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Relationship between the number of drugs used during percutaneous coronary intervention and adverse events in patients with chronic coronary syndrome: Analysis of CLIDAS database

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ABSTRACT

Background: Polypharmacy is associated with an increased risk of adverse events due to the higher number of drugs used. This is particularly notable in patients with chronic coronary syndrome (CCS), who are known to use a large number of drugs. Therefore, we investigated polypharmacy in patients with CCS, using CLIDAS, a multicenter database of patients who underwent percutaneous coronary intervention.

Method and results: Between 2017 and 2020, 1411 CCS patients (71.5 ± 10.5 years old; 77.3 % male) were enrolled. The relationship between cardiovascular events occurring during the median follow-up of 514 days and the number of drugs at the time of PCI was investigated. The median number of drugs prescribed was nine. Major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, stroke, heart failure, transient ischemic attack, or unstable angina, occurred in 123 patients, and all-cause mortality occurred in 68 patients. For each additional drug, the adjusted hazard ratios for MACE and all-cause mortality increased by 2.069 ($p = 0.003$) and 1.102 ($p = 0.010$). The adjusted hazard ratios for MACE and all-cause mortality were significantly higher in the group using nine or more drugs compared to the group using eight or fewer drugs (1.646 and 2.253, both $p < 0.001$).

Conclusion: This study showed that an increase in the number of drugs used for CCS may be associated with MACE and all-cause mortality. In patients with CCS, it might be beneficial to minimize the number of medications as much as possible, while managing comorbidities and using guideline-recommended drugs.

1. Introduction

According to the Japanese Ministry of Health, Labour and Welfare, heart disease was the second leading cause of death in 2022 at 14.8 % (Japanese Population Dynamics Statistics 2022; https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei22/dl/15_all.pdf), with 32,026

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deaths per 100,000 population from acute myocardial infarction, 41,1159 per 100,000 population from other ischemic heart diseases, and 98,671 per 100,000 population from heart failure. In addition, the Japanese Association of Cardiovascular Intervention and Therapeutics reported that over 200,000 percutaneous coronary intervention (PCI) procedures are performed annually in Japan [1]. Meanwhile, the number of drugs prescribed to treat coronary artery disease is a cause for concern among patients. Polypharmacy can be problematic because as the number of drugs taken increases, so too does the risk of adverse events such as increased drug interactions [2,3], increased medication errors [4], use of contraindicated drugs [5], increased medical care costs [6] and decreased medication adherence [7,8]. These drawbacks of polypharmacy have been recognized in the context of global aging, but few studies have provided conclusive evidence. Therefore, in the present study, we investigated the relationship between the number of drugs used and adverse events in patients with chronic coronary syndrome (CCS), who are candidates for elective PCI, which is commonly performed in Japan.

2. Methods

2.1. Patient population

In this study, we analyzed patients with CCS who were candidates for elective PCI. We extracted records for patients registered in Clinical Deep Data Accumulation System (CLIDAS), a multicenter database, between April 2017 and March 2020. During this period, antiplatelet therapy was considered essential for the prevention of stent thrombosis. Accordingly, the records of 2645 patients who used antiplatelet drugs at the time of PCI were extracted. Cases classified as acute coronary syndrome and those with unclear classification were excluded. Furthermore, in this study, patients were considered to have CCS if they fell into groups (i) to (vi) as defined by the 2019 European Society of Cardiology guidelines, excluding (v) coronary spasm and microvascular disease, in which left 1462 patients [9]. From this group, we excluded cases with incorrect records for age, sex, and body mass index, resulting in a final analysis cohort of 1411 patients (Fig. 1).

2.2. CLIDAS database

The CLIDAS database was launched in 2013 with the aim of contributing to society by accumulating and analyzing real-world data on cardiovascular treatment, in accordance with the SS-MIX2 and SEAMAT standards. As of this writing, data are provided to CLIDAS by seven Japanese medical institutions (six university hospitals and one national cardiovascular center). Data on patients undergoing PCI, including laboratory results (blood tests, electrocardiogram, echocardiogram, cardiac catheterization), PCI procedures, prescription data, and outcome data of major adverse cardiovascular events (MACE) and bleeding recorded in the electronic medical record, were collected.

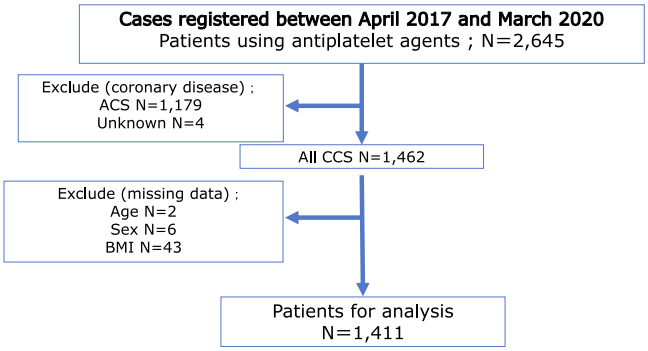

Fig. 1. Identification of patients for analysis.

Other background factors for patients included hypertension, diabetes, dyslipidemia, hemodialysis, family history of coronary artery disease, hospitalization for heart failure, treatment for coronary artery disease, history of myocardial infarction, history of stroke, presence of atrial fibrillation, presence of peripheral artery disease, and smoking history. The follow-up period continued until the patient's death was confirmed or until the last confirmation of survival was obtained during outpatient visits or by telephone inquiries. For more information on CLIDAS, see the previously published reports [10,11].

2.3. How to count the number of drugs

Medications transiently prescribed during the PCI period, including anxiolytics, sleep aids, and analgesics, were excluded unless they were identified outside the perioperative PCI period. Ointments, eye drops, and suppositories were also excluded. Antibiotics, antivirals, and antifungals were excluded if they were used only perioperatively during PCI, regardless of their form. Oral medical compounds were counted separately if the mixed components were divisible; for example, angiotensin II receptor blockers (ARB) and calcium channel blockers were counted separately as two drugs. Herbal medicines were counted as one drug. Nitroglycerin, beta-blocker patches, and nonsteroidal anti-inflammatory drug (NSAID) patches were also counted as drugs in this study.

2.4. Statistical analysis

This study is a retrospective analysis of a multicenter collaborative database. This study analyzed 1411 CCS patients, with a median follow-up period of 514 [238–893] days, using a multicenter collaborative database. First, the type and number of drugs used at the time of PCI were investigated. Next, the relationship of the number of drugs with the incidence of MACE and all-cause mortality was examined. In this study, MACE was defined as cardiovascular death, acute coronary syndrome, stroke, hospitalization due to heart failure, transit ischemic attack, or unstable angina.

The Cox proportional hazards model was used to analyze the relationship between several factors and events. Adjusting factors for the hazard ratio were age, sex, body mass index, smoking history, family history of coronary artery disease, hypertension, diabetes, dyslipidemia, chronic kidney disease, dialysis, history of heart failure hospitalization, old myocardial infarction, stroke, atrial fibrillation, and number of drugs. In addition, the median number of drugs was used as the cutoff value to obtain the adjusted hazard ratio of events when all patients were divided into two groups, and the log-rank test was applied. All statistical analyses were performed using IBM SPSS ver. 28.0 (IBM Corp., Armonk, NY). Hazard ratios are expressed as medians and 95 % confidence intervals, with $p < 0.05$ considered statistically significant.

2.5. Ethics

In accordance with the ethical guidelines for life science and medical research involving human subjects, information about this study was provided on each institution's website, and consent was obtained using the opt-out method.

2.6. Institutional review board information

This study was approved by the Ethics Committee of the Jichi Medical University School of Medicine (approval no. 23–054).

3. Results

Of the 1411 patients, 77 % were men, and the mean age was 71.5 years. Among the coronary risk factors, more than half of the patients had hypertension, dyslipidemia, and history of smoking (including past smokers) (Table 1). In addition, 13.5 % of patients had a history of

Table 1
Patient characteristics.

Category	Unit	Total	drug ≥ 9	drug ≤ 8	p-value
Age (n = 1411)	years old	72.7 [65.3–79.0]	73.5 [66.3–80.2]	71.7 [63.9–77.8]	<0.001
Sex (male) (n = 1411)	%	77.3	74.9	80.0	0.023
BMI (n = 1411)	kg/m^2	23.9 [21.8–26.3]	23.7 [21.4–26.1]	24.0 [22.1–26.4]	0.038
Hypertension (n = 1409)	%	79.6	83.0	75.8	<0.001
Diabetes (n = 1400)	%	45.0	54.6	34.1	<0.001
Dyslipidemia (n = 1407)	%	76.4	77.1	75.7	0.532
CKD (n = 1397)	%	49	59.3	37.4	<0.001
Dialysis (n = 1403)	%	7.6	10.0	4.5	<0.001
Family history (n = 1329)	%	1.3	1.4	1.3	0.835
Heart failure (n = 1408)	%	8.5	13.3	2.9	<0.001
Old myocardial infarction (n = 1402)	%	13.6	14.7	12.4	0.222
Stroke (n = 1407)	%	12.2	13.5	10.7	0.107
Atrial fibrillation (n = 1409)	%	10.9	15.1	6.1	<0.001
Smoking (n = 1390)	%	60.4	60.0	60.8	0.77
Total number of drugs (n = 1411)	–	9 [8–12]	11 [10–14]	6 [6–8]	<0.001
Follow up days (n = 1411)	days	514 [238–893]	563 [250–892]	438 [220–895]	0.071
All-cause mortality (n = 1411)	%	4.8	6.9	2.4	<0.001
MACCE (n = 1411)	%	8.7	11.6	5.5	<0.001
BNP (n = 1261)	pg/ml	56.2 [23.8–176.8]	95.3 [34.8–264.8]	38.3 [17.4–81.5]	<0.001
HbA1c (n = 1318)	%	6.2 [5.7–6.8]	6.3 [5.8–7.0]	6.1 [5.7–6.6]	<0.001
eGFR (n = 1397)	$mL/min/1.73\ m^2$	60.0 [43.1–73.7]	53.2 [33.6–68.8]	65.1 [53.1–77.6]	<0.001
Hb (n = 1398)	g/dl	12.6 [11.2–13.9]	12.2 [10.7–13.5]	13.1 [11.8–14.2]	<0.001
Alb (n = 1398)	g/dl	4.0 [3.6–4.2]	3.9 [3.5–4.2]	4.1 [3.8–4.3]	<0.001

Comparison of each category between patients using 9 or more drugs and those using 8 or fewer drugs.
BMI, body mass index; CKD, chronic kidney disease; MACE, major adverse cardiovascular events; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Alb, albumin.

myocardial infarction, 19.1 % had undergone PCI, 8.4 % had heart failure, 7.6 % were on dialysis, and 7.4 % had undergone coronary artery bypass surgery.

The median number of prescriptions per patient at the time of PCI was nine. When drugs were organized by indication, most of the top five prescription drugs with the highest prescription rates were those recommended by the ischemic heart disease guidelines, and their usage rates all exceeded 50 % (Supplementary Fig. 1). Meanwhile, oral medications prescribed for various symptoms such as constipation, anxiety, insomnia, and pain all exceeded 10 %.

During a median follow-up of 514 [238–893] days, MACE was observed in 123 patients. The most common MACE was hospitalization due to heart failure (29.3 %), followed by cardiovascular death (21.1 %) (Supplementary Table 1). Patients who experienced MACE used a higher number of medications at the time of PCI compared with those who did not experience MACE (12 [9–15] vs. 9 [7–13]; $p < 0.001$). During the follow-up period, 94 patients experienced one MACE, 17 experienced two MACE, and 6 experienced three MACE (Supplementary Fig. 2).

All-cause mortality was observed in 68 patients, with deaths related to cardiovascular events accounting for 47 % of the total (Supplementary Fig. 3). Risk factors for MACE and all-cause mortality were estimated using a Cox proportional hazards model adjusted for age, sex, hypertension, diabetes, dyslipidemia, smoking history, family history of coronary artery disease, presence of dialysis, heart failure, history of stroke, presence of atrial fibrillation, peripheral artery disease, number of prescribed drugs. The results showed that hemodialysis and a higher number of medications were common independent risk factors for MACE and all-cause mortality. Each additional drug increased the adjusted hazard ratio by 2.069 [1.285–3.331; $p = 0.003$] for MACE (Table 2A) and by 1.102 [1.024–1.185; $p = 0.010$] for all-cause mortality (Table 2B).

We performed a survival analysis of MACE and all-cause mortality in the two groups, using a cutoff value of nine for the number of drugs taken. Table 1 lists the characteristics of the two groups. Adjusted hazard ratios were significantly higher for MACE (Fig. 2A) and all-cause mortality (Fig. 2B) in the group using nine or more drugs (1.646 [1.044–2.595; $p = 0.032$]; 2.253 [1.176–4.318; $p = 0.014$], respectively).

4. Discussion

4.1. Definition of polypharmacy

As the global population ages, the number of patients with multiple diseases is increasing [2]. In addition to treatment in accordance with the guidelines for each disease, prescriptions are also given for underlying and comorbid conditions, thereby increasing the number of drugs prescribed [2,12]. According to statistics released by the Japanese Ministry of Health, Labour and Welfare (Summary of Statistics by Social Medical Practice in 2022; https://www.ajha.or.jp/topics/admininfo/), 23.8 % of patients aged 75 years or older who received out-of-hospital prescriptions were taking seven or more medications.

Polypharmacy is a worldwide problem, but a precise definition has yet to be established. A search for "polypharmacy" in PubMed revealed an increase in reports around 2010, but most previous studies considered polypharmacy to be the simultaneous use of five or more drugs. However, there is no consensus regarding the inclusion of abortive medications or subcutaneous injectable or patch medications [13,14].

In Japan, a significant increase in adverse events has been reported with the use of six or more drugs [4]. Given the urgent need to accumulate data on polypharmacy, it is desirable to standardize the global definition of polypharmacy [15,16]. In the present study, the median number of medications used at the time of PCI was 9, and a higher number of medications was associated with an increased incidence of MACE and all-cause mortality. However, because we evaluated the number of medications at the time of PCI, we could not investigate the direct causal relationship with prognosis. Although various studies have examined polypharmacy, a unified definition and evaluation method are needed to accurately grasp the relationship between medications and events. In a systematic review of polypharmacy definitions, Masnoon et al. demonstrated that polypharmacy encompasses various aspects, including the prescription of multiple medications across different health-care settings, long-term use of multiple drug types, potentially inappropriate medications, and the addition of drugs to manage the adverse effects of existing medications [15].

Table 2
Cox proportional hazards model analysis for (A) MACE and (B) all-cause mortality.

A

	Univariate regression model			Multivariate regression model		
Category	HR	95 % CI	p-value	HR	95 % CI	p-value
Age (per 1 year increase)	1.029	1.010–1.048	0.003	1.018	0.996–1.040	0.115
Sex (male)	0.604	0.410–0.892	0.011	0.760	0.450–1.283	0.305
BMI (per 1 kg/m^2 increase)	0.956	0.907–1.007	0.090	0.966	0.910–1.026	0.258
Coronary risk factor	HR	95 % CI	p-value	HR	95 % CI	p-value
SMOKING	0.665	0.465–1.007	0.026	0.905	0.562–1.457	0.682
Family history	2.327	0.858–6.316	0.097	4.841	1.730–13.547	0.003
Hypertension	1.957	1.122–3.414	0.018	2.064	1.044–4.083	0.037
Diabetes	1.815	1.268–2.599	0.001	1.399	0.934–2.097	0.104
Dyslipidemia	0.662	0.446–0.983	0.041	0.678	0.411–1.119	0.128
Past history	HR	95 % CI	p-value	HR	95 % CI	p-value
CKD	1.998	1.380–2.892	<0.001	1.184	0.769–1.822	0.444
Dialysis	2.961	1.832–4.788	<0.001	2.552	1.478–4.406	0.001
Heart failure	2.842	1.844–4.382	<0.001	2.069	1.285–3.331	0.003
Old myocardial infarction	1.336	0.835–2.138	0.227	1.299	0.789–2.139	0.303
Stroke	1.438	0.871–2.372	0.155	1.180	0.688–2.024	0.548
Atrial fibrillation	2.035	1.311–3.158	0.002	1.920	1.177–3.131	0.009
Drug number (per 1 increase)	1.108	1.058–1.161	<0.001	2.069	1.285–3.331	0.003
Drugs ≧9	2.055	1.394–3.031	<0.001	1.646	1.044–2.595	0.032

B

	Univariate regression model			Multivariate regression model		
Category	HR	95% CI	p-value	HR	95% CI	p-value
Age (per 1 year increase)	1.061	1.032–1.091	<0.001	1.057	1.023–1.093	0.001
Sex (male)	0.832	0.475–1.457	0.519	0.947	0.448–2.012	0.888
BMI (per 1 kg/m^2 increase)	0.839	0.778–0.906	<0.001	0.859	0.786–0.938	0.001
Coronary risk factor	HR	95% CI	p-value	HR	95% CI	p-value
Smoking	0.829	0.511–1.344	0.447	1.205	0.613–2.366	0.589
Family history	0.930	0.129–6.713	0.943	2.930	0.386–22.239	0.299
Hypertension	3.951	1.439–10.820	0.008	3.457	1.176–10.161	0.024
Diabetes	2.161	1.320–3.538	0.002	1.545	0.904–2.642	0.112
Dyslipidemia	0.528	0.318–0.879	0.014	0.546	0.305–0.978	0.042
Past history	HR	95% CI	p-value	HR	95% CI	p-value
CKD	2.489	1.487–4.164	<0.001	1.213	0.666–2.208	0.528
Dialysis	4.791	2.762–8.313	<0.001	4.094	2.174–7.710	<0.001
Heart failure	1.550	0.769–3.127	0.221	1.197	0.567–2.529	0.637
Old myocardial infarction	0.617	0.267–1.427	0.259	0.574	0.241–1.366	0.209
Stroke	2.185	1.212–3.940	0.009	2.098	1.110–3.965	0.022
Atrial fibrillation	1.488	0.780–2.839	0.227	1.153	0.569–2.335	0.142
Drug number (per 1 increase)	1.138	1.070–1.210	<0.001	1.102	1.024–1.185	0.010
Drugs ≧9	2.681	1.531–4.695	0.001	2.253	1.176–4.318	0.014

Adjusting factors for the hazard ratio were age, sex, body mass index, smoking history, family history of coronary artery disease, hypertension, diabetes, dyslipidemia, chronic kidney disease, dialysis, history of heart failure hospitalization, old myocardial infarction, stroke, atrial fibrillation, and number of drugs.

4.2. Examination of the impact of comorbidities

Many patients have hypertension, dyslipidemia, and hypertension as underlying ischemic heart disease [17]. However, CLIDAS does not collect data on comorbidities other than heart disease and coronary risk factors at the time of patient registration, so it is unclear what is being prescribed and for what conditions. With aging, there is a relative increase in diseases other than cardiac disease, and having multiple diseases has become a problem [5,18]. In addition, Tinetti et al. reported that death in patients with multiple chronic diseases was influenced by the severity of comorbidities, but administering guideline-recommended drugs for cardiac disease treatment did not increase the risk of death [18,19].

For example, a significant comorbidity is cancer. In this study, the most common cause of death among patients was cancer, which accounted for 12 % (Supplementary Fig. 3). CLIDAS does not collect information on when patients developed cancer, whether there was metastasis, or the stage of cancer at the time of registration. The presence of cancer is considered to have a significant potential impact on prognosis, so evaluating the timing of onset and treatment progression of comorbidities is also important. Since the number of drugs used may vary depending on the treatment methods for comorbidities, future research focusing on comorbidities is desirable.

Although the data are limited to the number of medications used at the time of PCI, multivariate analysis revealed that each additional medication increased the hazard ratio for MACE and all-cause mortality. Similarly, the presence of baseline hypertension and severe renal failure requiring dialysis significantly increased the adjusted hazard ratio. Both hypertension and renal failure are conditions for which multiple evidence-based medications are listed in the guidelines. In high-risk patients who are candidates for PCI, the presence of multiple comorbidities and unstable disease conditions may lead to the use of many medications. Additionally, for patients who experienced MACE, we also compiled the cumulative number of MACE during the follow-up period. Among these patients, 76.4 % (n = 94) experienced only one MACE, while 13.8 % (n = 17) experienced two MACEs. Some patients experienced more than two MACEs, primarily due to hospitalizations for worsening heart failure. It is known that heart failure tends to exacerbate over time, and the temporal risk changes of the disease itself should also be considered.

When discussing polypharmacy with a focus on adverse drug events, it is crucial to understand and monitor comorbid conditions such as cancer as well as the progress of treatment. In this study, we comprehensively evaluated the course of CCS patients without coronary spasm

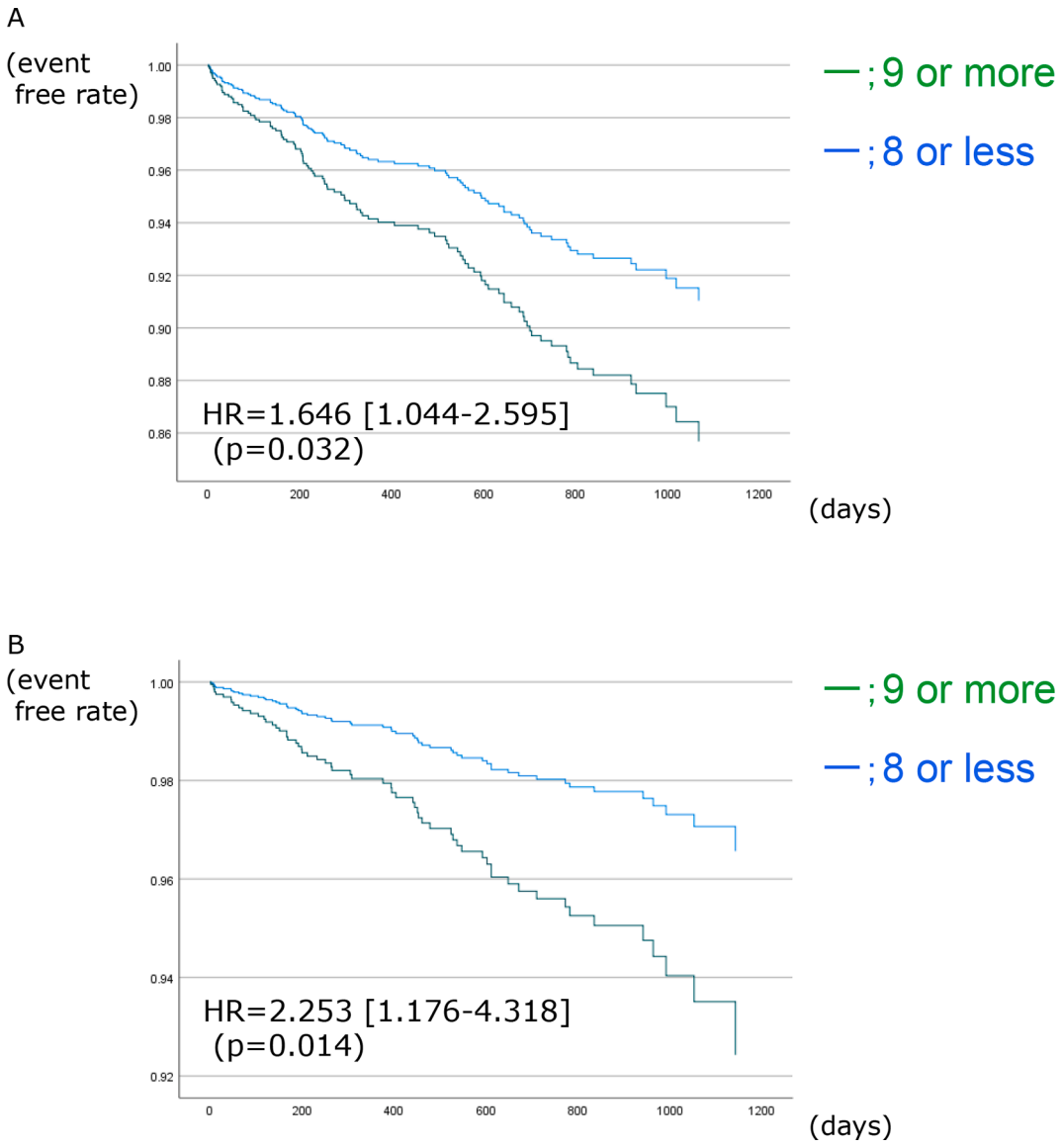

Fig. 2. Kaplan-Meier curves for (A) MACE and (B) all-cause mortality in the groups with drug use of 9 or more and those with drug use of 8 or less. The green line represents the group with 9 or more drugs and the blue line represents the group with 8 or less drugs. Adjusted hazard ratios between the two groups were statistically evaluated using the log-rank test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

or microcirculatory disorders. However, we believe that future research should prospectively investigate comorbidities.

4.3. Is the number of drugs used 9 is a lot?

Japanese guidelines related to PCI include aspirin, adenosine diphosphate receptor P2Y12 inhibitors, statins, and ezetimibe [20] as Class 1 recommended levels for evidence-based prescribing in the perioperative period. In Japan, ischemic heart disease accounts for almost half (47 %) of heart failure with reduced ejection fraction (HFrEF) [21]. Note that the current Japanese HFrEF treatment guidelines list angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor neprilysin inhibitors, beta-receptor blockers, mineralocorticoid receptor antagonists, loop diuretics, thiazide diuretics, and SGLT2 inhibitors as Class 1 indications [21].

Many patients with heart failure also have atrial fibrillation [21]. The concomitant use of anticoagulants for atrial fibrillation [20] is also classified as Class 1 if there are no contraindications at the time of PCI. As described above, because of the large number of basic drugs recommended by guidelines in patients with cardiac disease, including CCS, it is necessary to consider guideline-recommended drugs and other drugs separately when discussing polypharmacy [22]. In this study, more than 80 % of the patients used antiplatelet drugs, gastric mucosal protectants, and statins, in line with the CCS guidelines (Supplementary Fig. 1). Nonetheless, it was frequently observed that similar drugs were prescribed to patients, such as adding cilostazol to aspirin, clopidogrel, or prasugrel as antiplatelet drugs, or adding an H2 blocker to a proton pump inhibitor or potassium-competitive acid blocker for gastric protection. One reason for this may be the significant influence of the physician's discretion in response to vague symptoms that are not easily reflected in the data. For example, medications not listed in the guidelines may be prescribed for vague complaints such as a feeling of stomach fullness. In such cases, the Beers Criteria and the STOPP Criteria can also be useful. Clinicians should have the opportunity to review prescriptions regularly to avoid polypharmacy [4,23,24].

4.4. Updated guidelines may affect the number of drugs used

In our study, only 4.4 % of patients were using SGLT2 inhibitors at

the time of PCI. These figures were obtained before the guidelines on heart failure were updated, and it is assumed that the use of SGLT2 inhibitors is now increasing [20,25]. Similarly, recent evidence has led to the inclusion of new drugs such as vericiguat and omecamtiv mecarbil (a cardiac myosin activator) [25]. Thus, the number of drugs could be further increased if treatment follows the latest guidelines, and appropriate drug use should be updated accordingly.

4.5. Outlook for the future

To manage polypharmacy, it is necessary to consider whether adverse events can be reduced by (1) decreasing the number of drugs prescribed through the use of medical compounding, (2) changing administration methods such as patch formulations, (3) packaging drugs in a single package, and (4) reducing the number of administration days by changing to once-weekly formulations [12,26,27,28]. In the future, prospective studies should be conducted to determine how non-prescription drugs prescribed for cardiovascular disease affect prognosis. In this retrospective study, we were unable to confirm adherence. There are reports that medication adherence in cardiac patients is poor, and thus confirming adherence is important for ensuring accurate assessments [7,8].

5. Limitations

The sample size was relatively small because the patient enrollment period was limited to 3 years (2017–2020). In addition, because this was an observational study, the follow-up periods varied. The impact of drug changes during the follow-up period on MACE and all-cause mortality is unknown. If antiplatelet agents are added in anticipation of PCI, the number of prescriptions may be higher than during the stable phase of the patient's outpatient course. In addition, although CLIDAS automatically collects prescription data it cannot be used to confirm whether or not the prescribed drugs were actually taken. Many patients were treated for various diseases across multiple departments, but the CLIDAS database does not collect information on which drugs were prescribed for which diseases and in accordance with what guidelines. Therefore, this study could not confirm that the treatment was strictly in accordance with the guidelines, which may have affected the results. Similarly, data collection on diseases other than cardiovascular events occurring during follow-up was limited, so it was not possible to determine how these may have affected the results.

6. Conclusion

In patients with CCS, the incidence of all-cause mortality and MACE was significantly higher with each additional medication used at the time of PCI. However, in this study, due to the presence of many comorbidities beyond CCS, it was not possible to specify which medications were prescribed according to which guidelines. In the future, it will be necessary to investigate the use of guideline-adherent medications for each condition and to clarify the relationship between the use of medications not recommended by guidelines and adverse events through prospective studies.

CRediT authorship contribution statement

Yasuhiro Hitomi: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Yasushi Imai:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Masanari Kuwabara:** Conceptualization, Formal analysis, Methodology, Validation, Writing – review & editing. **Yusuke Oba:** Data curation. **Tomoyuki Kabutoya:** Data curation. **Kazuomi Kario:** Data curation, Project administration, Supervision. **Hisaki Makimoto:** Data curation. **Takahide Kohro:** Data curation, Resources, Project administration, Supervision. **Eiichi Shiraki:** Data curation. **Naoyuki Akashi:** Data curation. **Hideo Fujita:** Data curation, Project administration, Supervision, Funding acquisition. **Tetsuya Matoba:** Data curation, Project administration, Supervision, Funding acquisition. **Yoshihiro Miyamoto:** Data curation. **Arihiro Kiyosue:** Data curation. **Kenichi Tsujita:** Data curation. **Masaharu Nakayama:** Data curation. **Ryozo Nagai:** Project administration, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The deidentified participant data will not be shared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101507.

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