Influence of concomitant percutaneous transluminal angioplasty with percutaneous coronary intervention on cardiovascular and limb outcomes in patients with chronic stable lower extremity artery diseases

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Article

Keywords: Concomitant percutaneous transluminal angioplasty, Percutaneous coronary intervention, Cardiovascular outcomes, Limb outcomes, End-stage renal diseases

Posted Date: March 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1448182/v1

Abstract

Concomitant percutaneous transluminal angioplasty (PTA) at the time of percutaneous coronary intervention (PCI) is often performed because lower extremity artery disease (LEAD) often coincides with coronary artery disease. We investigated the impact of concomitant PTA on both cardiovascular and limb outcomes in the Korean National Health Insurance Service registry. Among 78,185 patients undergoing PCI, 6,563 patients with stable LEAD without limb ischemia were included. After 1:5 propensity score-matching was conducted, 279 patients in the PTA + PCI group and 1,385 patients in the PCI group were compared. Multivariate Cox proportional hazard models showed that the risk of all-cause death was higher in the PTA + PCI group than in the PCI group whereas the risks of myocardial infarction, repeat revascularization, stroke, cardiovascular death and bleeding event were not different between the 2 groups. In contrast, the risks of end-stage renal diseases and unfavorable limb outcomes were higher in the PTA + PCI group. Mediation analyses revealed that amputation and PTA after discharge significantly mediated the association between the concomitant PTA and all-cause death. Concomitant PTA was not associated with an increased risk of cardiovascular events but may increase the risk of all-cause death mediated by unfavorable renal and limb outcomes in patients with stable LEAD.

Introduction

For decades, percutaneous transluminal angioplasty (PTA) has been widely selected as a treatment strategy in patients who had stable lower extremity artery disease (LEAD) without critical limb ischemia, to improve their life-style limiting symptoms (1). Patients with stable LEAD frequently present atherosclerotic cardiovascular (CV) diseases in other vascular sites, including the coronary arteries and carotid arteries (1). Studies have shown that significant coronary artery disease (CAD) was found in up to 70% of patients with LEAD, while LEAD was also found in 16% of patients with significant CAD. Consequently, concomitant PTA at the time of percutaneous coronary intervention (PCI) is often performed for patients with significant CAD and symptomatic LEAD in current clinical practice (2, 3). These concomitant PTAs performed by skillful interventional cardiologists may be effective in rapidly improving the life-style limiting symptoms in patients with stable LEAD. However, concomitant endovascular procedures at the time of PCI would increase the use of radiocontrast media and parenteral anticoagulants, which may increase the risk of renal impairment and bleeding (4). Moreover, these procedures may promote systemic inflammatory responses through extensive injuries to the diseased vessels (5), which may eventually result in coronary instent restenosis (ISR) during follow-up (6, 7). Because it is crucial to determine how concomitant PTA affects clinical outcomes following PCI, we investigated the impact of concomitant PTA on CV, limb and renal outcomes in patients who underwent PCI using the Korean National Health Insurance System (KNHIS) database.

Methods

Data source

This study is an observational retrospective study conducted using the Korean National Health Insurance Sharing Service (KNIHSS) customized research database. The KNIHSS is a data sharing service operated by the KNHIS to facilitate the use of National Health information for research purposes from various disciplines, providing a sample cohort database as well as customized databases. Detailed profiles of the KNHISS customized database were described previously (8). The KNHIS is a government-run single payer health care system covering 97% of the entire Korean population; other programs, including the Medical Assistance Program, cover the remaining 3% of the population. The KNIHSS customized database includes insurance claim data from both patients covered by the KNHIS and those covered by the Medical Assistant Program and data from the National Health Screening (NHS) (9).

Information regarding demographics, socioeconomic status, admission records, clinical diagnosis, comorbidities, medications and medical procedures was obtained from the insurance claim data. The earliest measurements of height, weight, waist circumference (WC) and serum creatinine levels following the index PCI were obtained from the NHS database. Clinical outcomes were identified using the KCD-7 codes for the clinical diagnoses in the insurance claim database. The causes and dates of death were identified using KCD-7 codes and information on the discharge date obtained from the final admission during which death occurred.

All procedures in this study protocol adhered to the ethical principles of the Declaration of Helsinki. The Institutional Review Board (IRB) of Hanyang University Guri Hospital (IRB file number: GURI-2019-03-032) and the ethics committee of the KNIHS (REQ000026929-061; NHIS-2019-1-561) were reviewed and approved the protocol of this study, and informed consent from the subjects was exempted because the data were deidentified.

Study population

From the KNHISS database, we included patients with stable LEAD who underwent PCI between January 2014 and December 2015 in this study. Patients who had undergone any prior PCI or PTA between January 2012 and December 2014 or those who had any diagnosis codes or reimbursement codes related to acute limb ischemia (ALI), critical limb ischemia (CLI) and limb amputations were excluded. Because of the research ethics policy declared by the KNHISS, 30% of the entire population was randomly selected to produce the customized database for this study.

Definitions of clinical characteristics and outcomes

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation. The follow-up duration was defined from the day of the first visit to the outpatient office after index PCI to the day when the first clinical event occurred, when the reimbursement claims stopped emerging in the database, or when 5 years had passed after index PCI. All patients have been followed for at least 3 years. Comorbidities and clinical events were identified using KCD-7 codes. Charlson's comorbidity index (CCI) was used to represent the severity of comorbidities as previously described (10). Detailed KCD-7 codes used to define the comorbidities and clinical outcomes are described in Supplementary Table 1. Myocardial infarction (MI) was defined as the new diagnosis of

MI codes (I21-I24) during admission, coronary artery revascularization was defined as the insurance claim codes representing PCI and coronary artery bypass surgery (CABG), stroke was defined as the new diagnosis of the stroke codes (I60-I64) during admission, and CV death was defined as the death of CV disease (I20-I25, I42-I43, I50), cerebrovascular events (I60-I69) and peripheral vascular diseases (I70-I74). Repeat coronary revascularization was defined as a composite of repeated PCI and CABG after index PCI and was identified using the hospital claim codes for both procedures that are described in Supplementary Table 2. A major adverse CV event (MACE) was defined as a composite of CV death, MI, stroke and repeat coronary revascularization. Bleeding events were defined as a new diagnosis code related to bleeding events based on the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery) criteria (11) resulting in admission or transfusion (Supplementary Table 1). End-stage renal disease (ESRD) was defined as a new diagnosis of the ESRD code (N18.5). Critical limb ischemia was defined as a new diagnosis of diabetic foot ulcer/gangrene or amputation of any part on the lower extremities in presence of the diagnostic codes for LEAD (Supplementary Table 1). PTA after discharge was defined with the use of any plain angioplasty balloons, drug-coated balloons, bare-metal nitinol stents (BMSs) or drug eluting stents (DESs) for PTA during readmission after discharge from the index hospitalization. The detailed claim codes for PTA and PCI are described in Supplementary Table 3.

Statistical analysis

Because the patients undergoing concomitant PTA at the time of PCI were expected to have more severe atherosclerotic CV diseases with more comorbidities than those undergoing PCI alone, which were expected to be more numerous, we performed propensity score matching (PSM) to balance the covariates before conducting comparisons between the two groups. The propensity scores were created using a multivariate logistic regression model including age, sex, BMI, WC, eGFR, MI at index admission, numbers of coronary stents used, numbers of vessels intervened, income ≥ median, prior bleeding events, prior MI, prior LEAD, prior cerebrovascular events, prior hemiplegia, diabetes, hypertension, chronic kidney diseases, peptic ulcer, ESRD, and the CCI as covariates. The matching process was performed using a nearest neighbor method at a ratio of 1:5. The quality of the PSM was assessed using the absolute standard mean differences (SMDs) between the two groups.

Categorical variables such as sex, MI at index admission and DAPT use was compared using a chi-square test, whereas continuous variables such as age, BMI and eGFR were compared using Student's t test. A Kaplan–Meier survival analysis with a log-rank test was utilized to compare the cumulative incidences of the clinical outcomes, including all-cause death, CV death, MACEs, ESRD, amputation and PTA after discharge, between the PTA + PCI group and the PCI only group. Cox proportional hazard models were used to assess the association of concomitant PTA at the time of PCI with the clinical outcomes after index PCI. Multivariate Cox proportional hazard models were used to adjust the influences of confounding factors and reinforce the associations between concomitant PTAs and clinical outcomes. The multivariate models included age, sex, BMI, WC, MI at index admission, number of coronary stents used, income ≥ median, prior bleeding events, prior MI, prior LEAD, prior stroke, diabetes, hypertension,

peptic ulcer, DAPT duration, and statin use as covariates. The full multivariate models were reduced through a backward variable selection process with a cutoff point of $p > 0.05$ to minimize the overfitting biases and multicollinearity among variables.

To estimate the influence of unmeasured confounders on the multivariate Cox proportional hazard models, *E*-values were estimated for the hazard ratio (HR) and 95% confidence interval (CI). The *E*-value is a simple and powerful sensitivity analysis tool to evaluate the strength of a risk-outcome association (12). The *E*-value indicates the minimum strength of association (e.g., HR) that an unmeasured confounder should have with both the causal factor and outcome, to completely explain away the apparent risk-outcome association, while the *E*-value for an upper or lower CI limit indicates the minimum strength of association that the confounder should have, to make the CI include the null value. A high *E*-value indicates a strong causal relationship that would survive in the presence of a confounder having a HR < the *E*-value with both the causal factor and outcome.

Subgroup analyses were performed to detect the presence of differential impacts of the concomitant PTA on the risk of MACEs, ESRD and limb outcomes (amputation + PTA after discharge) in various subsets of the patients.

Mediation analyses were performed in the PSM cohort to identify the causal mediation effects of limb and renal outcomes on the association between concomitant PTA and all-cause death using a bootstrap technique (13). Parametric survival regression models with a Gaussian distribution, including the limb and renal outcomes as the time-varying covariates, were used as the model objects for the mediators and the outcome in the mediation analyses. A mediation analysis for each mediator was performed in a set of 1000 bootstrap samples, and average total, direct and indirect causal mediation effects on the coefficients of the parametric survival regression models were reported.

All statistical analyses other than mediation analyses were conducted using commercialized statistical software, SAS 7.1 (SAS Institute, Cary, NC, USA). The mediation analyses were performed using statistical software R-4.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and the statistical packages “survival” and “mediation” in RStudio-1.3 (RStudio Team, RStudio Inc, Boston, MA, USA). A *p value* of < 0.05 was considered significant.

Results

Among 78,185 patients who underwent PCI and were registered in the KNHIS customized database, 6,563 patients diagnosed with LEAD without any previous histories of foot ulcer or any limb ischemia-related diagnoses were included in the analyses (Fig. 1). Concomitant PTAs at the time of PCI were performed in 272 patients (PTA + PCI group), and PCI alone was performed in 6,284 patients (PCI only group). After PSM was performed at a 1:5 ratio, 1,385 patients remained in the PCI-only group. The quality of the PSM procedure was described using absolute SMDs before and after matching in Supplementary Fig. 1.

The median follow-up duration was 3.78 (interquartile range [IQR] 3.24–4.34) years in the entire cohort (23805.4 person-years) and 3.67 (IQR 3.16–4.22) years in the PSM cohort (5774.5 person-years). The follow-up duration was longer in the PCI only group in the entire cohort (3.61 [IQR 3.09–4.31] vs. 3.79 [IQR 3.25–4.34]; p = 0.002), but was not significantly different between the groups in the PSM cohort (3.61 [IQR 3.09–4.31] vs. 3.68 [3.16–4.2]; p = 0.345).

Baseline characteristics before and after PSM are described in Table 1. In the unmatched cohort, the mean age and CCI score were higher and BMI, WC, eGFR, DAPT duration were lower in the PTA + PCI group than in the PCI only group. Male sex, multivessel CAD, the use of oral anticoagulants and many comorbidities, including chronic lung disease, heart failure, diabetes, ischemic stroke or cerebral ischemia, hemiplegia, CKD and ESRD, were more frequent, whereas MI at the index PCI and previous histories of MI (at least 3 years or earlier) and stable LEAD were less frequent in the PTA + PCI group than in the PCI only group. In the matched cohort, all baseline characteristics were evenly balanced between the two groups with SMD < 0.1, except for DAPT duration and the frequency of statin use, which were marginally lower in the PTA + PCI group.

Table 1
Baseline characteristics of study population before and after propensity score matching.

	Before PSM			After PSM			
	PTA + PCI	PCI only		PTA + PCI	PCI only		
	N = 279	N = 6284	p value	N = 279	N = 1385	p value	SMD
Male	214 (76.7)	3749 (59.7)	< 0.001	214 (76.7)	1089 (78.6)	0.527	-0.042
Age (Years)	70.8 ± 9.0	69.4 ± 10.0	0.011	70.8 ± 9.0	70.8 ± 9.4	0.998	< 0.001
Income levels ≥ median	134 (48)	3146 (50.1)	0.546	134 (48)	663 (47.9)	0.999	-0.003
BMI (kg/m^2)	23.8 ± 2.4	24.6 ± 2.6	< 0.001	23.8 ± 2.4	23.8 ± 2.4	0.989	0.001
WC (cm)	84.9 ± 6.5	85.6 ± 7.1	0.091	84.9 ± 6.5	85.1 ± 6.9	0.705	-0.025
eGFR ($mL/min/1.73m^2$)	70.4 ± 20.2	75.2 ± 23.7	< 0.001	70.4 ± 20.2	70.3 ± 21.3	0.980	0.002
Index MI	51 (18.3)	1958 (31.2)	< 0.001	51 (18.3)	250 (18.1)	0.996	-0.005
Multi vessel CAD	53 (19)	1025 (16.3)	0.271	53 (19)	254 (18.3)	0.862	-0.017
Procedural Characteristics							
Number of coronary stents	1.97 ± 0.31	1.97 ± 0.25	0.795	1.97 ± 0.31	1.97 ± 0.25	0.992	0.022
Number of PCI vessels	1.24 ± 0.53	1.18 ± 0.46	0.099	1.24 ± 0.53	1.21 ± 0.50	0.464	0.049
Number of peripheral stents	1.71 ± 0.48	0.00 ± 0.00	-	1.71 ± 0.48	0.00 ± 0.00	-	-
Types of PTA						-	-
Plain balloon angiography	58 (20.8)	0 (0.0)		58 (20.8)	0 (0.0)		
Drug-eluting balloon	5 (1.8)	0 (0.0)		5 (1.8)	0 (0.0)		
Stenting	189 (67.7)	0 (0.0)		189 (67.7)	0 (0.0)		

	Before PSM			After PSM			
Others	27 (9.7)	6284 (100.0)		27 (9.7)	1385 (100.0)		
Types of PCI			0.233			0.435	-0.071
Plain balloon angiography	16 (5.7)	258 (4.1)		16 (5.7)	60 (4.3)		
Drug-eluting balloon	8 (2.9)	106 (1.7)		8 (2.9)	24 (1.7)		
Stenting	250 (89.6)	5826 (92.7)		250 (89.6)	1277 (92.2)		
Others	5 (1.8)	94 (1.5)		5 (1.8)	24 (1.7)		
DAPT duration (months)	14.2 ± 16.9	17.2 ± 16.7	0.003	14.2 ± 16.9	16.0 ± 16.3	0.088	-0.109
Medication							
DAPT	233 (83.5)	5515 (87.8)	0.044	233 (83.5)	1195 (86.3)	0.265	-0.079
Statin	238 (85.3)	5708 (90.8)	0.003	238 (85.3)	1240 (89.5)	0.052	-0.131
Oral and coagulants	14 (5.0)	169 (2.7)	0.034	14 (5)	52 (3.8)	0.413	0.066
Charlson's comorbidity index	5.3 ± 2.4	4.8 ± 2.5	< 0.001	5.3 ± 2.4	5.3 ± 2.7	0.889	0.009
≤ 3	75 (26.9)	2133 (33.9)	0.003	75 (26.9)	383 (27.6)	0.948	0.021
4–6	118 (42.3)	2716 (43.2)		118 (42.3)	587 (42.4)		
≥ 7	86 (30.8)	1435 (22.8)		86 (30.8)	415 (30.0)		
Comorbidities							
Any history of bleeding	31 (11.1)	588 (9.4)	0.381	31 (11.1)	130 (9.4)	0.437	-0.057
Peptic Ulcer	48 (17.2)	1047 (16.7)	0.876	48 (17.2)	236 (17)	1.000	-0.004
Chronic lung diseases	42 (15.1)	662 (10.5)	0.022	42 (15.1)	205 (14.8)	0.987	0.008
Connective tissue disease	4 (1.4)	59 (0.9)	0.606	4 (1.4)	12 (0.9)	0.583	0.052

	Before PSM			After PSM			
Heart failure	101 (36.2)	1948 (31.0)	0.075	101 (36.2)	489 (35.3)	0.784	0.019
Hypertension	256 (91.8)	5746 (91.4)	0.939	256 (91.8)	1269 (91.6)	1.000	-0.005
Diabetes	219 (78.5)	4549 (72.4)	0.030	219 (78.5)	1106 (79.9)	0.665	0.032
Myocardial infarction	79 (28.3)	2434 (38.7)	0.001	79 (28.3)	390 (28.2)	1.000	-0.003
Peripheral artery diseases	146 (52.3)	4146 (66)	< 0.001	146 (52.3)	733 (52.9)	0.908	0.012
Intracranial hemorrhage	4 (1.4)	63 (1.0)	0.533	4 (1.4)	17 (1.2)	0.768	0.019
Stroke or cerebral ischemia	107 (38.4)	1590 (25.3)	< 0.0001	107 (38.4)	513 (37.0)	0.684	0.028
Hemiplegia	17 (6.1)	109 (1.7)	< 0.001	17 (6.1)	59 (4.3)	0.238	-0.095
Dementia	13 (4.7)	294 (4.7)	1.000	13 (4.7)	94 (6.8)	0.235	-0.101
Chronic kidney diseases	40 (14.3)	491 (7.8)	< 0.001	40 (14.3)	188 (13.6)	0.808	-0.024
End-stage renal diseases	18 (6.5)	178 (2.8)	0.001	18 (6.5)	82 (5.9)	0.840	-0.025
Data are presented with the mean ± SD or N (%)							
PSM, propensity-score matching; PCI, percutaneous coronary intervention; PTA, Percutaneous transluminal angioplasty; BMI, body mass index; WC, waist circumference; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; DAPT, dual-antiplatelet therapy							

In the unmatched cohort, all clinical outcomes except MACEs occurred more frequently in the PTA + PCI group than in the PCI only group (Supplementary Fig. 2). In the matched cohort, all-cause deaths, ESRD, amputation and PTA after discharge were more frequent in the PTA + PCI group than in the PCI only group, whereas CV deaths were only marginally more frequent in the PTA + PCI group, and the cumulative incidence of MACEs was not different between the groups (Fig. 2).

Univariate Cox proportional hazard models showed that the risk of all-cause death, ESRD, amputation and PTA after discharge were higher in the PTA + PCI group than in the PCI only group, whereas the risk of MI, repeat coronary revascularization, ischemic stroke and bleeding events were not different between the two groups in either the unmatched or matched groups (Fig. 3). The risk of CV death was higher in the PTA + PCI group than in the PCI only group in the unmatched cohort, but the significance of the risk

difference was only marginal in the matched cohort. The *E*-values for the HR and the lower limit of the 95% CI (LLCI) were high for amputation and PTA after discharge and modest for all-cause death and ESRD but not significant for MACE, CV death, MI, repeat coronary revascularization, ischemic stroke and bleeding events in the matched cohort (Fig. 3 and Supplementary Table 4). Multivariate Cox proportional hazard models also showed results similar to those in the univariate models of the matched cohort (Table 2). Concomitant PTA at the time of PCI was associated with a higher risk of all-cause death, ESRD and amputation, whereas it was not associated with the risk of CV death, MI, repeat coronary revascularization, stroke or bleeding events.

Table 2
Multivariate Cox proportional hazard models for the association between concomitant PTA at the time of PCI and clinical outcomes.

	Before PSM				After PSM			
	Events		Models*		Events		Models*	
Clinical outcomes	N = 279	N = 6284	HR (95% CI)	P value	N = 279	N = 1385	HR (95% CI)	P value
Death	73 (26.2)	919 (14.6)	1.69 (1.32–2.15)	< 0.001	73 (26.2)	273 (19.7)	1.52 (1.17–1.98)	0.002
CV death	21 (7.5)	283 (4.5)	1.54 (0.99–2.42)	0.058	21 (7.5)	69 (5.0)	1.59 (0.97–2.59)	0.065
MACEs	79 (28.3)	1611 (25.6)	1.11 (0.89–1.40)	0.358	79 (28.3)	393 (28.4)	1.00 (0.78–1.27)	0.969
Myocardial infarction	13 (4.7)	414 (6.6)	0.87 (0.50–1.52)	0.625	13 (4.7)	80 (5.8)	0.85 (0.47–1.53)	0.591
Revascularization	49 (17.6)	962 (15.3)	1.25 (0.93–1.66)	0.136	49 (17.6)	237 (17.1)	1.09 (0.80–1.48)	0.594
Stroke	16 (5.7)	344 (5.5)	1.09 (0.66–1.81)	0.727	16 (5.7)	101 (7.3)	0.88 (0.52–1.50)	0.639
Any bleeding	9 (3.2)	209 (3.3)	0.97 (0.50–1.89)	0.920	9 (3.2)	49 (3.5)	0.91 (0.44–1.85)	0.787
ESRD	28 (10.0)	206 (3.3)	2.05 (1.37–3.06)	< 0.001	28 (10.0)	93 (6.7)	1.60 (1.05–2.45)	0.029
Amputation	20 (7.2)	108 (1.7)	3.81 (2.36–6.16)	< 0.001	20 (7.2)	34 (2.5)	3.41(1.96–5.92)	< 0.001
PTA after discharge	68 (24.4)	168 (2.7)	9.27 (6.93–12.4)	< 0.001	68 (24.4)	70 (5.1)	5.94 (4.25–8.30)	< 0.001

PSM, propensity score matching; PCI, percutaneous coronary intervention; PTA, Percutaneous transluminal angioplasty; CV cardiovascular; MACE, major adverse cardiovascular events; ESRD, endstage renal disease; HR, hazard ratio; CI, confidence interval

Before PSM	After PSM

* The multivariate model includes age, sex, BMI, waist circumference, MI at index admission, number of coronary stents used, income ≥ median, prior bleeding events, MI, PAD, stroke, diabetes, hypertension, peptic ulcer, DAPT duration and statin use as covariates. The model was reduced using a backward selection method (cutoff criterion, p > 0.1).

Subgroup analyses showed that the risk of MACE and ESRD were not different between the PTA + PCI group and the PCI only group in all subgroups according to age, sex, index event, diabetes mellitus, CKD, multivessel CAD and CCI (Fig. 4 and Supplementary Table 5). However, the association of the concomitant PTA with the risk of the composite events of amputation and PTA after discharge was stronger in females, nondiabetic patients, patients with CKD and those with low CCI (< 7).

Time-varying Cox proportional hazard models tested in the PSM cohort showed that amputation (HR 2.38; 95% CI 1.42-4.00), PTA after discharge (HR 2.27; 95% CI 1.62–3.17) and the development of ESRD (HR 4.43; 95% CI 3.22–5.82) during the follow-up period were associated with higher risks of all-cause death (Fig. 5). Mediation analyses revealed that undergoing amputation (93.9%; $p < 0.001$) and PTAs after discharge (91.7%; $p < 0.001$) strongly mediated the association between concomitant PTAs and the risk of all-cause death, whereas ESRD did not mediate the association (Fig. 5 and Supplementary Table 6).

Discussion

In our results, we found that concomitant PTA at the time of PCI was associated with an increased risk of all-cause death, ESRD, amputation and PTA after discharge, whereas it was not associated with increased risks of CV deaths, repeat coronary revascularization, MI, stroke or bleeding events. Our results also showed that experiencing amputation and PTAs after discharge strongly mediated the association between concomitant PTAs and the risk of all-cause death.

Symptomatic LEADs are frequently found in patients with significant CAD (1). The presence of LEAD in patients with acute coronary syndrome indicates widespread atherosclerosis and is often associated with higher CV mortality and morbidity (14, 15). Therefore, revascularization for symptomatic LEADs is often required in patients undergoing PCI, and concomitant PTA is frequently performed at the time of PCI as a default strategy worldwide. Bartus et al. reported a case series of 66 patients undergoing PTA and PCI during a single hospital stay and claimed that concomitant PTA was safe and should be encouraged for patients' better quality of life (3). A recent study by Koren et al. also reported in a small retrospective cohort that concurrent PTA had a similar 1-year MACE and mortality as staged PTA in patients undergoing PCI, advocating concurrent PTA (16). However, concomitant PTA at the time of PCI still concerns various aspects, including procedure complexity, high contrast media exposure, repeated use of parenteral anticoagulants, multiple puncture sites and higher rates of ISR and acute thrombosis in PTA compared to PCI. PTA is also known to be followed by extensive systemic inflammation, which might promote coronary artery ISR (5, 7). Therefore, the safety and efficacy of concomitant PTAs should be investigated thoroughly. Our results may provide some confidence in the safety of concomitant PTAs

regarding CV outcomes and bleeding but may imply potential hazards of concomitant PTAs regarding all-cause deaths and unfavorable renal and limb outcomes, which demands further investigation. Our results are particularly more concerning because the rates of revascularization and amputation have been reported as < 3% per year in patients with stable LEAD in a recent randomized controlled trial (17) and in an observational study (18), which are similar to those in the PCI-only group in our results (Fig. 2).

CV outcomes, including MACE, MI and repeat coronary revascularization, would be driven by coronary ISRs, which are uncommon in the second-generation DES era. In fact, the incidences of MI (concomitant PTA vs. PCI only, 4.7% vs. 5.8%) and repeat coronary revascularization (17.6% vs. 17.1%) during 5 years of observation were quite low in the both groups in our results. The similar risks of bleeding events and stroke between the groups are expected because parenteral anticoagulants would not affect the bleeding risk after discharge, and the same dual-antiplatelet agent therapy regimens were used in the two groups (1, 8). In contrast, the greater exposure to radiocontrast media may have contributed to the higher incidences of ESRD in the PTA + PCI group (19).

Because patients underwent PTA between 2014 and 2015 in the current study, the majority of PTAs were performed using plain balloon angioplasty and BMSs, which exhibit ISR rates as high as 30–50% in a year (20, 21). These high ISR rates after PTA may have resulted in the higher incidences of PTA after discharge and amputation in the PTA + PCI group. The development of CLI has already been recognized as a predictor of death (22). Repeat hospitalization and procedures for limb revascularization and wound care may have to be followed by the risk of procedural complications, malnutrition, infection, bleeding and thrombotic events, thus eventually leading to death. Our results also showed that experiencing PTAs after discharge or amputation significantly mediated the association between concomitant PTAs and a higher risk of all-cause death. Although DES has been preferred to BMS in recent PTAs, the ISR rate of DES was still not remarkably different from that of BMS after PTA for femoropopliteal lesions (23). Therefore, the association between concomitant PTA and unfavorable limb outcomes may not have been different, although the study population included more patients undergoing PTA with DES.

The associations between concomitant PTA and unfavorable limb outcomes were stronger in the subgroups of females, patients with CKD and those with CCIs < 7; this may also imply the role of ISR in worsening the outcomes of patients undergoing concomitant PTA. Patients with CKD typically have more severe LEAD and thus would have experienced amputation or PTA after discharge more frequently. However, it is difficult to apply this reasoning to the results in females and patients with fewer comorbidities. A high ISR rate rather than a heavy LEAD burden may explain the results more easily, given that females could develop ISR more easily because of their smaller vessel diameter (24) and that frequent deaths may have interfered with the observation of amputation/PTA after discharge as a competing event in the patients with a high CCI.

The *E*-values for the LLCI of the HRs for all-cause deaths and ESRD were only 1.17 and 1.21 in the PSM cohort, which indicates that potential unmeasured confounders including fragility might explain the association of the concomitant PTA with these outcomes. In contrast, the *E*-values for the LLCI of the HR

for amputation and PTA after discharge were substantially high (3.33 and 7.75), and it is unlikely for any potential unmeasured factors to cancel the associations in the PSM cohort. Furthermore, to minimize the concern that patients in the PTA + PCI group might have had more severe LEADs than those in the PCI only group, we excluded patients with any conditions potentially related to ALI, CLI and limb amputation and included patients only with stable LEAD who had not undergone any endovascular procedures for the 3 preceding years. In fact, a previous study showed that in patients with stable LEAD, an ankle-brachial index < 0.5 increased the risk of amputation and limb revascularization, but when age, sex, CLI, CKD and diabetes were adjusted, the HRs of having an ankle-brachial index < 0.5 were only 1.96 and 2.69 for amputation and limb revascularization, respectively, which are smaller than the *E*-values observed in our results (25).

This study has several limitations. First, since this study is a retrospective observational study, interpretation of the associations shown in the results as causality should be cautious. Although we adjusted confounders using multiple statistical methods, including PSM, and displayed the strength of the associations using the *E*-values, unmeasured confounders may still significantly impact the associations shown in the results. In particular, the severity of symptoms could not be investigated but may be significantly different between the two groups. Moreover, the *E*-values for the LLCI of the HR for all-cause deaths and ESRD were small; thus, the associations may be explained by unmeasured confounders such as fragility or atherosclerosis burdens. Second, although this study was conducted using a nationwide insurance claim database, the number of patients included in the PTA + PCI group was only 279, because the enrollment period was only 2 years, only 30% of the eligible patients were randomly selected for the study population because of the KNIHSS policy, and those with ALI or CLI were excluded. Larger-scale investigations with longer enrollment periods are desired to fully reflect contemporary clinical practice. Third, our study was focused on investigating the clinical outcomes related to concomitant PTA in patients undergoing PCI. Therefore, our results did not include any data producing insights into the mechanisms behind the associations of concomitant PTAs with worse renal and limb outcomes and deaths. Although our results showed that the increased risk of all-cause death was significantly mediated by worse limb outcomes, we could only speculate that worse limb outcomes may have resulted from ISR, without any related data analysis results. Finally, we did not investigate the quality of life, which is the most important reason for any patients with stable LEAD to undergo concomitant PTA and may have compensated for the unfavorable clinical outcomes.

In conclusions, concomitant PTA at the time of PCI was not associated with an increased risk of CV events or death, whereas it was associated with increased risks of renal impairment, repeat PTA after discharge and amputation. Experiencing PTAs after discharge and amputation may lead to an increased risk of death in patients undergoing concomitant PTAs. Although no mechanisms underlying these results were revealed in our study, the negative impacts of concomitant PTA on renal and limb outcomes suggest that concomitant PTA should be more cautiously selected as a treatment strategy for stable LEAD in patients undergoing PCI. Further investigations are required, including large-scale randomized controlled trials comparing clinical outcomes, including renal and limb outcomes, between concomitant PTA and delayed PTA in patients undergoing PCI.

Declarations

Acknowledgements

This work was supported by grants from the National Research Foundation of Korea (NRF) and funded by the Korean government (MSIP; Ministry of Science, ICT & Future Planning) (NRF-2018R1C1B5047123). This work was also supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (HI19C1055).

Competing interests

All authors declare no conflicts of interest to disclose.

Author contributions

YL and YHL conceived the original idea, YL, JHS and BSK designed the study protocol, MP and SP analyzed the data, YL and YHL interpreted the results, YL drafted the manuscript, JHS, BSK, HCP, HK and WHK revised it critically and all authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data availability

The dataset is achieved in a data storage facility operated by the KNHISS (website: https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do), and the KNHIS and the Korean Ministry of Health and Welfare regulate the access to this dataset. The data are accessible to any researchers under permission of the KNHISS granted after a review process for the researcher's applications. A researcher will be provided with a dataset consisting of data from 30% of patients randomly selected from the entire Korean population eligible for the researcher's study, according to a KNHISS research policy, therefore a different researcher will have a different dataset harboring equivalent results.

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Figures

Figure 1

Patient selection process.

Among the 30,972 patients who underwent PCI between Jan 2014 and Dec 2015, 6,563 patients (279 for the PTA+PCI group; 6,284 for the PCI only group) diagnosed with stable LEAD were analyzed. The

baseline characteristics between the PTA+PCI group and the PCI only group were matched in a 1:5 ratio through a PSM procedure.

Figure 2

Cumulative incidences of clinical outcomes according to the treatment strategies.

The cumulative incidences of all-cause death, ESRD, amputation and PTA after discharge were significantly higher in the PTA+PCI group than in the PCI only group, whereas there were no significant differences in the cumulative incidences of CV death and MACEs.

Figure 3

Univariate Cox proportional hazard models on the association of concomitant PTA at the time of PCI with clinical outcomes.

Concomitant PTA was associated with higher risks of all-cause death, ESRD, amputation and PTA after discharge but was not associated with the risks of MACE, coronary revascularization, stroke or bleeding events in either the entire cohort or the PSM cohort. The concomitant PTA was significantly associated with a higher risk of CV deaths in the entire cohort but was not associated with the risk of CV deaths in the PSM cohort.

**E*-values indicate the HRs of unmeasured variables that could explain away the association between the concomitant PTA and the clinical outcomes and were estimated using the HRs and their lower limits of 95% CIs from the PSM cohort.

Figure 4

Subgroup analysis for the relationship between the concomitant PTA at the time of PCI and clinical outcomes.

The HRs and CIs were derived from univariate Cox proportional hazard models constructed in the PSM cohort.

* p-values for the interaction between the categories in each subgroup. For CCI, p values represent the interaction of the categories with the reference category (CCI $\leq$3).

Figure 5

Mediation effects of amputation, PTA after discharge and ESRD on the association between concomitant PTA and all-cause death.

Amputation and PTA after discharge significantly mediate the association between concomitant PTA and all-cause death, whereas ESRD does not mediate the association.

The mediation analyses were performed in the PSM cohort using a bootstrap method. Statistical models used in the mediation analyses were time-varying survival regression models with a Gaussian distribution, while the associations presented in the diagrams were produced from Cox proportional hazard models (Model a and Model b) and time-varying Cox proportional hazard models (Model c).

Supplementary Files

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