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Effect of delayed hospitalization on 3-year clinical outcomes according to renal function in patients with non-ST-segment elevation myocardial infarction

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Abstract

Background: *We evaluated the effect of delayed hospitalization (symptom-to-door time [STD] ≥ 24 h) on 3-year clinical outcomes according to renal function in patients with non-ST-segment elevation myocardial infarction (NSTEMI) undergoing new-generation drug-eluting stent (DES) implantation.*

Methods: *A total of 4513 patients with NSTEMI were classified into chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2, n = 1118) and non-CKD (eGFR ≥ 60 mL/min/1.73 m^2, n = 3395) groups. They were further sub-classified into groups with (STD ≥ 24 h) and without (STD < 24 h) delayed hospitalization. The primary outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause death, recurrent myocardial infarction, any repeat coronary revascularization, and stroke. The secondary outcome was stent thrombosis.*

Results: *After multivariable-adjusted and propensity score analyses, the primary and secondary clinical outcomes were similar in patients with or without delayed hospitalization in both CKD and non-CKD groups. However, in both the STD < 24 h and STD ≥ 24 h groups, MACCE (p < 0.001 and p < 0.006, respectively) and mortality rates were significantly higher in the CKD group than in the non-CKD group. However, stent thrombosis rates were similar between the CKD and non-CKD groups and between the STD < 24 h and STD ≥ 24 h groups.*

Conclusions: *Chronic kidney disease appears to be a much more important determinant of MACCE and mortality rates than STD in patients with NSTEMI.* (Cardiol J)

Key words: chronic kidney disease, drug-eluting stent, non-ST-segment elevation myocardial infarction, pre-hospital delay

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Introduction

The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZON-AMI) trial [1] showed that early infarct-related artery (IRA) patency is an independent predictor of lower 1-year mortality in patients with ST-segment-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) (2.5% vs. 3.9%, p = 0.04). Current guidelines [2–4] recommend that the early invasive strategy (coronary angiography [CAG] and PCI within 24 h of admission) is preferred over the delayed invasive strategy in patients with non-STEMI (NSTEMI) and those with at least one high-risk criterion. However, the early invasive strategy did not always result in decreased mortality compared with the delayed invasive strategy in high-risk patients with NSTEMI [5–7]. Thus, the optimal timing of PCI in NSTEMI is yet to be fully evaluated, and more data are needed. In patients with STEMI, recent [8] and previous research [9] show that long-term mortality is strongly related to total ischemic time rather than door-to-balloon time (DTB). In contrast, in patients with NSTEMI, very few studies have investigated the long-term clinical outcomes in patients with delayed hospitalization (symptom-to-door time [STD] ≥ 24 h) [10]. The prevalence of chronic kidney disease (CKD) in patients with NSTEMI is from 25–30% [11, 12] to as much as 42.9% [12] compared with 30.5% in patients with STEMI. In patients with acute myocardial infarction (MI) and estimated glomerular filtration rate (eGFR) below 81.0 mL/min/1.73 m^2, each drop in eGFR by 10 mL/min/1.73 m^2 was associated with a hazard ratio for death and nonfatal cardiovascular outcomes of 1.10 (95% confidence interval [CI] 1.08–1.12) [11] Although CKD leads to high mortality and morbidity in patients with NSTEMI [13], patients with CKD have rarely been included in NSTEMI randomized clinical trials [14]. Therefore, data on the long-term effects of delayed hospitalization on long-term clinical outcomes according to renal function in patients with NSTEMI are limited. The current guideline [15] recommends drug-eluting stent (DES) over bare-metal stent (BMS) implantation if PCI is indicated in patients with CKD. In this study, we evaluated the effect of delayed hospitalization on 3-year clinical outcomes in patients with NSTEMI with or without CKD undergoing new-generation DES implantation to reflect real-world current practice.

Methods

Study population

This nonrandomized, multicenter, prospective cohort study included 13,104 patients with acute MI between November 2011 and December 2015 from the Korea Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH) [16]. KAMIR-NIH is a nationwide prospective multicenter registry integrated from 20 high-volume centers in the Republic of Korea. All patients aged ≥ 18 years at the time of hospital admission were included. Patients who did not receive PCI (n = = 1369, 10.4%), received unsuccessful PCI (n = = 155, 1.2%), plain old balloon angioplasty (n = 739, 5.6%), BMS or first-generation (1G)-DES (n = 563, 4.3%), or coronary artery bypass graft (CABG, n = 38, 0.3%), had STEMI (n = 5342, 40.8%), cardiogenic shock, or in-hospital death (n = 228, 1.7%), or were unavailable for follow-up (n = 157, 1.2%) were excluded (Fig. 1). Overall, a total of 4513 patients with NSTEMI who underwent successful PCI using new-generation DES were enrolled and classified into CKD (eGFR < 60 mL/min/1.73 m^2, n = 1118 [24.8%]) and non-CKD (eGFR ≥ 60 mL/ /min/1.73 m^2, n = 3395 [75.2%]) groups. Thereafter, these two groups were further sub-classified into those without delayed hospitalization (STD < 24 h, group A [n = 756] and group C [n = 2516]) or those with delayed hospitalization (STD ≥ 24 h, group B [n = 362], and group D [n = 879]) (Fig. 1). The types of new-generation DESs used are listed in Table 1. Using a web-based case report form in the internet-based Clinical Research and Trial management system (iCReaT, iCReaT Study No. C110016), the attending physicians with the assistance of trained clinical research coordinators used a web-based case report form in a clinical data management system to collect all data. Patients who registered for the study were subsequently given a unique number in sequential order. In accordance with the ethical guidelines of the 2004 Declaration of Helsinki, this study was approved by the ethics committee of each participating center and the Chonnam National University Hospital Institutional Review Board Ethics Committee (CNUH-2011-172). All 4513 patients included in the study provided written informed consent prior to enrollment. They also completed a 3-year clinical follow-up through face-to-face interviews, phone calls, or chart reviews. Event adjudication processes have been described in a previous pub-

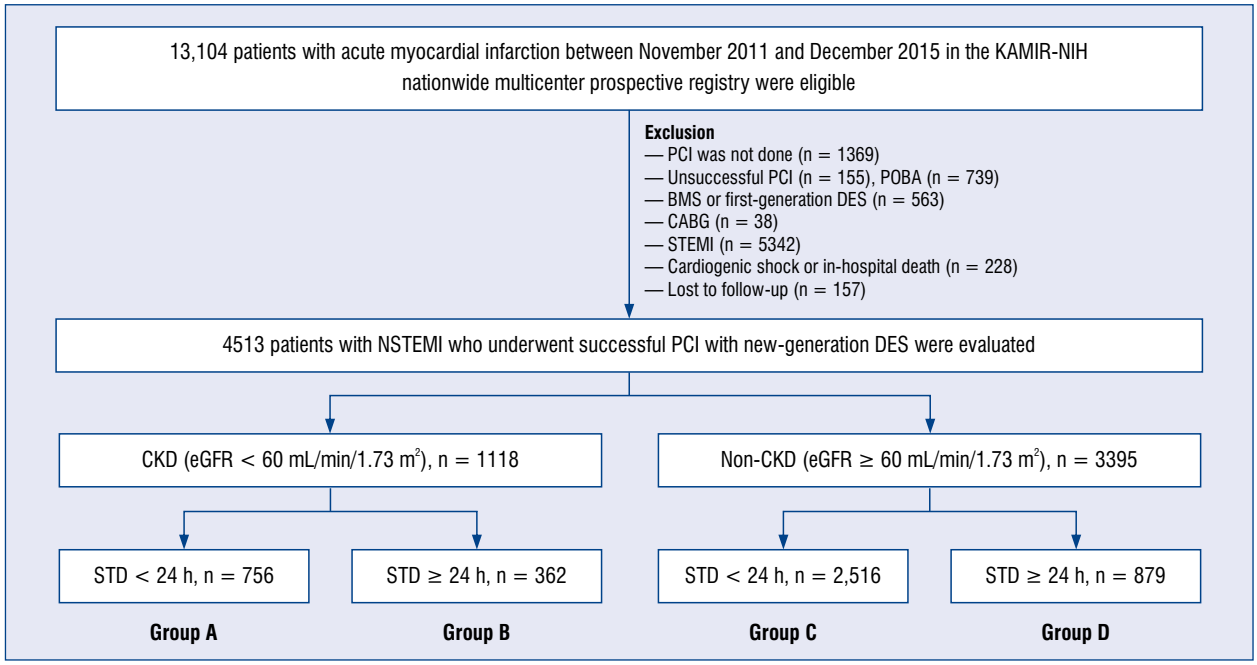

Figure 1. Flowchart. KAMIR-NIH — Korea Acute Myocardial Infarction Registry-National Institute of Health; PCI — percutaneous coronary intervention; POBA — plain old balloon angioplasty; BMS — bare-metal stent; DES — drug-eluting stent; CABG — coronary artery bypass graft; STEMI — ST-segment-elevation myocardial infarction; NSTEMI — non-STEMI; CKD — chronic kidney disease; eGFR — estimated glomerular filtration rate; STD — symptom-to-door time.

Table 1. Baseline characteristics.

Variables	CKD, n = 1118			Non-CKD, n = 3395		
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	P	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	P
Male	481 (63.6%)	189 (52.2%)	< 0.001	1980 (78.7%)	637 (72.5%)	< 0.001
Age [years]	70.1 ± 10.0	72.0 ± 10.3	0.003	61.0 ± 11.7	63.8 ± 11.7	< 0.001
LVEF [%]	51.1 ± 11.9	48.4 ± 12.5	0.001	55.5 ± 9.4	55.5 ± 10.1	0.921
BMI [kg/m^2]	23.9 ± 3.2	23.8 ± 3.5	0.758	24.3 ± 3.3	24.1 ± 3.2	0.293
SBP [mmHg]	136.6 ± 30.1	132.9 ± 25.9	0.036	136.8 ± 25.6	133.8 ± 23.2	0.002
DBP [mmHg]	79.9 ± 16.7	78.8 ± 15.6	0.256	82.6 ± 15.3	80.8 ± 13.5	0.001
STD [h]	3.7 (1.4–8.0)	72.0 (39.5-168.0)	< 0.001	3.9 (1.8–8.5)	68.3 (32.5–120.0)	< 0.001
DTB [h]	12.9 (3.6–28.7)	17.4 (4.2-40.3)	0.009	13.3 (3.9–24.2)	16.0 (3.8–24.3)	0.089
Atypical chest pain	168 (22.2%)	126 (34.8%)	< 0.001	244 (9.7%)	140 (15.9%)	< 0.001
Dyspnea	260 (34.4%)	163 (45.0%)	0.001	469 (18.6%)	202 (23.0%)	0.003
ECG on admission:						
Q-wave	89 (11.8%)	67 (18.5%)	0.003	369 (14.7%)	156 (17.7%)	0.034
ST-segment depression	236 (31.2%)	92 (25.4%)	0.049	518 (20.6%)	140 (15.9%)	0.002
T-wave inversion	150 (19.8%)	77 (21.3%)	0.579	485 (19.3%)	223 (25.4%)	< 0.001
Atrial fibrillation	47 (6.2%)	23 (6.4%)	0.930	79 (3.1%)	27 (3.1%)	0.920
Killip class 1I/III	207 (27.4%)	126 (34.8%)	0.012	240 (9.5%)	97 (11.0%)	0.213
First medical contact:						
EMS	118 (15.6%)	15 (4.1%)	< 0.001	285 (11.3%)	31 (3.5%)	< 0.001
Non-PCI center	355 (47.0%)	215 (59.4%)	< 0.001	1299 (51.6%)	505 (57.5%)	0.003
PCI center	283 (37.4%)	132 (36.5%)	0.791	932 (37.0%)	343 (39.0%)	0.312

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Table 1 (cont.). Baseline characteristics.

Variables	CKD, n = 1118			Non-CKD, n = 3395		
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	P	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	P
Hypertension	552 (73.0%)	266 (73.5%)	0.886	1126 (44.8%)	438 (49.8%)	0.010
Diabetes mellitus	361 (47.8%)	199 (55.0%)	0.025	569 (22.6%)	227 (25.8%)	0.058
Dyslipidemia	91 (12.0%)	44 (12.2%)	0.955	322 (12.8%)	97 (11.0%)	0.190
Previous MI	78 (10.3%)	39 (10.8%)	0.835	141 (5.6%)	45 (5.1%)	0.667
Previous PCI	126 (16.7%)	42 (11.6%)	0.032	202 (8.0%)	67 (7.6%)	0.772
Previous CABG	13 (1.7%)	9 (2.5%)	0.369	9 (0.4%)	2 (0.2%)	0.739
Previous HF	22 (2.9%)	14 (3.9%)	0.469	16 (0.6%)	5 (0.6%)	0.827
Previous stroke	71 (9.4%)	40 (11.0%)	0.394	107 (4.3%)	46 (5.2%)	0.257
Current smokers	176 (23.3%)	68 (18.8%)	0.089	1093 (43.4%)	319 (36.3%)	< 0.001
Peak CK-MB [mg/dL]	20.3 (5.7–62.1)	11.3 (5.0-34.5)	< 0.001	31.1 (7.8–100.4)	12.3 (4.3–43.5)	< 0.001
Peak troponin-I [ng/mL]	10.5 (2.1–21.6)	6.5 (2.0-21.6)	0.017	11.3 (2.2–23.1)	4.9 (1.3–21.4)	0.009
Blood glucose [mg/dL]	188.0 ± 101.0	179.2 ± 107.5	0.191	150.8 ± 62.0	140.3 ± 54.3	< 0.001
Serum creatinine [mg/L]	2.13 ± 2.45	2.02 ± 2.17	0.446	0.81 ± 0.18	0.79 ± 0.17	0.005
eGFR [mL/min/1.73 m^2]	37.1 ± 17.7	36.8 ± 17.5	0.779	112.3 ± 51.9	110.6 ± 48.5	0.381
Total cholesterol [mg/dL]	169.9 ± 46.3	172.9 ± 46.2	0.264	184.1 ± 42.5	179.0 ± 42.9	0.002
Triglyceride [mg/L]	130.6 ± 103.3	133.0 ± 99.3	0.710	135.3 ± 120.5	127.6 ± 87.2	0.043
HDL cholesterol [mg/L]	41.7 ± 11.6	40.8 ± 11.7	0.240	43.6 ± 11.0	42.3 ± 10.9	0.001
LDL cholesterol [mg/L]	104.0 ± 35.3	107.6 ± 35.9	0.114	117.3 ± 35.9	114.1 ± 35.5	0.022
GRACE risk score:	157.0 ± 41.4	161.5 ± 38.7	0.076	118.0 ± 34.5	123.2 ± 33.6	< 0.001
> 140	485 (64.2%)	259 (71.5%)	0.015	615 (24.4%)	262 (29.8%)	0.002
Pre-PCI antiplatelet agents:						
ASA	755 (99.9%)	360 (99.4%)	0.246	2,506 (99.6%)	874 (99.4%)	0.555
Clopidogrel	615 (81.3%)	302 (83.4%)	0.454	1,713 (68.1%)	627 (71.3%)	0.075
Ticagrelor	103 (13.6%)	38 (10.5%)	0.150	525 (20.9%)	165 (18.8%)	0.189
Prasugrel	38 (5.0%)	22 (6.1%)	0.480	278 (11.0%)	87 (9.9%)	0.376
Discharge medications:						
ASA	752 (99.5%)	358 (98.9%)	0.282	2,502 (99.4%)	869 (98.9%)	0.099
Clopidogrel	616 (81.5%)	303 (83.7%)	0.404	1,715 (68.2%)	628 (71.4%)	0.075
Ticagrelor	102 (13.5%)	38 (10.5%)	0.177	525 (20.9%)	165 (18.8%)	0.189
Prasugrel	38 (5.0%)	21 (5.8%)	0.571	276 (11.0%)	86 (9.8%)	0.342
BBs	643 (85.1%)	292 (80.7%)	0.070	2,180 (86.6%)	757 (86.1%)	0.688
ACEI or ARBs	618 (81.7%)	285 (78.7%)	0.256	2,114 (84.0%)	735 (83.6%)	0.790
Statin	694 (91.8%)	335 (92.5%)	0.724	2,433 (96.7%)	845 (96.1%)	0.452
Anticoagulant	25 (3.3%)	21 (5.8%)	0.054	34 (1.4%)	16 (1.8%)	0.330
Infarct-related artery:						
Left main	30 (4.0%)	13 (3.6%)	0.869	58 (2.3%)	30 (3.4%)	0.084
LAD	309 (40.9%)	163 (45.0%)	0.196	1,099 (43.7%)	360 (41.0%)	0.166
LCx	176 (23.3%)	70 (19.3%)	0.143	690 (27.4%)	214 (24.3%)	0.076
RCA	241 (31.9%)	116 (32.0%)	0.956	669 (26.6%)	275 (31.3%)	0.009
Treated vessel:						
Left main	41 (5.4%)	19 (5.2%)	0.903	93 (3.7%)	48 (5.5%)	0.030
LAD	432 (57.1%)	238 (65.7%)	0.006	1,440 (57.2%)	494 (56.2%)	0.607
LCx	296 (39.2%)	131 (36.2%)	0.357	967 (38.4%)	338 (38.5%)	0.992
RCA	305 (40.3%)	145 (40.1%)	0.948	899 (35.7%)	363 (41.3%)	0.004

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Table 1 (cont.). Baseline characteristics.

Variables	CKD, n = 1118			Non-CKD, n = 3395		
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	P	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	P
Extent of CAD:						
1-vesssel disease	255 (33.7%)	125 (34.5%)	0.788	1,243 (49.4%)	385 (43.8%)	0.004
2-vessel disease	270 (35.7%)	122 (33.7%)	0.547	822 (32.7%)	308 (35.0%)	0.212
≥ 3-vessel disease	231 (30.6%)	115 (31.8%)	0.679	451 (17.9%)	186 (21.2%)	0.035
ACC/AHA type B2/C lesions	635 (84.0%)	307 (84.8%)	0.792	2,116 (84.1%)	739 (84.1%)	0.984
Pre-PCI TIMI flow grade 0/1	306 (40.5%)	147 (40.6%)	0.967	986 (39.2%)	330 (37.5%)	0.399
GP IIb/IIIa inhibitor	50 (6.6%)	25 (6.9%)	0.898	231 (9.2%)	85 (9.7%)	0.686
Transradial approach	264 (34.9%)	149 (41.2%)	0.047	1,383 (55.0%)	545 (62.0%)	< 0.001
IVUS/OCT	160 (21.2%)	84 (23.2%)	0.440	668 (26.6%)	231 (26.3%)	0.984
FFR	10 (1.3%)	5 (1.4%)	0.937	66 (2.6%)	26 (3.0%)	0.629
Drug-eluting stents*:						
ZES	199 (26.3%)	82 (22.7%)	0.210	619 (24.6%)	190 (21.6%)	0.081
EES	423 (56.0%)	210 (58.0%)	0.520	1283 (51.0%)	448 (51.0%)	0.989
BES	112 (14.8%)	63 (17.4%)	0.291	541 (21.5%)	219 (24.9%)	0.039
Others	22 (2.9%)	7 (1.9%)	0.423	73 (2.9%)	22 (2.5%)	0.635
Stent diameter [mm]	3.05 ± 0.41	3.03 ± 0.40	0.411	3.09 ± 0.42	3.08 ± 0.43	0.619
Stent length [mm]	31.2 ± 14.9	32.9 ± 16.1	0.097	29.0 ± 13.3	29.2 ± 14.5	0.735
Number of stents	1.24 ± 0.48	1.28 ± 0.51	0.159	1.19 ± 0.44	1.19 ± 0.45	0.776

*Drug-eluting stents were composed of ZES (Resolute Integrity stent; Medtronic, Inc., Minneapolis, MN), EES (Xience Prime stent, Abbott Vascular, Santa Clara, CA; or Promus Element stent, Boston Scientific, Natick, MA), and BES (BioMatrix Flex stent, Biosensors International, Morges, Switzerland; or Nobori stent, Terumo Corporation, Tokyo, Japan); Values are means ± standard deviation or median (interquartile range) or numbers and percentages. The p values for continuous data were obtained from the unpaired t-test. The p values for categorical data were obtained from the chi-square or Fisher's exact test; CKD — chronic kidney disease; LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; STD — symptom-to-door time; DTB — door-to-balloon time; ECG — electrocardiogram; EMS — emergency medical service; PCI — percutaneous coronary intervention; MI — myocardial infarction; CABG — coronary artery bypass graft; HF — heart failure; CK-MB — creatine kinase myocardial band; eGFR — estimated glomerular filtration rate; HDL — high-density lipoprotein; LDL— low-density lipoprotein; GRACE — Global Registry of Acute Coronary Events; ASA — acetylsalicylic acid; BBs — beta-blockers; ACEIs — angiotensin converting enzyme inhibitors; ARBs — angiotensin receptor blockers; LAD — left anterior descending coronary artery; LCx — left circumflex coronary artery; RCA — right coronary artery; CAD — coronary artery disease; ACC/AHA — American College of Cardiology/American Heart Association; TIMI — Thrombolysis In Myocardial Infarction; GP — glycoprotein; IVUS — intravascular ultrasound; OCT — optical coherence tomography; FFR — fractional flow reserve; ZES — zotarolimus-eluting stent; EES — everolimus-eluting stent; BES — biolimus-eluting stent

lication by KAMIR investigators. An independent event-adjudicating committee in the KAMIR-NIH evaluated all clinical events [16].

Percutaneous coronary intervention procedure and medical treatment

According to general guidelines [17], CAG and PCI were performed via a transfemoral or transradial approach. Acetylsalicylic acid (ASA; 200–300 mg) and clopidogrel (300–600 mg), ticagrelor (180 mg), or prasugrel (60 mg) were prescribed as loading doses before PCI. After PCI, ASA (100 mg/day) was recommended in all patients, along with clopidogrel (75 mg/day), ticagrelor (90 mg twice a day), or prasugrel (5–10 mg/day) for at least 1 year. The access site, revascularization strategy, and DES selection were left to the discretion of the individual operators.

Study definitions and clinical outcomes

Non-STEMI was defined as the absence of persistent ST-segment elevation with increased levels of cardiac biomarkers in the appropriate clinical context [2, 4]. A successful PCI was defined as residual stenosis of < 30% and thrombolysis in MI flow grade 3 in the IRA. The glomerular function for eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [18]. Based on the definition of the National Kidney Foundation [19], CKD was defined as an eGFR < 60 mL/min/1.73 m^2. The Global Registry of Acute Coronary Events (GRACE) risk score [20] was calculated for all patients. Patients with STD ≥ 24 h were included in the delayed hospitalization group based on the findings of a recent report [10]. The symptom onset time was defined as the

time of onset of the last sustained chest pain [21]. Typical chest pain was defined as substernal chest discomfort of characteristic quality and duration, triggered by exertion or emotional stress and relieved by rest or nitroglycerin [2, 4]. Atypical chest pain was defined as chest pain that was inconsistent with the characteristics of typical chest pain. The primary clinical outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause death, recurrent MI (re-MI), and any repeat coronary revascularization, including target lesion revascularization (TLR), target vessel revascularization (TVR), non-TVR, and stroke. According to the American Heart Association/American Stroke Association guidelines, an acute cerebrovascular event resulting in death or neurological deficit for > 24 h or the presence of acute infarction demonstrated by brain imaging studies was defined as a stroke [22]. All-cause death was considered cardiac death (CD) unless an undisputed non-cardiac cause was present [23]. The secondary clinical outcome was definite or probable stent thrombosis (ST) during the 3-year follow-up period. ST was defined according to the definition provided by the Academic Research Consortium [24]. The definitions of re-MI, TLR, TVR, and non-TVR have been previously published [25].

Statistical analyses

For continuous variables, intergroup differences were evaluated using the unpaired t-test, and data are expressed as mean ± standard deviation or median (interquartile range). For categorical variables, intergroup differences were analyzed using the chi-squared test or, if not applicable, Fisher's exact test, and data are expressed as counts and percentages. Univariate analysis was performed for all variables in the groups with or without delayed hospitalization, with the p value set at < 0.05. Subsequently, a multicollinearity test [26] was performed between the included variables to confirm non-collinearity between them. The variance inflation factor values were calculated to measure the degree of multicollinearity among the variables. A variance inflation factor > 5 indicates high correlation [27]. Multicollinearity was considered when the tolerance value was < 0.1 [28] or the condition index was > 10 [27]. The variables included in the multivariable analysis were male sex, age, left ventricular ejection fraction (LVEF), body mass index, systolic blood pressure, diastolic blood pressure, DTB, atypical chest pain, dyspnea, Q-wave on electrocardiogram (ECG), ST-segment depression, T-wave inversion, Killip class II/III, use of emergency medical service, non-PCI center, hypertension, diabetes mellitus (DM), dyslipidemia, previous MI, previous PCI, previous CABG, previous heart failure, previous stroke, current smoker, levels of peak creatine kinase myocardial band (CK-MB), peak troponin-I, blood glucose, high-sensitivity C-reactive protein (hs-CRP), total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and beta-blockers. Moreover, to adjust for potential confounders, a propensity score (PS)-adjusted analysis was performed using a logistic regression model. We tested all potentially relevant variables, including baseline clinical, angiographic, and procedural factors (Table 1). The c-statistic for the PS-matched analysis in this study was 0.704. Patients in the delayed hospitalization group (STD ≥ 24 h) were matched to those in the non-delayed hospitalization group (STD < 24 h) (1:1) using the nearest available pair-matching method according to PSs. The subjects were matched using a caliper width of 0.01. This procedure yielded 2274 well-matched pairs (**Suppl. Table S1**). Various clinical outcomes were estimated using Kaplan-Meier curve analysis, and group differences were compared using the log-rank test. Statistical significance was defined as a 2-tailed p value of < 0.05. All statistical analyses were performed using the SPSS software version 20 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

Baseline characteristics of the study population are summarized in Table 1. In both the CKD and non-CKD groups, the mean values of peak CK-MB and peak troponin-I were higher in the STD < 24 h group, and the mean age, mean value of hs-CRP, number of patients with high GRACE risk score (> 140), and number of patients who received the transradial approach for PCI were higher in the STD ≥ 24 h group. Additionally, in both the CKD and non-CKD groups, the number of patients with atypical chest pain, dyspnea, Q-wave on ECG, and first medical contact outside of a PCI-capable center were significantly higher in the STD ≥ 24 h group than in the STD < 24 h group.

Clinical outcomes

The rates of major clinical outcomes at 3 years are listed in Tables 2, 3, and Figure 2. Multivariable-adjusted analysis revealed that in patients with CKD, MACCE (adjusted hazard ratio [aHR]:

Table 2. Clinical outcomes of the STD < 24 hours and STD ≥ 24 hours groups in patients with CKD or non-CKD at 3 years.

Outcomes	CKD, n = 1118			Unadjusted		Multivariable-adjusted*		Propensity score-adjusted	
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
MACCE	158 (20.9)	72 (19.9)	0.656	1.065 (0.806–1.408)	0.656	1.131 (0.844–1.516)	0.409	1.555 (0.871–1.614)	0.400
All–cause death	76 (10.2)	40 (11.0)	0.637	0.912 (0.622–1.337)	0.637	1.063 (0.710–1.591)	0.768	1.005 (0.627–1.542)	0.983
Cardiac death	43 (5.7)	29 (8.0)	0.155	0.712 (0.444–1.140)	0.157	1.007 (0.610–1.661)	0.979	1.097 (0.614–1.959)	0.755
Non-cardiac death	33 (4.5)	11 (3.0)	0.292	1.440 (0.728–2.849)	0.295	1.272 (0.621–2.609)	0.511	1.184 (0.522–2.583)	0.686
Recurrent MI	34 (4.7)	16 (4.6)	0.952	1.019 (0.562–1.845)	0.952	1.192 (0.636–2.235)	0.584	1.085 (0.530–2.220)	0.823
Any repeat revascularization	83 (11.6)	32 (9.2)	0.271	1.257 (0.836–1.890)	0.272	1.209 (0.788–1.857)	0.385	1.311 (0.819–2.098)	0.259
Stroke	19 (2.6)	16 (4.6)	0.086	0.563 (0.289–1.094)	0.090	1.469 (0.735–2.938)	0.276	1.499 (0.760–3.302)	0.316
ST (definite or probable)	6 (0.8)	2 (0.6)	0.652	1.442 (0.291–7.146)	0.654	1.604 (0.301–8.457)	0.622	1.631 (0.321–9.761)	0.592
Outcomes	**Non-CKD, n = 3395**			**Unadjusted**		**Multivariable-adjusted***		**Propensity score-adjusted**	
	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	p	HR (95% CI)	P
MACCE	280 (11.1)	93 (10.6)	0.622	1.061 (0.839–1.341)	0.622	1.139 (0.894–1.450)	0.292	1.217 (0.920–1.610)	0.170
All-cause death	60 (2.4)	27 (3.1)	0.267	0.774 (0.491–1.219)	0.268	1.096 (0.682–1.962)	0.704	1.056 (0.606–1.839)	0.847
Cardiac death	27 (1.1)	14 (1.6)	0.224	0.672 (0.352–1.281)	0.227	1.253 (0.624–2.518)	0.526	1.026 (0.461–2.285)	0.949
Non-cardiac death	33 (1.3)	13 (1.5)	0.705	0.884 (0.465–1.679)	0.705	1.049 (0.501–2.235)	0.887	1.138 (0.526–2.460)	0.743
Recurrent MI	67 (2.7)	22 (2.5)	0.798	1.065 (0.658–1.724)	0.798	1.275 (0.775–2.098)	0.339	1.713 (0.974–3.012)	0.062
Any repeat revascularization	215 (8.6)	64 (7.4)	0.238	1.183 (0.895–1.563)	0.239	1.249 (0.937–1.665)	0.130	1.242 (0.892–1.630)	0.199
Stroke	36 (1.4)	22 (2.5)	0.033	0.566 (0.333–0.963)	0.036	1.619 (0.934–2.805)	0.086	1.502 (0.887–2.663)	0.104
ST (definite or probable)	11 (0.4)	6 (0.7)	0.373	0.638 (0.236–1.726)	0.377	1.265 (0.437–5.123)	0.665	1.231 (0.376–4.032)	0.732

*Adjusted by male sex, age, LVEF, BMI, SBP, DBP, DTB, atypical chest pain, dyspnea, Q-wave in electrocardiogram, ST-segment depression, T wave inversion, Killip class II/III, emergency medical service, non-PCI center, hypertension, diabetes mellitus, dyslipidemia, previous MI, previous PCI, previous CABG, previous heart failure, previous stroke, current smoker, peak CK-MB, peak troponin-I, blood glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, and beta-blocker; CKD — chronic kidney disease; STD — symptom-to-door time; HR — hazard ratio; CI — confidence interval; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; ST — stent thrombosis, LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; DTB — door-to-balloon time; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; CK-MB — creatine kinase myocardial band; HDL — high-density lipoprotein; LDL — low-density lipoprotein

Table 3. Clinical outcomes of the CKD and non-CKD groups in both STD < 24 hours and STD ≥ 24 hours groups at 3 years.

Outcomes	STD < 24 h (n = 3272)			Unadjusted		Multivariable-adjusted*		Propensity score-adjusted#	
	CKD (n = 756, group A)	Non-CKD (n = 2516, group C)	Log-rank	HR (95% CI)	P	HR (95% CI)	p	HR (95% CI)	P
MACCE	158 (20.9)	280 (11.1)	< 0.001	2.001 (1.647–2.432)	< 0.001	1.681 (1.361–2.076)	< 0.001	1.856 (1.374–2.505)	< 0.001
All-cause death	76 (10.2)	60 (2.4)	< 0.001	4.399 (3.136–6.171)	< 0.001	3.327 (2.097–4.816)	< 0.001	3.603 (2.155–6.025)	< 0.001
Cardiac death	43 (5.7)	27 (1.1)	< 0.001	5.507 (3.403–8.911)	< 0.001	3.797 (2.241–6.434)	< 0.001	4.942 (2.431–7.845)	< 0.001
Non-cardiac death	33 (4.5)	33 (1.3)	< 0.001	3.489 (2.153–5.652)	< 0.001	2.918 (1.731–5.214)	< 0.001	2.450 (1.133–5.097)	0.023
Recurrent MI	34 (4.7)	67 (2.7)	0.006	1.775 (1.175–2.682)	0.006	1.246 (0.595–2.014)	0.502	1.288 (0.699–2.371)	0.417
Any repeat revascularization	83 (11.6)	215 (8.6)	0.014	1.370 (1.063–1.765)	0.015	1.234 (0.584–1.530)	0.114	1.348 (0.949–1.658)	0.090
Stroke	19 (2.6)	36 (1.4)	0.030	1.833 (1.052–3.196)	0.033	1.343 (0.741–2.434)	0.331	1.484 (1.036–2.584)	0.294
ST (definite or probable)	6 (0.8)	11 (0.4)	0.204	1.884 (0.697–5.095)	0.212	1.587 (0.546–4.614)	0.396	1.698 (0.406–4.743)	0.468
Outcomes	**STD ≥ 24 h (n = 1241)**			**Unadjusted**		**Multivariable-adjusted***		**Propensity score-adjusted#**	
	CKD (n = 362, group B)	Non-CKD (n = 879, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
MACCE	72 (19.9)	93 (10.6)	< 0.001	1.994 (1.466–2.713)	< 0.001	1.751 (1.225–2.483)	0.006	1.938 (1.232–3.047)	0.004
All-cause death	40 (11.0)	27 (3.1)	< 0.001	3.748 (2.300–6.107)	< 0.001	2.162 (1.234–3.692)	0.011	2.531 (1.255–5.102)	0.009
Cardiac death	29 (8.0)	14 (1.6)	< 0.001	5.222 (2.759–9.883)	< 0.001	2.506 (1.254–5.009)	0.009	4.882 (1.661–8.235)	0.004
Non-cardiac death	11 (3.0)	13 (1.5)	0.055	2.154 (0.965–4.808)	0.061	1.714 (0.707–4.155)	0.233	1.184 (0.429–3.265)	0.744
Recurrent MI	16 (4.6)	22 (2.5)	0.056	1.854 (0.974–3.530)	0.060	1.704 (0.828–3.506)	0.147	1.433 (0.576–3.462)	0.439
Any repeat revascularization	32 (9.2)	64 (7.4)	0.247	1.284 (0.840–1.963)	0.248	1.679 (0.776–3.441)	0.142	1.588 (0.674–2.990)	0.152
Stroke	16 (4.6)	22 (2.5)	0.056	1.855 (0.974–3.532)	0.060	1.481 (0.728–3.013)	0.278	1.070 (0.455–2.521)	0.876
ST (definite or probable)	2 (0.6)	6 (0.7)	0.835	0.844 (0.170–4.181)	0.835	1.362 (0.104–4.346)	0.721	1.937 (0.176–5.374)	0.589

*Adjusted by male sex, age, LVEF, BMI, DBP, DTB, atypical chest pain, dyspnea, ST-segment depression, atrial fibrillation, Killip class II/III, emergency medical service, non-PCI center, hypertension, diabetes mellitus, previous MI, previous PCI, previous CABG, previous heart failure, previous stroke, current smoker, peak CK-MB, blood glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, beta-blocker, and statin. #Propensity score-adjusted analysis was performed using a logistic regression model. We tested all potentially relevant variables such as baseline clinical, angiographic, and procedural factors (Table 1). The c-statistic for the propensity score-matched analysis in this study was 0.715. Patients in the CKD were matched to those in the non-CKD group (1:1) using the nearest available pair-matching method according to propensity scores. The subjects were matched with a caliper width of 0.01. This procedure yielded 1624 well-matched pairs; STD — symptom-to-door time; CKD — chronic kidney disease; HR — hazard ratio; CI — confidence interval; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; ST — stent thrombosis, LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; DTB — door-to-balloon time; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; CK-MB — creatine kinase myocardial band; HDL — high-density lipoprotein; LDL — low-density lipoprotein

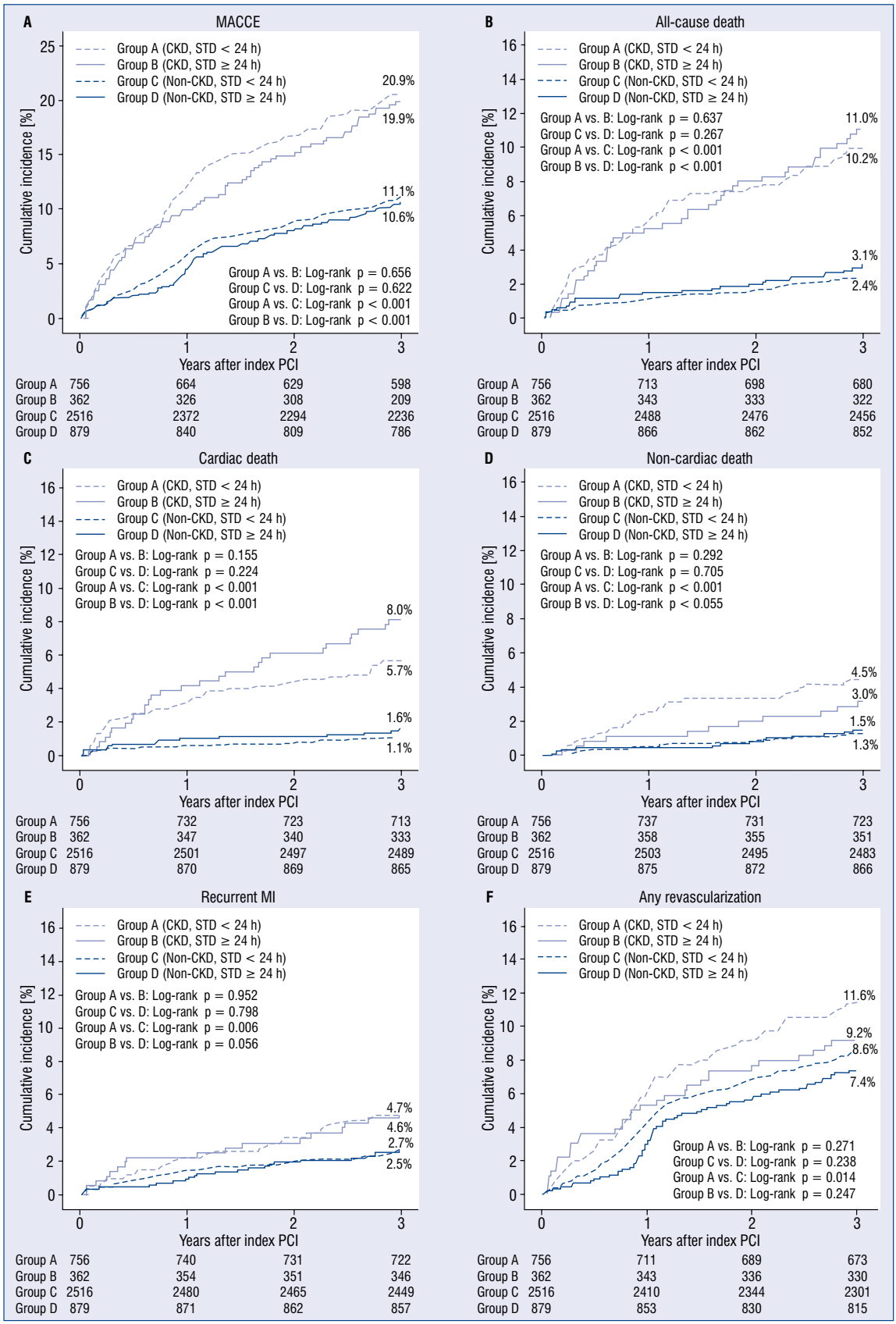

Figure 2. Kaplan-Meier curved analysis for major adverse cardiac and cerebrovascular events (MACCE) (**A**), all-cause death (**B**), cardiac death (**C**), non-cardiac death (**D**), recurrent myocardial infarction (MI) (**E**), any repeat revascularization (**F**), stroke (**G**), and stent thrombosis (**H**); CKD — chronic kidney disease; STD — symptom-to-door time; PCI — percutaneous coronary intervention.

1.131; 95% CI: 0.844–1.516; p = 0.409), all-cause death (aHR: 1.063; p = 0.768), CD (aHR: 1.007; p = 0.979), non-CD (NCD; aHR: 1.272; p = 0.511), re-MI (aHR: 1.192; p = 0.584), any repeat revascularization (aHR: 1.209; p = 0.385), stroke (aHR: 1.469; p = 0.276), and ST (aHR: 1.604; p = 0.622) rates were not significantly different between the STD < 24 h and STD ≥ 24 h groups. Furthermore, in patients without CKD, the MACCE (aHR: 1.139; 95% CI: 0.894–1.450; p = 0.292), all-cause death (aHR: 1.096; p = 0.704), CD (aHR: 1.253; p = = 0.526), NCD (aHR: 1.049; p = 0.887), re-MI (aHR: 1.275; p = 0.339), any repeat revascularization (aHR: 1.249; p = 0.130), stroke (aHR: 1.619; p = 0.086), and ST (aHR: 1.265; p = 0.665) rates were not significantly different between the STD < 24 h and STD ≥ 24 h groups. These results were confirmed by the PS-adjusted analysis, which showed that the primary and secondary clinical outcomes were not significantly different between the STD < 24 h and STD ≥ 24 h groups in both CKD and non-CKD groups (Table 2). Table 3 shows the comparison of clinical outcomes between patients with and without CKD in both the STD < 24 h and STD ≥ 24 h groups. Multivariable-adjusted analysis revealed that in both STD < 24 h and STD ≥ 24 h groups, MACCE (aHR: 1.681; p < 0.001 and aHR: 1.751; p = 0.006, respectively), all-cause death (aHR: 3.327; p < 0.001 and aHR: 2.162; p = 0.011, respectively), and CD (aHR: 3.797; p < 0.001 and aHR: 2.506; p = 0.009, respectively) rates were significantly higher in the CKD group than in the non-CKD group. Moreover, in the STD < 24 h group, the NCD rate (aHR: 2.918; p < 0.001) was significantly higher in the CKD group than in the non-CKD group. **Supplementary Figure S1** shows the subgroup analysis for MACCE in the CKD and non-CKD groups using a Cox logistic regression model. The results revealed that patients in all subgroups except for those showing significant p-for-interaction demonstrated comparable MACCE rates between the STD < 24 h and STD ≥ 24 h groups. **Supplementary Table S2** shows the independent predictors of MACCE. Reduced LVEF (< 50%) and multivessel disease were common independent predictors of MACCE in both CKD and non-CKD groups. Although STD and DBT were not significant independent predictors of MACCE, CKD (aHR: 1.404; 95% CI: 1.161–1.696; p < 0.001) was a significant predictor of MACCE in the total study population. Furthermore, in the total study population, CKD was significant independent predictor of all-cause death (aHR: 2.106; 95% CI: 1.537–2.886; p < 0.001), CD (aHR: 2.646; 95% CI: 1.713–4.085; p < 0.001), and NCD (aHR: 1.595; 95% CI: 1.002–2.539; p = 0.047; **Suppl. Table S2**).

Discussion

The main findings of this study are as follows: (1) MACCE, all-cause death, CD, NCD, re-MI, any repeat revascularization, stroke, and ST rates were not significantly different between the STD < 24 h and STD ≥ 24 h groups in multivariable--adjusted and PS-adjusted analyses in both the CKD and non-CKD groups; (2) Regardless of analyzed STD, MACCE, all-cause death, and CD rates were significantly higher in the CKD group than in the non-CKD group in multivariable-adjusted and PS-adjusted analyses; furthermore, the NCD rate was higher in the CKD group than in the non-CKD group in patients with STD < 24 h; (3) In the total study population, although STD and DTB were not significant independent predictors of MACCE and mortality, the presence of CKD was a significant independent predictor of MACCE and mortality.

Pre-hospital delay is the total amount of time taken by patients to present to the emergency department following acute symptom onset [29]. Previous research [29, 30] demonstrated that delayed hospitalization in patients with acute coronary syndrome (ACS) was associated with atypical symptoms and decreased ambulance use. In this study, in both CKD and non-CKD groups, the number of patients who presented atypical chest pain (CKD group: 34.8% vs. 22.2%, p < 0.001; non-CKD group: 15.9% vs. 9.7%, p < 0.001) was significantly higher in the STD ≥ 24 h group than in the STD < 24 h group (Table 1). Furthermore, the number of patients who used emergency medical service was significantly lower in the STD ≥ 24 h groups than in the STD < 24 h groups (CKD group: 4.1% vs. 15.6%, p < 0.001; non-CKD group: 3.5% vs. 11.3%, p < 0.001). Moreover, atypical chest pain was a significant independent predictor of MACCE in the CKD group (aHR: 1.508; 95% CI: 1.129–2.015; p = 0.005) and in the total study population (aHR: 1.322; 95% CI: 1.075–1.626; p = 0.008) (**Suppl. Table S2**), and a significant independent predictor of all-cause death (aHR: 1.779; p < 0.001) and NCD (aHR: 2.248; p = 0.001) (**Suppl. Table S2**).

According to a recent report [10], patients with NSTEMI and STD ≥ 24 h had higher long-term all--cause mortality (17.0% vs. 10.5%; p < 0.001) than those with STD < 24 h. These data are valuable in showing the clinical importance of pre-hospital

delay in patients with NSTEMI. However, approximately 15% of this study population did not receive PCI or had unsuccessful PCI; furthermore, patients who received BMS or 1G-DES and those who experienced cardiogenic shock or in-hospital death were included. To date, second-generation DES is the preferred revascularization option because it can reduce restenosis and mortality rates compared to 1G-DES during long-term follow-up [31]. However, because long-term outcomes can be affected by the occurrence of in-hospital death [32], individuals who experienced in-hospital death or cardiogenic shock should not be included in the analysis during the estimation of long-term mortality. In these aspects, their research [10] has limitations in reflecting the current real-world practice and in showing long-term prognosis of patients with NSTEMI. To overcome these limitations, we excluded patients with in-hospital death or cardiogenic shock, as shown in Figure 1.

The current European guideline suggest [15] that the target DTB should be decreased to < 60 min to achieve the lowest mortality in patients with STEMI. However, DTB was not an independent predictor of MACCE and mortality in patients with NSTEMI in our study (**Suppl. Table S2**), which is consistent with previous studies [10, 33–35]. In a meta-analysis of randomized controlled trials including 5324 patients with NSTEMI [33], reduced DTB did not reduce mortality. Bonello et al. [34] also showed that the rate of mortality and MI was not affected by the median time between randomization and CAG (range: 0.5–14.0 h and 18.3–86.0 h). In the subgroup analysis of the most recent meta-analysis including 3422 patients from 11 randomized trials [36], the all-cause death rate was lower in the revascularization group than in the medical therapy group in patients with NSTE-ACS and CKD (relative risk: 0.73; 95% CI: 0.51–1.04; p = 0.08). Because patients presenting with NSTEMI often have many comorbidities, including CKD [11, 12], an early invasive strategy may worsen the outcomes in those patients, becuase the renal function can be further reduced due to contrast dye administration and sub-optimal fluid support prior to the procedure. In a recent publication [35], consistent with previous reports [33, 34], the 2-year major clinical outcomes were similar between the early invasive and delayed invasive groups in patients with NSTEMI (n = 8241) in the four different renal function groups. Kim et al. [37] also suggested that culprit-only PCI may be a better reperfusion option for patients with NSTEMI with multivessel disease and CKD rather than multivessel PCI, including complete revascularization and incomplete revascularization, with regard to the procedure time and the risk of contrast-induced nephropathy. In our study, as shown in **Supplementary Table S2**, STD (< 24 h vs. ≥ 24 h) was not an independent predictor of MACCE, all-cause death, CD, and non-CD in both the CKD and non-CKD groups. However, the presence of CKD was an independent predictor of all-cause death (aHR: 2.106; p < 0.001), CD (aHR: 2.646; p < 0.001), and non-CD (aHR: 1.595; p = 0.047) compared to the non-CKD group. Additionally, in the total study population, CKD was an independent predictor of MACCE (aHR: 1.404; p < 0.001). Therefore, our results suggest that CKD may be a stronger determinant of worse outcomes in NSTEMI patients compared to SDT (< 24 h vs. ≥ 24 h). In patients presenting STEMI, the relative mortality was found to increase by 7.5% for every 30-min delay in reperfusion [38], and pre-hospital activation and direct cardiac catheterization laboratory transfer were related to lower 1-year mortality (adjusted odds ratio: 5.3; 95% CI: 2.2–12.4; p < 0.001) [39].

Although we could not precisely determine the causative factors for our results, several factors can be considered. First, patients with STEMI often have complete occlusion of the coronary artery, while patients with NSTEMI more often have partial or incomplete occlusion [40]. In the case of completely absent blood supply, available oxygen in the ischemic zone of the myocardium disappears within seconds, and after a certain duration of complete ischemia there is no treatment modality that can salvage ischemic myocardium [41]. A necrotic cardiomyocyte cannot be brought back to life [42]. In contrast, cardiomyocytes exposed to low residual oxygen levels may be able to maintain sufficient adenosine triphosphate levels to survive for an extended period, even if the amount of adenosine triphosphate is insufficient to allow their contraction [42]. Hence, the impact of delayed hospitalization on major clinical outcomes in the NSTEMI group may be lower than that in the STEMI group. However, in our study, the number of patients with pre-PCI Thrombolysis in Myocardial Infarction flow grade 0/1 was not significantly different between the STD ≥ 24 h and STD < 24 h groups (Table 1, **Suppl. Table S1**) or between the CKD and non-CKD groups. Second, in our study, patients with CKD had lower LVEF and higher incidence of Killip class II/III, hypertension, DM, previous MI, PCI, CABG, heart failure, and stroke, left main as IRA, 3-vessel disease, and higher mean age,

hs-CRP level, and GRACE risk scores than those with non-CKD in both the STD < 24 h and STD ≥ 24 h groups and in the total study population. Hence, these worse baseline characteristics in the CKD group may be related to worse 3-year clinical outcomes in patients with CKD, as shown in Table 3. Additionally, the number of patients presenting with atypical chest pain and dyspnea was higher in patients with CKD than in patients without CKD. Atypical chest pain was a significant independent predictor of MACCE in the CKD group and in the total study population (**Suppl. Table S2**) and a significant independent predictor for all-cause death and NCD (**Suppl. Table S2**) in our study.

Despite the limited availability of data on patients with NSTEMI and CKD [14], the number of patients with CKD has increased over the past decade and is expected to increase owing to decreased mortality and increased incidence of DM and obesity [41]. As the GFR declines, the risk of coronary artery disease and vascular calcification increases [11]. Moreover, calcification of the intima and media of the large vessels in CKD is associated with all-cause death and cardiovascular mortality [43]. Consistent with previous reports [13, 44], CKD was an independent predictor of all-cause and cardiovascular mortality in our study. Therefore, although STD could be considered an important predictor of long-term outcomes in patients with STEMI [38, 39], the obtained results underline the important effects of CKD on the long-term clinical outcomes in patients with NSTEMI. Although the population size may have been insufficient in our study, the used registry based on 20 tertiary high-volume university hospitals may provide meaningful results.

Limitations of the study

This study has some limitations. First, although the main predictors of prehospital delay include sociodemographic, clinical, situational, appraisal, and behavioral factors [29], this study may have induced some bias regarding educational level, marital status, employment status, and any other important factors that were not assessed because the used registry did not include these variables. Second, there may have been some underreported and/or missing data. Third, because the estimation of renal function was based on a single eGFR measurement at the time of presentation to the hospital, eGFR may have changed during the follow-up period. However, the follow-up results for eGFR were incomplete. This is an important source of bias in this study. Fourth, because of the limitations of the medical insurance system in Korea, the use of fractional flow reserve to estimate intermediate lesions was very low in this study (Table 1). Fifth, the 3-year follow-up period in this study was relatively short for estimating the long-term clinical outcomes.

Conclusions

In conclusion, in the era of new-generation DES, the presence of CKD appears to be a much more important determinant of MACCE and mortality rates than STD in patients with NSTEMI. ST is one of the most concerning events after DES implantation, given its grim prognosis. However, ST rates were similar between the CKD and non-CKD groups and between the STD < 24 h and STD ≥ 24 h groups in our study. Further well-designed large-scale studies are warranted to confirm these results.

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