Heart and Vessels (2019) 34:1917–1924
https://doi.org/10.1007/s00380-019-01444-8

ORIGINAL ARTICLE

Clinical features of potential after-effects of percutaneous coronary intervention in the treatment of silent myocardial ischemia

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Received: 25 October 2018 / Accepted: 31 May 2019 / Published online: 6 June 2019

Abstract
Clinical predictors for later adverse cardiovascular events in patients undergoing percutaneous coronary intervention (PCI) for silent myocardial ischemia remain undetermined. We investigated clinical features leading to later adverse cardiovascular events in patients who underwent PCI for silent myocardial ischemia. Of a total of 294 consecutive patients with a diagnosis of silent myocardial ischemia who successfully underwent contemporary PCI in our institute between January 2013 and December 2014, an initial event of any of all-cause death, hospitalized heart failure, acute coronary syndromes, and target vessel revascularization were identified as later adverse cardiovascular events and evaluated an association of them with baseline clinical characteristics. Silent myocardial ischemia was defined by an assessment of either electrocardiogram, myocardial perfusion imaging, coronary angiogram, or coronary fractional flow reserve. During a median follow-up of 565 days (interquartile range 361–816), later adverse cardiovascular events were identified in 38 patients (13%) consisting of 6 deaths, 5 hospitalized heart failures, 2 acute coronary syndromes, and 25 target vessel revascularizations. A presence of chronic kidney disease and/or insulin-treated diabetes mellitus, but not other clinical features, was strongly associated with later adverse cardiovascular events (hazard ratio 8.22; 95% confidential interval 2.95–29.25, $P<0.0001$). Those events were increased in accordance with advanced stages of chronic kidney disease ($P=0.0003$). A presence of chronic kidney disease and/or insulin-treated diabetes mellitus may lead the potential after-effects of PCI in the treatment of silent myocardial ischemia.

Keywords Silent myocardial ischemia · Percutaneous coronary intervention · After-effects · Insulin · Diabetes mellitus · Chronic kidney disease

Introduction

Percutaneous coronary intervention (PCI) has widely underwent relief myocardial ischemia irrespective of whether symptomatic or asymptomatic stable coronary artery diseases, and also silent myocardial ischemia has been placed a main part of the diseases [1–4]. An extensive clinical research could not establish a superiority of PCI over medical treatments with respect to a prevention of future cardiovascular events and an improvement of symptoms in patients with stable coronary artery diseases [5, 6]. Of those unresolved issues, any clinical hazards of PCI leading to later cardiovascular events in patients with silent myocardial ischemia remain undetermined. Thus, to address the potential after-effects of PCI in the treatment of silent myocardial ischemia, the present study evaluated clinical features leading to later adverse cardiovascular events in patients with silent myocardial ischemia who successfully underwent contemporary PCI.

Methods

Study patients

Between January 2013 and December 2014, 294 patients with silent myocardial ischemia were identified from 1277

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consecutive patients who successfully underwent contemporary PCI in our institute (Fig. 1). Silent myocardial ischemia was defined by both an absence of angina pectoris and any of the following criteria: (1) new ischemic ST-T change at rest on 12-lead electrocardiogram (≥ 1 mm in ≥ 2 contiguous leads), (2) exercise-induced ischemic electrocardiographic changes (≥ 1 mm horizontal or down-sloping ST-segment depression 80 ms after the J point) [7], (3) reversible myocardial perfusion imaging defects during exercise or pharmacologic vasodilator stress (evaluation of summed stress score and summed rest score) [8], (4) vessel diameter stenosis of ≥ 90% by coronary angiogram, and (5) fractional flow reserve (FFR) less than 0.80 [9]. Exercise or pharmacologic stress testing were frequently used to screen asymptomatic, but high-risk persons regardless of whether a history of treatment of coronary artery diseases were presented. FFR was measured with a coronary pressure guidewire (Pressure Wire Certus, St. Jude Medical, Uppsala, Sweden, or Prime Wire Prestige, Volcano Ltd., San Diego, USA) during maximal hyperemia induced by intravenous infusion of adenosine (140 μg/kg/min) or intracoronary injection of papaverine (8–12 mg) [10]. All patients underwent a contemporary PCI mostly with use of intravascular ultrasound. A deployment of stent with pre-dilatation or direct with dual anti-platelet therapy and the stent types (i.e., bare metal stent of drug-eluting stent) was up to a physician in charge. Successful PCI was defined according to an achievement of post-PCI procedural thrombolysis in myocardial infarction flow grade 3, ranging from 0 to 3 with the highest grade indicating normal coronary reflow [11], and free of symptoms from any cardiovascular events during hospital admission. To evaluate the complexity of coronary artery diseases for PCI, Syntax score ranged from 0 to 115, with the highest number indicating the most complex coronary anatomy for PCI, was calculated [12].

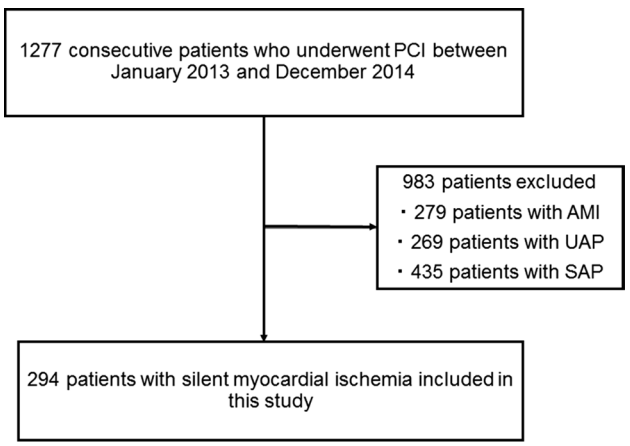

Fig. 1 Study flow chart in the present study. *AMI* acute myocardial infarction, *UAP* unstable angina pectoris, *SAP* stable angina pectoris

Clinical assessments

All of demographic and PCI procedural characteristics were abstracted from the hospital records. Regarding later adverse cardiovascular events as the main outcome of the present study, an initial event of any of all-cause death, hospitalized heart failure, acute coronary syndromes, and target vessel revascularization were identified from the Sakakibara Health Integrative Profile cohort system [13]. This cohort system was launched in 2006 for the purpose of improving healthy life expectancy in patients with any cardiovascular diseases who were admitted to our institute. The system used a continuous surveillance system to track all subsequent cardiovascular and non-cardiovascular events, via direct contact in the outpatient department, hospital records, and a mailed questionnaire after hospital discharge at least once a year. A diagnosis of chronic kidney disease as well as hypertension, dyslipidemia, diabetes mellitus and acute coronary syndromes was evaluated in accordance with the universal criteria [14, 15]. Briefly, chronic kidney disease is defined by a presence of kidney dysfunction for 3 or more months showing estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, and each stage was classified using eGFR as follows; stage 1 > 90 ml/min/1.73 m^2, stage 2 60 to 89 ml/min/1.73 m^2, stage 3a 45–59 ml/min/1.73 m^2, stage 3b 30–44 ml/min/1.73 m^2, stage 4 15–29 ml/min/1.73 m^2, stage 5 < 15 ml/min/1.73 m^2 or dialysis.

Statistical analysis

Data are expressed as mean ± SD for continuous variables and numbers with percentages for categorical variables. A difference between patients with and without later adverse cardiovascular events was analyzed using an unpaired *t* test or a Mann–Whitney *U* test for continuous variables and a Chi-square test or a Fisher's exact test for categorical variables. Event-free survival curve was drawn using a Kaplan–Meier method, and a log-rank test was used to compare two event-free survival curves. To determine possible confounding factors associated with later adverse cardiovascular evens, the Cox proportional hazards regression analysis was performed. A significance for the trend of incidence of later adverse cardiovascular events across each stage of chronic kidney disease was evaluated by a Chi-square test. Statistical significance was defined as P value < 0.05. All statistical analyses were conducted by SAS 11.0 (SAS Institute Inc., Cary, NC, USA). The present study had complied with the Declaration of Helsinki, and was approved by the local ethics committee of our institute. All the patients gave written informed consent for study participation.

Results

During a median follow-up of 565 days (interquartile range 361–816 days), a total of 38 (13%) patients had later adverse cardiovascular events, which were composed of six any-cause death (one ventricular fibrillation, one amyloidosis, one ischemic colitis, one myelodysplastic syndrome, and two sudden deaths), five refractory heart failures with a necessity of hospitalization, two acute coronary syndromes, and 25 symptomatic target vessel revascularizations. Baseline demographic characteristics were relatively similar between those with and without later adverse cardiovascular events except a prevalence of chronic kidney disease and/or insulin-treated diabetes mellitus (Table 1). Regarding PCI-related procedure characteristics, complexity of coronary lesion (i.e., Syntax score) and also a degree of myocardial ischemia evaluated by myocardial perfusion imaging were not different between those with and without later adverse cardiovascular events. None of 20 patients with a FFR-guided PCI who included 2 patients with chronic kidney disease and none with insulin-treated diabetes mellitus revealed later adverse cardiovascular events. As to post-PCI medications, a frequency of use of beta-blockers was only different between them. Regarding baseline coronary characteristics of patients with chronic kidney disease or insulin-treated diabetes mellitus, no difference was observed between those with and without later adverse cardiovascular events (Table 2). There was a high incidence of later adverse cardiovascular events in accordance with a presence of chronic kidney disease and/or insulin-treated diabetes mellitus with a significant hazard ratio (Fig. 2a and Table 3). Later adverse cardiovascular events also demonstrated an incremental risk in accordance with advance stages of chronic kidney disease (Fig. 2b).

Discussion

In the present study, we found a presence of chronic kidney disease and/or insulin-treated diabetes mellitus, but not other clinical features, was strongly associated with later adverse cardiovascular events in patients with a successful contemporary PCI for silent myocardial ischemia. There is an incremental risk of later adverse cardiovascular events in accordance with advanced stages of chronic kidney disease. Thus, the present study may imply a presence of chronic kidney disease and/or insulin-treated diabetes mellitus as the pivotal clinical features for potential after-effects of PCI in the treatment of silent myocardial ischemia.

A presence of chronic kidney disease is well recognized as an independent risk with a substantial increase in atherosclerotic cardiovascular diseases [16]. The incidence of cardiovascular mortality is much higher than an incidence of renal-replacement therapy in patients with mild-to-moderate chronic kidney disease, indicating an onset of cardiovascular diseases as the true burden of chronic kidney disease. Especially a presence of both chronic kidney disease and myocardial ischemia may increase a twofold higher annual cardiac death than an absence of both [17], while most of previous clinical studies had underpowered to conclude clinical benefits of coronary revascularization using PCI [18] and/or coronary artery bypass grafting [6]. Furthermore, differential impact on clinical outcomes in accordance with the severity of chronic kidney disease has been reported even in the era of second-generation drug-eluting stent [19]. Since the present study also found an incremental risk with advanced stages of chronic kidney disease, we believe a possible clinical advantage of PCI as an early stage as possible in patients with chronic kidney disease with silent myocardial ischemia.

As one of the reasons why twofold higher risk of acute coronary syndromes and/or sudden cardiac death in patients with diabetes mellitus [20], high prevalence of silent myocardial ischemia in those population might be presented [21, 22]. With regard to a possible association of a greater extent of coronary artery diseases with later adverse cardiovascular events in diabetes mellitus [22], we did not find any differences in Syntax score between those with and without later adverse cardiovascular events. Since most patients with insulin-treated diabetes mellitus supposed to be long-term suboptimal glycemic control under the treatment of maximally oral antidiabetic agents, there is a possibility of an advanced myocardial tissue-level endothelial dysfunction [23] and also coagulation abnormalities [24] partly associated with both microvascular and macrovascular complications [25]. A large number of recent registry data including 6–7% of silent myocardial ischemia also documented 3 years unsatisfactory clinical outcomes after PCI in insulin-treated diabetic patients when compared with those without insulin even in the era of second-generation drug-eluting stent [26]. Future basic and clinical research to address the underlying mechanisms, such as a role of increased end products of advanced glycation [27], for less clinical benefits of PCI in patients with insulin-treated diabetic mellitus with silent myocardial ischemia need to be investigated.

Although a couple of cohort studies demonstrated an increased risk of ischemic events and cardiac death in the setting of untreated silent myocardial ischemia [2, 28–31], limited studies evaluated an effectiveness of PCI for silent myocardial ischemia [32–35]. According to a current study [35] in particular, a proof of resolution of myocardial ischemia may be one of key issues to prevent clinical adverse events of PCI in the treatment of silent myocardial ischemia. The concept of an optimal medical treatment

Table 1 Baseline clinical characteristics of the study patients, in accordance with a presence or absence of later adverse cardiovascular events

	Overall	Adverse cardiovascular events		*P* value
		Yes	No	
	n = 294	*n* = 38	*n* = 256	
Demography				
Age, years	70 ± 11	69 ± 9	70 ± 11	0.85
Male sex, no. (%)	246 (84)	30 (79)	216 (84)	0.41
Hypertension, no. (%)	232 (79)	32 (84)	200 (78)	0.38
Dyslipidemia, no. (%)	231 (79)	27 (71)	204 (80)	0.24
Diabetes mellitus, no. (%)	104 (35)	18 (47)	86 (34)	0.10
Insulin-treated diabetes mellitus, no. (%)	13 (4)	5 (13)	8 (3)	0.02
Current smoking, no. (%)	43 (15)	4 (11)	39 (15)	0.43
Family history of coronary artery diseases, no. (%)	40 (14)	3 (8)	37 (15)	0.24
Chronic kidney disease, no. (%)	110 (38)	26 (68)	84 (33)	< 0.0001
Prior myocardial infarction, no. (%)	122 (41)	17 (45)	105 (41)	0.57
Ejection fraction, %	56 ± 11	52 ± 11	56 ± 11	0.08
Hemoglobin, g/dL	13 ± 2	13 ± 2	13 ± 2	0.25
eGFR, mL/min/1.73 m^2	63 ± 18	53 ± 19	64 ± 18	0.0003
Creatinine, mg/dL	1.1 ± 1.1	1.4 ± 1.9	1.0 ± 0.9	0.029
Hemoglobin A1c, %	6.2 ± 0.8	6.4 ± 1.0	6.1 ± 0.8	0.039
Diagnosis process				
New ischemic ST-T changes in ECG at rest, no. (%)	29 (10)	1 (3)	28 (11)	0.07
Ischemic ST-T changes in exercise stress ECG, no. (%)	10 (3)	3 (8)	7 (3)	0.15
Stress myocardial perfusion imaging, no. (%)	81 (28)	15 (40)	66 (26)	0.09
Summed stress score, unit	10 ± 7	12 ± 9	9 ± 6	0.19
Summed rest score, unit	5 ± 6	5 ± 6	7 ± 9	0.28
> 90% coronary stenosis, no. (%)	154 (52)	19 (50)	135 (53)	0.75
Fractional flow reserve, no. (%)	20 (7)	0	20 (8)	0.02
PCI procedure				
Syntax score	9 ± 6	8 ± 6	9 ± 6	0.66
LAD culprit coronary artery, no. (%)	138 (47)	19 (50)	119 (46)	0.69
Multi-vessel disease, no. (%)	82 (28)	10 (28)	72 (29)	0.93
Bare metal stent, no. (%)	50 (17)	7 (18)	43 (17)	0.81
Drug-eluting stent, no. (%)	209 (71)	23 (61)	186 (73)	0.13
Post-PCI medications				
Aspirin, no. (%)	288 (98)	36 (95)	252 (98)	0.19
Adenosine diphosphate receptor blocker, no. (%)	293 (99.7)	38 (100)	255 (99)	0.60
Beta-blockers, no. (%)	202 (69)	33 (87)	169 (66)	0.01
Renin–angiotensin system inhibitors, no. (%)	193 (66)	29 (76)	164 (64)	0.13
Calcium channel blockers, no. (%)	135 (46)	19 (50)	116 (45)	0.59
Vasodilators, no. (%)	37 (13)	3 (8)	34 (13)	0.32
Statin, no. (%)	240 (82)	31 (82)	209 (82)	0.99

Data are numbers (%) of patients or mean ± SD

ECG electrocardiogram, *eGFR* estimated glomerular filtration rate, *PCI* percutaneous coronary intervention, *LAD* left anterior descending

also provided equivalent clinical outcomes compared with PCI in patients with stable coronary artery diseases, regardless of whether symptomatic or silent myocardial ischemia [5, 36, 37]. These scientific rationales deeply consider us the crucial issue to determine which categories and how degrees of silent myocardial ischemia may have clinical advantages when attempting PCI. Although a current guideline [38] adopted a class I recommendation of revascularization to improve clinical outcomes when presented a large (> 10%) area of myocardial ischemia by

Table 2 Baseline coronary characteristics of the study patients with chronic kidney disease or insulin-treated diabetes mellitus

	Chronic kidney disease			Insulin-treated diabetes mellitus		
	Adverse cardiovascular events			Adverse cardiovascular events		
	Yes ($n=26$)	No ($n=84$)	*P* value	Yes ($n=5$)	No ($n=8$)	*P* value
Age, years	72 ± 9	75 ± 9	0.15	66 ± 4	72 ± 10	0.22
Male sex, no. (%)	19 (73)	70 (83)	0.26	4 (80)	8 (100)	0.15
Summed stress score, unit	14 ± 10	11 ± 8	0.44	15 ± 4	14 ± 2	0.66
> 90% coronary stenosis, no. (%)	13 (50)	45 (54)	0.75	3 (60)	3 (38)	0.43
Multi-vessel disease, no. (%)	7 (27)	22 (26)	0.94	3 (60)	2 (25)	0.21
Syntax score	8 ± 5	10 ± 6	0.13	12 ± 6	9 ± 7	0.43

Data are numbers (%) of patients or mean ± SD

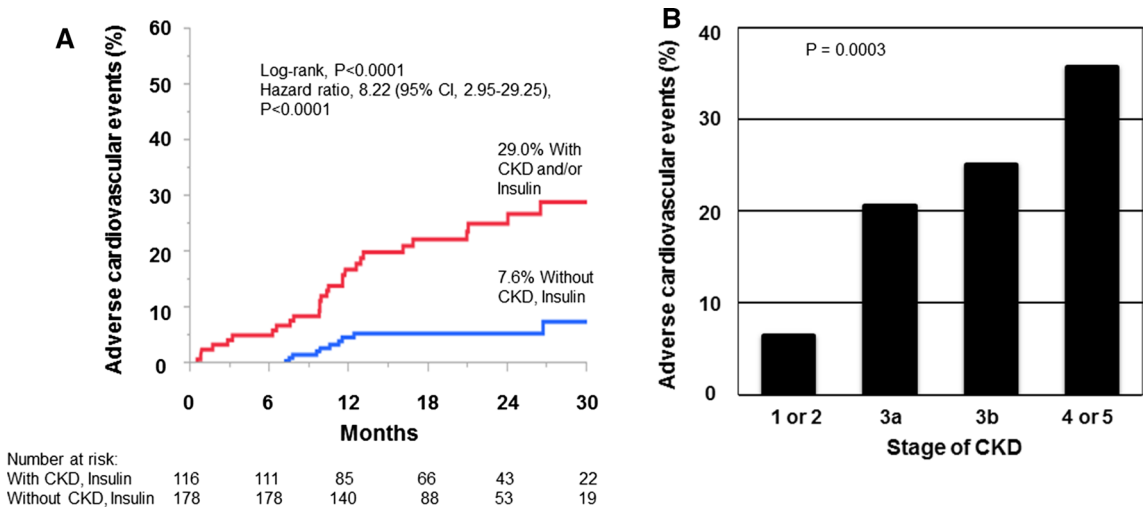

Fig. 2 **a** Time-to-event curves and hazard ratio of later adverse cardiovascular events in accordance with a presence or absence of chronic kidney disease and/or insulin-treated diabetes mellitus. Hazard ratio was calculated using the multivariate Cox proportional hazards regression model, including possible confounding factors associated with later adverse cardiovascular evens, such as age, ejection fraction, prior myocardial infarction, chronic kidney disease, and insulin-treated diabetes mellitus. *CKD* chronic kidney disease. **b** Incidence of later adverse cardiovascular events in accordance with each stage of chronic kidney disease. *P* value revealed a significant trend according to advanced stages of chronic kidney disease. *CKD* chronic kidney disease

Table 3 The Cox proportional hazards regression analysis for an incidence of later adverse cardiovascular events

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI	*P* value	Hazard ratio (95% CI)	*P* value
Age (for each 1 year)	0.997 (0.968–1.028)	0.8243	0.980 (0.942–1.022)	0.3466
Ejection fraction (for each 1%)	0.977 (0.950–1.008)	0.1405	0.993 (0.963–1.027)	0.6653
Prior myocardial infarction	1.077 (0.561–2.040)	0.8196	0.729 (0.305–1.673)	0.4573
Chronic kidney disease	3.688 (1.902–7.582)	< 0.0001	–	–
Insulin-treated diabetes mellitus	3.649 (1.248–8.555)	0.0212	–	–
Chronic kidney disease and/or insulin-treated diabetes mellitus	4.396 (2.207–9.519)	< 0.0001	8.223 (2.946–29.249)	< 0.0001

95% CI 95% confidence intervals

myocardial perfusion imaging, there was not a clear consensus on a reliability of this assessment alone to determine revascularization in the setting of silent myocardial ischemia [14]. In fact, we did not find any difference in a severity of myocardial perfusion imaging between those with and without later adverse cardiovascular events. By contrast, as with the growing evidence of clinical benefits of PCI with a proof of functional coronary stenosis in stable coronary artery diseases [39], none of those with silent myocardial ischemia who underwent a FFR-guided PCI had later adverse cardiovascular events in the present study. To accomplish the optimization of PCI for silent myocardial ischemia, we have to design the robust clinical studies addressing the vast uncertainties behind silent myocardial ischemia.

Study limitations

Due to a relatively small number of the study population in a single center study, a couple of study limitations need to be considered to interpret our data. First, a paradoxically higher frequency of use of beta-blockers in patients with later adverse cardiovascular events than those without adverse events may provide a new question as to an efficacy of this drug to prevent after-effects of PCI in the treatment of silent myocardial ischemia. Second, the present study showed a valuable possibility of a FFR-guided PCI in the treatment of silent myocardial ischemia, while a quite few patients limited a conclusion. Third, with respect of an assessment of chronic kidney disease and/or diabetic microangiopathy, the present study did not evaluate a degree of microalbuminuria which was established as a potential biomarker to predict an adverse cardiovascular events in those [40]. ISCEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial (NCT01471522) and ISCHEMIA-CKD (NCT01985360) informed us somewhat of endorsements to address our limitations and uncertainty of the risk of PCI in patients with silent myocardial ischemia.

Conclusions

The present study may imply a presence of chronic kidney disease and/or insulin-treated diabetes mellitus as the pivotal clinical features for potential after-effects of PCI in the treatment of silent myocardial ischemia.

Acknowledgements We are sincerely grateful to Toshiaki Masuda for his profound contributions in managing the data in the present study, and are appreciative of all of the staff of Sakakibara Heart Team.

Compliance with ethical standards

Conflict of interest This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest to disclose.

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