (880)	2.63	2.89	3.35	4.27
Incidence rate of AMI	0.83 (233)	0.6	0.77	0.85	1.07
Incidence rate of stroke	1.32 (377)	1.27	1.33	1.19	1.52
Incidence rate of all-cause death	3.47 (1002)	3.1	2.88	3.26	4.69
Incidence rate of 3-point MACE (AMI/stroke/death)	5.05 (1396)	4.44	4.39	4.79	6.62
Incidence rate of 4-point MACE (death/AMI/stroke/HF)	7.17 (1857)	6.08	6.28	6.94	9.56

AMI, acute myocardial infarction; HF, heart failure; MACE, major adverse cardiovascular event; WBC, white blood cell.

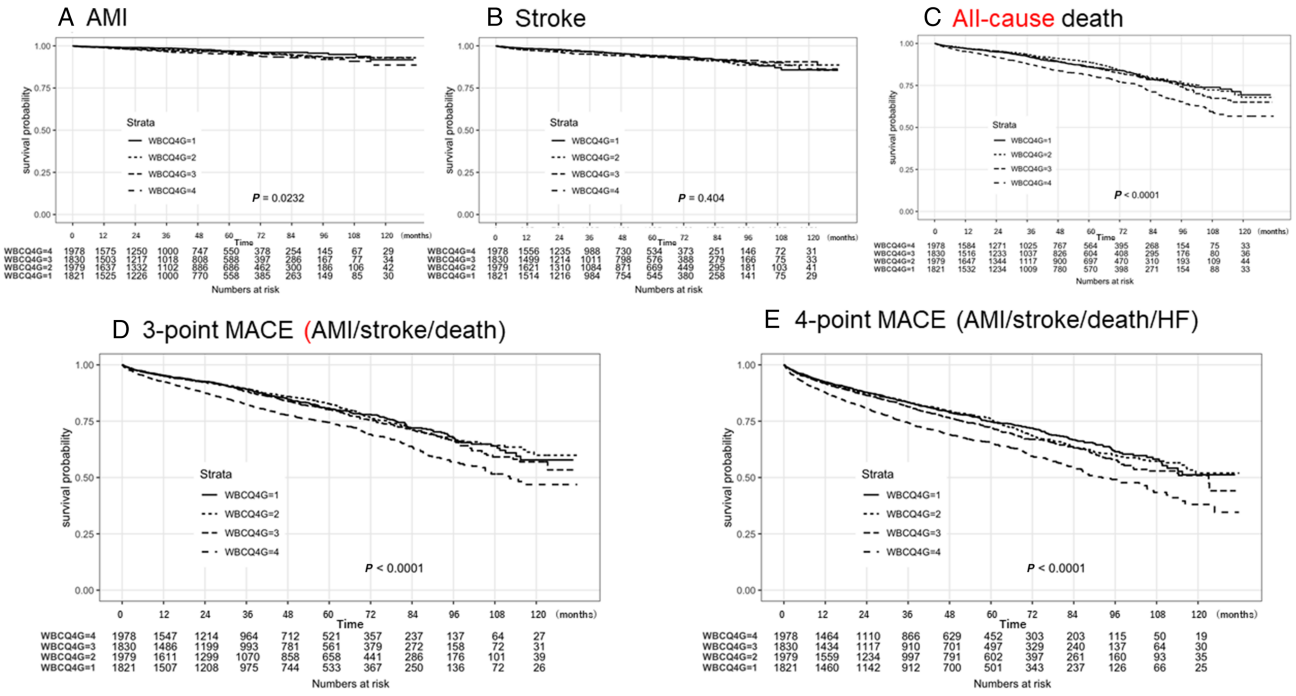
DOI: 10.1002/ehf2.13513

Table 3B Incidence rate of heart failure (100 person-years) in patients with a clear history of heart failure ($n = 4908$)

	All	WBC < 5300	5300 ≤ WBC <	6400 6400 ≤ WBC < 7700	7700 ≤ WBC
	$n = 4908$	$n = 1220$	$n = 1225$	$n = 1223$	$n = 1240$
Incidence rate of hospitalization for HF	3.03	2.28	2.65	3.16	4.02

HF, heart failure.

Figure 2 Cumulative incidences of the secondary outcomes based on the baseline WBC count at registration. Kaplan–Meier curves of (A) fatal and non-fatal AMI, (B) fatal and non-fatal stroke events, (C) all-cause death, (D) 3-point MACE (AMI/stroke/death) and (E) 4-point MACE (AMI/stroke/death/heart failure hospitalization event) stratified by the baseline WBC count.AMI, acute myocardial infarction; HF, heart failure; MACE, major adverse cardiovascular event; WBC, white blood cell; WBCQG = white blood cell quartile group. WBCQG1 = (WBC counts < 5300 cells/μL), WBCQG2 = (5300 ≤ WBC < 6400), WBCQG3 = (6400 ≤ WBC < 7700), WBCQG4 = (≥7700 cells/μL).

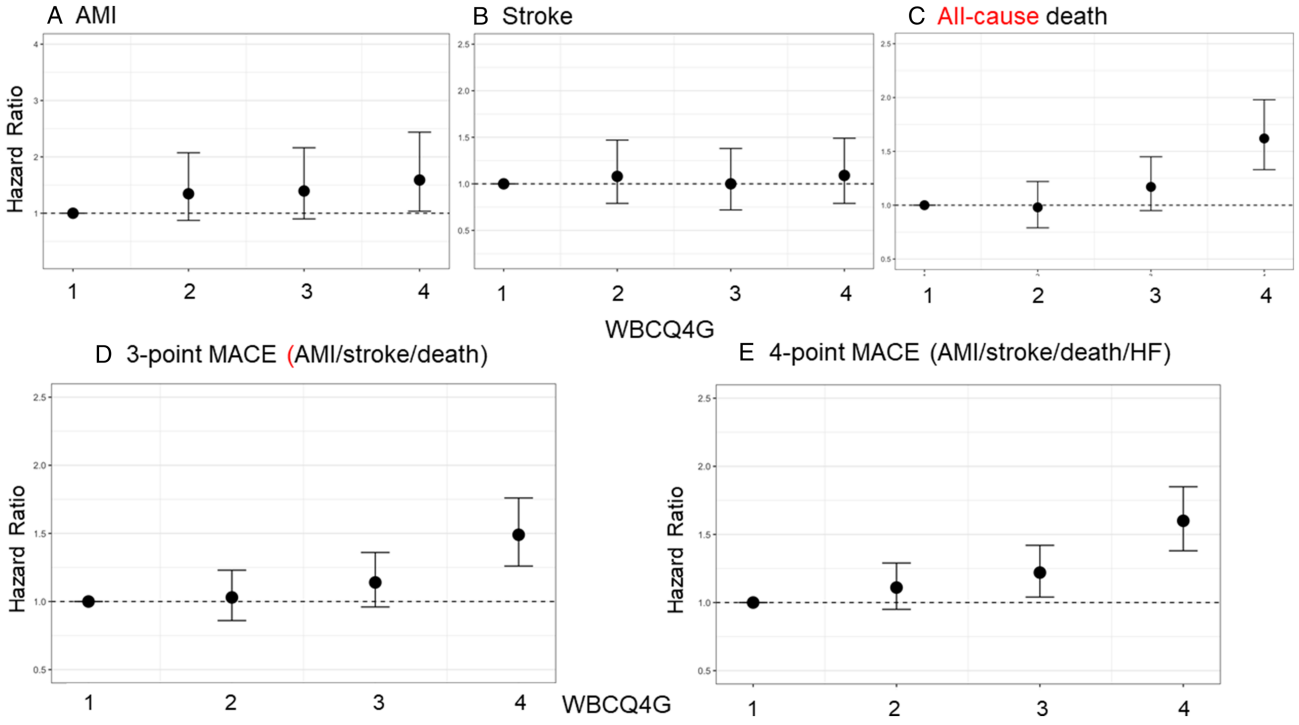


AMI in patients of WBC Quartiles 1–4 was 0.6/100 person-years, 0.77/100 person-years, 0.85/100 person-years and 1.07/100 person-years, respectively, and the overall incidence rate was 0.83/100 person-years (*Table 3A*).

During follow-up, 362 patients had a new stroke episode, which included 326 patients with non-fatal stroke. No significant association was observed between the WBC count and stroke events (*Figures 2B* and *3B* and *Tables 3A* and *S5b*). During follow-up, 1002 patients died. *Figure 2C* shows the all-cause death based on the Kaplan–Meier curves. WBC Quartile 1 patients had a significantly lower death-free rate (log-rank test, $P < 0.001$). The adjusted death HR for WBC Quartile 4, compared with WBC Quartile 1, was 1.62 (95% CI, 1.33–1.98; $P < 0.001$) (*Figure 3C* and *Table S5c*). Incidence rate of death in patients of WBC Quartiles 1–4 was 3.1/100 person-years, 2.88/100 person-years, 3.26/100 person-years and 4.69/100 person-years, respectively, and the overall incidence rate was 3.47/100 person-years (*Table 3A*).

The Kaplan–Meier curves of 3-point MACE (i.e. AMI, stroke and all-cause death)-free survival and 4-point MACE (i.e. AMI, stroke, all-cause death and HF hospitalization)-free survival in relation to the quartiles of WBC count are shown in *Figure 2* and *2E*. WBC Quartile 4 patients had a significantly lower composite-free survival rate (log-rank test, $P < 0.0001$). The adjusted HRs for 3-point MACE and 4-point MACE composite outcomes with each WBC quartile compared with the WBC Quartile 1 are shown in *Figure 3D* and *3E* and *Tables S5d* and *S5e*. The incidence rates of 3-point MACE and 4-point MACE for each WBC quartile are shown in *Table 3A*.

Figure 3 Adjusted hazard ratio of each secondary outcome: (A) AMI, (B) stroke, (C) all-cause death, (D) 3-point MACE (AMI/stroke/death) and (E) 4-point MACE (AMI/stroke/death/heart failure hospitalization event) stratified by the baseline WBC count. AMI, acute myocardial infarction; HF, heart failure; MACE, major adverse cardiovascular event; WBC, white blood cell.



Discussion

In this study, a multi-institute cohort database in Japan was used to determine whether WBC count could predict cardiovascular outcome, including HF, mortality, AMI and stroke, in patients with Type 2 diabetes and established CAD. We found an incremental association between the baseline WBC count and the primary cardiovascular outcome of HF event requiring hospitalization, even in the subgroup excluding maintenance dialysis patients. Similarly, an association with secondary outcomes, such as AMI and mortality, but not stroke, in consecutively registered patients with Type 2 diabetes and established CAD was observed. Our data aligned with the findings of previous reports in population-based cohort studies,[11,12,14,15] a postmenopausal women cohort study,[9] and in patients with established CAD after PCI[10] and before CABG surgery.[16] To the best of our knowledge, this study is the first to demonstrate that the WBC count is a strong predictor of the incidence of hospitalization due to HF in a dose–response manner in patients with concurrent Type 2 diabetes and established CAD.

Our patient cohort included 10% with end-stage renal failure on maintenance dialysis. According to the annual survey of the Japanese Society for Dialysis Therapy Renal Data Registry, 339 841 patients (2688 patients per million population) with end-stage renal failure were under maintenance dialysis in 2018.[17] Diabetic nephropathy was the most common primary disease among the patients on dialysis (39.0%), followed by chronic glomerulonephritis (26.8%) and nephrosclerosis (10.8%).[17] Accordingly, our cohort represents a real-world population from Japan. A sensitivity analysis of WBC counts' association with HF requiring hospitalization in a subgroup excluding maintenance dialysis patients also showed consistent findings.

Engström et al.[12] measured WBC counts of 16 940 men from the general population who had a mean age of 44 years and no history of myocardial infarction or stroke. During 23 years of follow-up, 436 men were hospitalized due to HF. The adjusted HR (95% CI) for HF hospitalization was 1.00 as the reference, 1.26 (0.93–1.7), 1.24 (0.91–1.7) and 1.73 (1.3–2.3) for men in the first, second, third and fourth WBC count quartiles, respectively. An increase in the WBC count and activation of WBCs have key roles in organ injury induced by atherosclerotic disease, diabetes mellitus or increased free fatty acid associated with diabetes via microcirculatory dysfunction.[18–21] Due to the larger volume and higher cellular viscosity, each WBC is equivalent to approximately 700 erythrocytes in its tendency to block capillary channels.[22] The rheology of leukocytes has significant implications on their functional behaviour such as flow-through

capillaries and interactions with endothelial cells.[23,24] Cohort studies have shown that blood viscosity is a strong predictor of cardiovascular events,[25] particularly in patients with diabetes.[26,27] Ates et al.[28] reported that WBC counts were associated with the presence, severity and extent of coronary atherosclerosis, as evaluated with multislice computed tomographic coronary angiography, among 817 patients with suspected CAD.

In contrast to HF requiring hospitalization, AMI or death, no significant association was shown between the WBC count and non-fatal stroke events. This result is consistent with the findings of a population-based cohort study by Li et al.[15] An explanation of the different relationships between WBC counts and the incidences of stroke and other events remains unclear. Another risk factor other than the WBC count may more strongly contribute to the incidence of stroke. A population-based study by Gillum et al.[29] demonstrated that white men with a WBC count $>$ 8100 cells/mm^3 had a 39% increase in age-adjusted stroke incidence, compared with white men with a WBC count of $<$6600 cells/mm^3. However, controlling for cigarette smoking reduced the association and rendered it statistically insignificant. No significant associations of the WBC count with stroke incidence were observed in white women or in black women and men. In white men, an elevated WBC count may be a mediator of the cardiovascular effects of smoking, an indicator of smoking exposure or both. In our study, 1635 (21.5%) patients were current smokers.

The prevalence of Type 2 diabetes mellitus, another condition of low-grade inflammation as well as CAD, is increasing throughout the world. The number of affected individuals is expected to be approximately 640 million in the year 2040.[30] Patients with diabetes mellitus have an approximately two times greater risk of developing macroangiopathy (e.g. CAD and stroke)[31] and two- to fourfold risk of HF,[32] compared with individuals without diabetes. Multivariable HF risk models showed diabetes mellitus as an independent risk factor for death.[33] A meta-analysis reported that diabetes mellitus is associated with the risk of HF.[34,35] The risk of hospitalization for HF is up to 50% higher in patients with diabetes mellitus than in those without it.[36,37] Patients with diabetes mellitus and HF have worse QOL than patients with HF alone.[38,39] Our data suggest that WBC count helps stratify the risk of HF in patients with diabetes mellitus and CAD. The goal of diabetes mellitus treatment is to prevent complications from developing or worsening, to ensure the same quality of life as that of non-diabetic individuals and to maximize life expectancy. The present results may be useful to approach the goal.

Leukocyte-associated inflammation has been demonstrated as the next target for residual cardiovascular event risk by pharmacological intervention in recent randomized controlled trials.[4–6] In addition, canakinumab, an IL-1 beta-neutralizing antibody, is used to treat patients with stable atherosclerosis, a history of prior myocardial infarction and a CRP level $>$ 2 mg/L.[5] Canakinumab resulted in a 15% reduction in cardiovascular events and a 31% reduction in all-cause death if the CRP level decreased below the median in response to the first treatment of canakinumab. Colchicine has potent anti-inflammatory properties and has been used for gout attack, familial Mediterranean fever and pericarditis. Solomon et al.[40] have reported beneficial effects of colchicine on the risk of cardiovascular events and mortality among patients with gout in a cohort study. Colchicine also has been reported to improve survival, left ventricular remodelling and chronic cardiac function in AMI mice model.[41] Moreover, the COLCOT trial showed that colchicine was effective in preventing MACE after AMI.[6] In fact, colchicine was associated with an absolute reduction of 1.6% in the primary endpoint of MACE at a median of 22.6 months.[6]

Our study had several limitations. First, the findings of our retrospective cohort study could be limited by unknown confounding factors. Second, a cohort study based on data obtained from the medical records of patients visiting for routine clinical practice has been intentionally and systematically not been collected for research and therefore has several inherent limitations (e.g. lack of detailed description of medical history and events and missing data). Third, we measured the patients' WBC count only at the baseline. Fourth, we did not collect data regarding left ventricular ejection fraction at the hospitalization for HF.

Conclusions

A higher WBC count is a predictor of hospitalization for HF, all-cause death and AMI but not for stroke in patients with Type 2 diabetes mellitus and established CAD. WBC count is proven to be a less expensive and readily available surrogate marker for secondary prevention of cardiovascular events in such a high-risk population. Further research is needed to evaluate whether high WBC counts can predict adverse clinical outcomes such as HF and AMI in other populations.

Acknowledgements

The authors thank K. Yoshizawa for her administrative assistance and Editage (www.editage.com) for English language editing.

Conflict of interest

Dr. Yasu reports receiving grant support and lecture fees from AstraZeneca K.K., Ono Pharmaceutical Co., Ltd., and Kowa Co., Ltd., and grant support from MTG Co., Ltd., lecture fees from

Actelion Pharmaceuticals Ltd, Sanofi S.A., Daiichi Sankyo Co., Ltd., and Takeda Pharmaceutical Co. Ltd.; Dr. Morimoto reports receiving lecture fees from Daiichi Sankyo Co., Ltd., Japan Lifeline Co., Ltd., Kowa Co., Ltd., and Toray Industries, Inc., and lecture fees from Bristol-Myers Squibb Co., and Kowa Co., Ltd.; Dr. Tokushige reports receiving lecture fees from Pfizer Japan Inc., Daiichi Sankyo Co., Ltd., Kowa Co., Ltd., and Ono Pharmaceutical Co., Ltd.; Dr. Sakakura reports receiving advisory fees and lecture fees from Boston Scientific and lecture fees from Abbott Vascular Japan Co., Ltd., Medtronic Japan Co., Ltd., Terumo Japan Co., Ltd., Kaneka Japan Co., Ltd., Daiichi Sankyo Co., Ltd., and Kowa Co., Ltd.; Dr. Node reports receiving grant support and lecture fees from Astellas Pharma Inc., Bayer Yakuhin, Ltd., Boehringer Ingelheim Japan, Daiichi Sankyo Healthcare Co., Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corporation, Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd., grant support from Amgen Inc., Astellas BioPharma K.K., Asahi Kasei Corporation, Bristol-Myers Squibb, Ono Pharmaceutical Co., Ltd., Kowa Co., Ltd., Lifeline Co., Ltd., Novartis Pharma K. K, Sanofi K.K., and Terumo Corporation, and lecture fees from AstraZeneca K.K., Kowa Co., Ltd., MSD K.K., Novo Nordisk Pharma Ltd.; Dr Inoue reports receiving lecture fees from Bristol-Myers Squibb, Bayer Yakuhin, Ltd., Boehringer Ingelheim Japan, Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Otsuka Pharmaceutical Co., Ltd.; Dr. Ueda reports receiving grant support and lecture fees from Kowa Co., Ltd., grant support from Bristol-Myers Squibb and Bayer Yakuhin, Ltd., and lecture fees from Taiho Pharmaceutical Co., Ltd.

Funding

This work was supported by Grants-in-Aid from the Ministry of Health, Labour and Welfare of Japan (013 to SU); Japan Agency for Medical Research and Development [171k0201068h001, 181k0201068h002, 191k0201068h003 and 201k0201068h004 to SU]; and the Vehicle Racing Commemorative Foundation (to SM and TY).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of baseline characteristics according to presence or absence of heart failure requiring hospitalisation.
Table S2. Hazard ratio for heart failure requiring hospitalisation in the sub-group excluding patients who showed baseline WBC more than 10,600 (mean+2SD) adjusted for confounders in a multivariate Cox-regression model (n = 7,277).
Table S3. Cochran-Armitage trend test.
Table S4. Hazard ratio for heart failure requiring hospitalisation in the sub-group excluding patients on maintenance dialysis (n = 6,834), adjusted for confounders in a multivariate Cox-regression model, compared to the lowest quartile white blood cell count of <5,300 cells/μL.
Table S5a. Hazard ratio for acute myocardial infarction, adjusted for confounders in a multivariate Cox-regression model, compared to the lowest quartile white blood cell count of <5300 cells/μL.
Table S5b. Hazard ratio for stroke, adjusted for confounders in a multivariate Cox-regression model, compared to the lowest quartile white blood cell count of <5,300 cells/μL.
Table S5c. Hazard ratio for all-cause death, adjusted for confounders in a multivariate Cox-regression model, compared to the lowest quartile white blood cell count of <5300 cells/μL.
Table S5d. Hazard ratio for the 3-point major adverse cardiovascular events (acute myocardial infarction, stroke, death), adjusted for confounders in a multivariate Cox-regression model, and compared to the lowest quartile white blood cell count of <5,300 cells/μL.
Table S5e. Hazard ratio for the 4-point major adverse cardiovascular events (acute myocardial infarction, stroke, death, heart failure event requiring hospitalisation), adjusted for confounders in a multivariate Cox-regression model, and compared to the lowest quartile white blood cell count of <5,300 cells/μL.

References

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352**: 1685–1695.
2. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990; **323**: 236–241.
3. Ferrari R, Bachetti T, Confortini R, Opasich C, Febo O, Corti A, Cassani G, Visioli O. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. *Circulation* 1995; **92**: 1479–1486.
4. Bäck M, Hansson GK. Anti-inflammatory therapies for atherosclerosis. *Nat Rev Cardiol* 2015; **12**: 199–211.
5. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377**: 1119–1131.

6. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; **381**: 2497–2505.
7. Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, Mabuchi N, Sawaki M, Kinoshita M. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998; **31**: 391–398.
8. Nahrendorf M. Myeloid cell contributions to cardiovascular health and disease. *Nat Med* 2018; **24**: 711–720.
9. Margolis KL, Manson JE, Greenland P, Rodabough RJ, Bray PF, Safford M, Grimm RH Jr, Howard BV, Assaf AR, Prentice R, Women's Health Initiative Research Group. Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the women's health initiative observational study. *Arch Intern Med* 2005; **165**: 500–508.
10. Shah B, Baber U, Pocock SJ, Krucoff MW, Ariti C, Gibson CM, Steg PG, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Iakovou I, Dangas G, Aquino MB, Sartori S, Chieffo A, Moliterno DJ, Colombo A, Mehran R. White blood cell count and major adverse cardiovascular events after percutaneous coronary intervention in the contemporary era: insights from the PARIS study (patterns of non-adherence to anti-platelet regimens in stented patients registry). *Circ Cardiovasc Interv* 2017; **10**: e004981.
11. Pfister R, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Differential white blood cell count and incident heart failure in men and women in the EPIC-Norfolk study. *Eur Heart J* 2012; **33**: 523–530.
12. Engström G, Melander O, Hedblad B. Leukocyte count and incidence of hospitalizations due to heart failure. *Circ Heart Fail* 2009; **2**: 217–222.
13. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham heart study subjects. *Circulation* 1993; **88**: 107–115.
14. Brown DW, Giles WH, Croft JB. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. *J Clin Epidemiol* 2001; **54**: 316–322.
15. Li C, Engström G, Hedblad B. Leukocyte count is associated with incidence of coronary events, but not with stroke: a prospective cohort study. *Atherosclerosis* 2010; **209**: 545–550.
16. Newall N, Grayson AD, Oo AY, Palmer ND, Dihmis WC, Rashid A, Stables RH. Preoperative white blood cell count is independently associated with higher perioperative cardiac enzyme release and increased 1-year mortality after coronary artery bypass grafting. *Ann Thorac Surg* 2006; **81**: 583–589.
17. Nitta K, Goto S, Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, Nakai S, Atsushi Wada A, Hamano T, Hoshino J, Joki N, Abe M, Yamamoto K, Nakamoto H. The Japanese Society for Dialysis Therapy Renal Data Annual dialysis data report for 2018, JSDT renal data registry: survey methods, facility data, incidence, prevalence, and mortality. *Ren Replace Ther* 2020; **6**: 41.
18. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; **362**: 801–809.
19. Garcia-Prieto J, Villena-Gutiérrez R, Gómez M, Bernardo E, Pun-García A, García-Lunar I, Crainiciuc G, Fernández-Jiménez R, Sreeramkumar V, Bourio-Martínez R, García-Ruiz JM, Del Valle AS, Sanz-Rosa D, Pizarro G, Fernández-Ortiz A, Hidalgo A, Fuster V, Ibanez B. Neutrophil stunning by metoprolol reduces infarct size. *Nat Commun* 2017; **8**: 14780.
20. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res* 2019; **124**: 315–327.
21. Azekoshi Y, Yasu T, Watanabe S, Tagawa T, Abe S, Yamakawa K, Uehara Y, Momomura S, Urata H, Ueda S. Free fatty acid causes leukocyte activation and resultant endothelial dysfunction through enhanced angiotensin II production in mononuclear and polymorphonuclear cells. *Hypertension* 2010; **56**: 136–142.
22. Chien S, Sung KL, Schmid-Schönbein GW, Skalak R, Schmalzer EA, Usami S. Rheology of leukocytes. *Ann N Y Acad Sci* 1987; **516**: 333–347.
23. Yasu T, Kobayashi M, Mutoh A, Yamakawa K, Momomura S, Ueda S. Dihydropyridine calcium channel blockers inhibit non-esterified-fatty-acid-induced endothelial and rheological dysfunction. *Clin Sci (Lond)* 2013; **125**: 247–255.
24. Yasu T, Mutoh A, Wada H, Kobayashi M, Kikuchi Y, Momomura S, Ueda S. Renin-angiotensin system inhibitors can prevent intravenous lipid infusion-induced myocardial microvascular dysfunction and leukocyte activation. *Circ J* 2018; **82**: 494–501.
25. Lowe GD, Lee AJ, Rumley A, Price JF, Fowkes FG. Blood viscosity and risk of cardiovascular events: the Edinburgh artery study. *Br J Haematol* 1997; **96**: 168–173.
26. Tamariz LJ, Young JH, Pankow JS, Yeh HC, Schmidt MI, Astor B, Brancati FL. Blood viscosity and hematocrit as risk factors for type 2 diabetes mellitus: the atherosclerosis risk in communities (ARIC) study. *Am J Epidemiol* 2008; **168**: 1153–1160.
27. Jax TW, Peters AJ, Plehn G, Schoebel FC. Hemostatic risk factors in patients with coronary artery disease and type 2 diabetes – a two year follow-up of 243 patients. *Cardiovasc Diabetol* 2009; **8**: 48.
28. Ates AH, Canpolat U, Yorgun H, Kaya EB, Sunman H, Demiri E, Taher A, Hazirolan T, Aytemir K, Tokgözoglu L, Kabakçi G, Oto A. Total white blood cell count is associated with the presence, severity and extent of coronary atherosclerosis detected by dual-source multislice computed tomographic coronary angiography. *Cardiol J* 2011; **18**: 371–377.
29. Gillum RF, Ingram DD, Makuc DM. White blood cell count and stroke incidence and death. The NHANES I epidemiologic follow-up study. *Am J Epidemiol* 1994; **139**: 894–902.
30. Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 diabetes: demystifying the global epidemic. *Diabetes* 2017; **66**: 1432–1442.
31. Kimura K, Minematsu K, Kazui S, Yamaguchi T, Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC). Mortality and cause of death after hospital discharge in 10981 patients with ischemic stroke and transient ischemic attack. *Cerebrovasc Dis* 2005; **19**: 171–178.
32. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, Deswal A, Dickson VV, Kosiborod MN, Lekavich CL, McCoy RG, Mentz RJ, Piña IL, American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing; and the Heart Failure Society of America. Type 2 diabetes mellitus and heart failure: a scientific statement from the American heart association and the heart failure society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation* 2019; **140**: e294–e324.
33. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013; **34**: 1404–1413.
34. Aune D, Schlesinger S, Neuenschwander M, Feng T, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of heart failure: a systematic review and meta-analysis of prospective studies. *Nutr Metab Cardiovasc Dis* 2018; **28**: 1081–1091.
35. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of

47 cohorts including 12 million individuals. *Diabetologia* 2019; **62**: 1550–1560.
36. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, Roger VL. Hospitalizations after heart failure diagnosis: a community perspective. *J Am Coll Cardiol* 2009; **54**: 1695–1702.
37. Chaudhry SI, McAvay G, Chen S, Whitson H, Newman AB, Krumholz HM, Gill TM. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the cardiovascular health study. *J Am Coll Cardiol* 2013; **61**: 635–642.
38. Fotos NV, Giakoumidakis K, Kollia Z, Galanis P, Copanitsanou P, Pananoudaki E, Brokalaki H. Health-related quality of life of patients with severe heart failure: a cross-sectional multicentre study. *Scand J Caring Sci* 2013; **27**: 686–694.
39. Allen LA, Gheorghiade M, Reid KJ, Dunlay SM, Chan PS, Hauptman PJ, Zannad F, Konstam MA, Spertus JA. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. *Circ Cardiovasc Qual Outcomes* 2011; **4**: 389–398.
40. Solomon DH, Liu CC, Kuo IH, Zak A, Kim SC. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. *Ann Rheum Dis* 2016; **75**: 1674–1679.
41. Fujisue K, Sugamura K, Kurokawa H, Matsubara J, Ishii M, Izumiya Y, Kaikita K, Sugiyama S. Colchicine improves survival, left ventricular remodeling, and chronic cardiac function after acute myocardial infarction. *Circ J* 2017; **81**: 1174–1182.