Effect on Outcomes: Infections Complicating Percutaneous Coronary Interventions in Patients ≥80 Years of Age

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Data on the prevalence of infections in patients who underwent percutaneous coronary intervention (PCI) and their impact on outcomes are scarce. In this study, a total of 644 patients ≥80 years of age who underwent PCI were stratified according to the presence/absence of infections requiring antibiotic therapy. The primary end point was major adverse cardiovascular events (MACE) after discharge, a composite of all-cause mortality, nonfatal myocardial infarction, and rehospitalization for heart failure. Median follow-up was 1.2 (interquartile range 0.1 to 3.4) years. Of the 644 patients, 186 (28.9%) had infections during index hospitalization, with 84 (13%) and 59 (9.2%) patients having pneumonia and urinary tract infections, respectively. Patients with infections were older, more often women, and had an increased prevalence of atrial fibrillation and congestive heart failure. Infections prolonged hospital stay (10 [7 to 16] vs 5 [3 to 7] days, p <0.001), but were not related to rates of MACE (20% vs 19%, adjusted hazard ratio [HR] 1.41, 95% confidence intervals 0.84 to 2.38, p = 0.20). Pneumonia was significantly associated with increased rates of MACE (27% vs 18%, adjusted HR 2.19, 95% confidence intervals 1.23 to 3.91, p = 0.008) and rehospitalization for heart failure (17% vs 10%, adjusted HR 2.66 (1.25 to 5.63, p = 0.01), whereas urinary tract infections were not. In conclusion, concomitant infections are frequent in patients ≥80 years of age who underwent PCI, and associated with an increased risk of adverse events when affecting the respiratory system. **(Am J Cardiol 2019;123:1806−1811)**

The number of elderly patients who undergo percutaneous coronary intervention (PCI) is steadily increasing and expected to rise further given the ageing of the population.[1,2] Comprehensive risk assessment and careful patient selection is key in a frail elderly patient population at increased risk for adverse events.[3-8] Data on the impact of concomitant infections on outcomes of patients who underwent PCI are scarce, and studies mostly restricted to the investigation of future cardiovascular events in survivors of severe sepsis.[9-12] Severe sepsis has been related to an increased risk of cardiovascular events,[9-11] and in-hospital mortality in patients with sepsis and secondary acute myocardial infarction was shown to be higher than in patients with sepsis alone.[13] The occurrence of infectious complications in patients who underwent PCI, although rarely investigated, is considered to be rather low.[12,14,15] The relevance of in-hospital infections in elderly patients with coronary artery disease is uncertain. The aim of this study was therefore to assess the impact of in-hospital infections on outcomes in a large, unrestricted cohort of elderly (≥80 years) patients who underwent PCI.

Methods

A total of 644 consecutive patients ≥80 years of age who underwent PCI at our institution from January 2009 to December 2014 and surviving to hospital discharge (or >30 days) were included in this analysis. All patients received evidence-based medical care and were treated with coronary revascularization according to current guidelines and recommendations.[16-18] In-hospital infections were defined as signs and symptoms of infections requiring antibiotic therapy during the index hospitalization, and patients divided into patients with and without in-hospital infections.[14] Further, patients were divided according to the point in time of the initiation of antibiotic therapy, for example, before (pre-existing infection) or after (infectious complication) PCI. Sites of infections were identified based on patient records. All aspects of the study were approved by the institutional review board. The study was conducted in full conformance with the principles of the Declaration of Helsinki.

The primary end point was defined as rates of major adverse cardiovascular events (MACE), a composite of all-cause mortality, nonfatal myocardial infarction, and rehospitalization for heart failure. Bleeding was defined as bleeding requiring red blood cell transfusion.[19]

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), and

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categorical variables as frequencies (percentages). The Mann-Whitney *U* test was used to test continuous variables, and the Pearson's chi-square test or the Fisher's exact test categorical variables, respectively. Kaplan-Meier survival curves were generated to compare event rates among groups. Cox proportional hazards regression models were applied to estimate risks of the outcome measures. Baseline variables significantly (p <0.05) associated with the outcome measures in univariate analysis were included in the multivariate models. Variables included in the model for infection complications were age, female gender, previous coronary artery disease, previous PCI, atrial fibrillation, congestive heart failure, left ventricular ejection fraction, and acute coronary syndrome (ACS) as index event. Variables included in the model for MACE were age, type 2 diabetes, previous coronary artery bypass grafting, chronic obstructive pulmonary disease, congestive heart failure, chronic kidney disease stage 4 (estimated glomerular filtration rate <30 ml/min according to the Cockcroft-Gault formula), and left ventricular ejection fraction. Cox proportional hazards regression test of interaction was performed to investigate a potential differential effect of the infection status by gender on the outcome measure. All testing was 2-sided and a p value of <0.05 considered as statistically significant. All statistical analyses were performed using IBM-SPSS version 24 (IBM Corp.).

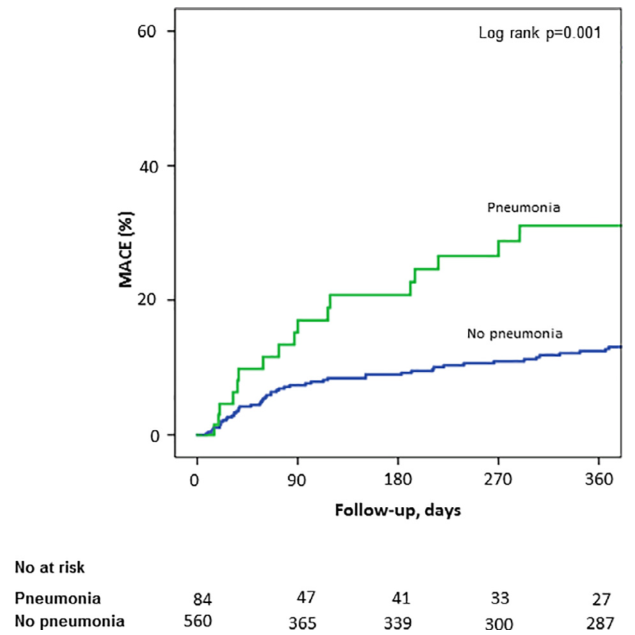

Figure 1. Kaplan-Meier estimates for rates of major adverse cardiovascular events (MACE) according to the presence/absence of pneumonia. Major adverse cardiovascular events comprise all-cause mortality, nonfatal myocardial infarction, and rehospitalization for heart failure.

Results

Of the 644 patients, 186 (29%) had any infection during the index hospitalization (Table 1). Type of antibiotic therapy was known in 177 (95%) patients, with penicillin (46% of patients), cephalosporins (25% of patients), quinolones (23% of patients), and lincosamides (20% of patients) being most frequently used. In 116 (62%) patients, antibiotic therapy was initiated after PCI. Patients with infections had significantly longer hospital stay (10 [7 to 16] vs 5 [3 to 7] days, p <0.001), and increased rates of vascular access site complications (14% vs 6.0%, p = 0.001) and bleeding events requiring red blood cell transfusions (17% vs 2.0%, p <0.001). Predictors of in-hospital infections are given in Table 2.

Median follow-up was 1.2 (0.1 to 3.4) years. MACE occurred in 37 (20%) and 89 (19%) patients with and without in-hospital infections (log-rank p = 0.15). In-hospital infections were not related to rates of MACE (adjusted hazard ratio [HR] 1.41, 95% confidence intervals [CI] 0.84 to 2.38, p = 0.20). MACE occurred in 23 (27%) and 103 (18%) patients with and without pneumonia (log-rank p = 0.001, Figure 1), and pneumonia was significantly related to rates of MACE (adjusted HR 2.19, 95% CI 1.23 to 3.91, p = 0.008, Table 3). Predictors of MACE are summarized in Table 4.

The investigation of the association between infectious complications after PCI and rates of MACE yielded similar results. Whereas infectious complications (adjusted HR 1.52, 95% CI 0.83 to 2.78, p = 0.17) and urinary tract infections (adjusted HR 1.99, 95% CI 0.61 to 6.47, p = 0.25) after PCI were not associated with MACE, trends were observed for pneumonia (adjusted HR 1.73, 95% CI 0.54 to 5.60, p = 0.36). Of 186 patients with infections, 139 (75%) had troponin-positive ACS. When including patients with troponin-positive ACS only, there was no relation of infectious complications (adjusted HR 1.28, 95% CI 0.59 to 2.76, p = 0.53) and urinary tract infections (adjusted HR 0.47, 95% CI 0.06 to 3.59, p = 0.45) with MACE, but associations were observed for pneumonia (adjusted HR 2.48, 95% CI 1.15 to 5.33, p = 0.02). No significant relations were observed in patients with unstable angina or stable coronary artery disease. Adjustment for bleeding events did not affect the observed associations.

A total of 98 (34%) women and 88 (25%) men had any in-hospital infection (p = 0.01), with women having predominantly urinary tract infections (13% vs 5.9%, p = 0.002). Rates of pneumonia were similar (14% vs 12%, p = 0.64). Rates of MACE were 23% and 22% in men with and without infections (log-rank p = 0.12, adjusted HR 1.24, 95% CI 0.64 to 2.44, p = 0.53), and corresponding rates in women were 16% and 17% (log-rank p = 0.58, adjusted HR 1.92, 95% CI 0.79 to 4.67, p = 0.15). There was no interaction of infection status and gender status on rates of MACE (interaction p = 0.55).

Discussion

This study for the first time investigated the prevalence and impact of concomitant infections in a large, elderly (≥80 years) patient cohort who underwent PCI. The prevalence of concomitant infections needing antibiotic therapy was high in elderly patients who underwent PCI reaching almost 30%, and particularly affected patients presenting with troponin-positive ACS. Infections significantly prolonged hospital stay, and were associated with adverse events when affecting the respiratory system.

Table 1
Baseline and procedural characteristics

Variable	Total population (644)	Infection YES (n = 186)	Infection NO (n = 458)	p value
Age (years)	83.6 [81.5-86.1]	84.3 [82.0-87.1]	83.3 [81.3-85.8]	0.002
Women	289 (45%)	98 (53%)	191 (42%)	0.01
Hypertension	551 (86%)	155 (83%)	396 (87%)	0.32
Dyslipidemia	344 (54%)	84 (45%)	260 (57%)	0.09
Diabetes mellitus	190 (30%)	62 (33%)	124 (27%)	0.18
Body mass index (kg/m^2)	25.6 [23.4-28.0]	25.2 [22.6-28.3]	25.7 [23.6-28.0]	0.42
Known coronary artery disease	295 (46%)	68 (37%)	227 (50%)	0.004
Prior percutaneous coronary intervention	206 (32%)	42 (23%)	164 (36%)	0.001
Prior coronary bypass	96 (14%)	24 (13%)	72 (16%)	0.40
Peripheral arterial disease	63 (10%)	23 (12%)	40 (8.7%)	0.19
Prior stroke	101 (16%)	29 (16%)	75 (16%)	0.91
Atrial fibrillation	219 (34%)	79 (43%)	140 (31%)	0.004
Congestive heart failure	116 (18%)	62 (33%)	54 (12%)	<0.001
Chronic obstructive pulmonary disease	60 (9%)	19 (10%)	41 (9.0%)	0.65
Malignancy	105 (16%)	28 (15%)	77 (17%)	0.64
Left ventricular ejection fraction	57 [45-66]	49 [50-60]	60 [50-69]	<0.001
Index event				
Stable coronary artery disease	112 (17%)	19 (10%)	93 (20%)	0.001
Unstable angina pectoris	199 (31%)	28 (15%)	171 (37%)	<0.001
Non-ST segment elevation myocardial infarction	199 (31%)	85 (46%)	114 (25%)	<0.001
ST segment elevation myocardial infarction	134 (21%)	54 (29%)	80 (18%)	0.002
Estimated glomerular filtration rate (Cockcroft-Gault, ml/min)	51 [40-63]	50 [39-59]	51 [41-63]	0.13
C-reactive protein (mg/L)	1.4 [0.3-5.0]	3.9 [0.7-13.5]	0.8 [0.3-3.2]	<0.001
Type of infection				
Pneumonia		84 (13%)	-	
Urinary tract infection		59 (9.2%)	-	
Hematoma		21 (3.2%)	-	
Other		36 (5.6%)	-	
Procedural characteristics				
Drug-eluting stent	494 (77%)	132 (71%)	362 (79%)	0.03
Fluoroscopy time (min)	14.0 [8.9-20.3]	14.0 [9.4-20.3]	13.9 [8.7-20.3]	0.70
Kerma-area-product (cGy*cm^2)	8,145 [5,010-11,685]	7,750 [4,909-10,738]	8,382 [5,158-11,882]	0.23
Contrast volume (ml)	198 [160-249]	198 [160-248]	198 [160-250]	0.44
Medication at discharge				
Aspirin	628 (98%)	179 (98%)	449 (98%)	1.00
Clopidogrel	527 (82%)	140 (77%)	387 (85%)	0.03
Ticagrelor	110 (17%)	40 (22%)	70 (15%)	0.05
Oral anticoagulation	79 (12%)	20 (11%)	59 (13%)	0.51
Statins	565 (88%)	163 (90%)	402 (88%)	0.59
Beta blocker	577 (90%)	169 (93%)	408 (89%)	0.19
Renin-angiotensin system blockers	595 (93%)	167 (92%)	428 (93%)	0.61

Diagnosis of dyslipidemia was based on laboratory analyses and diagnosis of hypertension on patient records, respectively.

Concomitant infections in patients presenting with coronary artery disease have only rarely been investigated, and may mostly be underestimated in clinical practice. The prevalence of serious infectious complications after ST-segment elevation myocardial infarction was reported to be 2.4% in patients enrolled in the Assessment of Pexelizumab in Acute Myocardial Infarction trial and <5% in patients included in cohort studies.[12-14] In patients diagnosed with sepsis, secondary acute myocardial infarction was observed in about 5% of patients.[13] The higher rates of in-hospital infections observed in our elderly patient cohort may not surprise given the reported relation between infectious complications and age,[12,14] along with the frailty and high burden of comorbidities observed in elderly patients who underwent PCI. As expected, in-hospital infections predominantly affected the lower respiratory and the urinary tract. Whereas urinary tract infections were more frequently observed in women, rates of pneumonia did not differ among women and men.

Length of hospital stay was longer and rates of periprocedural complications including vascular access site and bleeding complications higher in patients with in-hospital infections. There was no relation between in-hospital infections and rates of MACE after hospital discharge. Pneumonia, however, either diagnosed before PCI or occurring after PCI during the index hospitalization, was significantly

Table 2
Predictors of infection complications

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	1.09 (1.04-1.15)	0.001	1.08 (1.01-1.15)	0.03
Female sex	1.56 (1.11-2.19)	0.02	1.52 (0.96-2.41)	0.08
Body mass index (kg/m^2)	0.98 (0.94-1.01)	0.18		
Diabetes mellitus	1.29 (0.89-1.86)	0.18		
Hypertension	0.78 (0.49-1.25)	0.31		
Known coronary artery disease	0.59 (0.42-0.84)	0.004	0.85 (0.45-1.62)	0.62
Prior myocardial infarction	0.67 (0.44-1.04)	0.07		
Prior percutaneous coronary intervention	0.52 (0.35-0.78)	0.001	0.64 (0.38-1.06)	0.08
Prior coronary bypass	0.79 (0.48-1.31)	0.36		
Prior stroke	0.94 (0.59-1.51)	0.81		
Peripheral arterial disease	1.48 (0.89-2.54)	0.16		
Atrial fibrillation	1.68 (1.18-2.39)	0.004	1.69 (1.04-2.73)	0.03
Congestive heart failure	3.74 (2.47-5.67)	<0.001	2.44 (1.41-4.25)	0.002
Chronic obstructive pulmonary disease	1.16 (0.65-2.05)	0.62		
Malignancy	0.88 (0.55-1.40)	0.58		
Left ventricular ejection fraction	0.97 (0.95-0.98)	<0.001	0.97 (0.96-0.99)	<0.001
Acute coronary syndrome as index event	2.24 (1.32-3.79)	0.003	2.45 (1.22-4.90)	0.01
Chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73^2)	1.21 (0.60-2.45)	0.59		

associated with increased rates of MACE, and differences were mainly driven by an increased need for hospitalization for heart failure in patients with pneumonia. Urinary tract infections, probably representing mostly less severe infections, were not related to future adverse cardiovascular events, although analyses are limited by the rather low number of events in this patient group. These findings are supported by a previous study reporting an increased risk of myocardial infarction after a diagnosis of respiratory tract infection, and a significant, but weaker association with a previous diagnosis of urinary tract infection.[20] The relation between infectious diseases and future cardiovascular events is plausible and has previously been reported in different patient cohorts.[9-11,20] Possible pathophysiological mechanisms underlying this association comprise persistent vascular inflammation,[21-23] prolonged activation of coagulation,[24] and an altered metabolic state in patients suffering from infectious diseases, along with reversible myocardial depression.[25] Most interestingly, relevant and prolonged alterations in inflammation and coagulation are not only considered to occur in severe sepsis, but also in patients with less severe infections such as community-acquired pneumonia.[26] Further, organ dysfunction may persist after clinical resolution of inflammation and may contribute at

Table 3
Clinical outcomes after discharge stratified according to the presence/absence of infectious complications

			Crude		Adjusted	
Variable			HR (95% CI)	p value	HR (95% CI)	p value
	Infection (n = 186)	*No infection* (n = 458)				
MACE	37 (20%)	89 (19%)	1.33 (0.90-1.96)	0.15	1.41 (0.84-2.38)	0.20
All-cause mortality	13 (7.0%)	29 (6.3%)	1.48 (0.77-2.86)	0.24	0.72 (0.23-2.30)	0.58
Nonfatal myocardial infarction	13 (7.0%)	35 (7.6%)	1.20 (0.63-2.27)	0.58	1.16 (0.50-2.71)	0.73
Hospitalization for heart failure	19 (10%)	51 (11%)	1.24 (0.73-2.10)	0.44	1.67 (0.83-3.38)	0.15
	Pneumonia (n = 84)	*No pneumonia* (n = 560)				
MACE	23 (27%)	103 (18%)	2.19 (1.39-3.45)	0.001	2.19 (1.23-3.91)	0.008
All-cause mortality	7 (8.3%)	35 (6.3%)	1.89 (0.84-4.26)	0.13	0.26 (0.05-1.38)	0.11
Nonfatal myocardial infarction	5 (6.0%)	43 (7.7%)	1.03 (0.41-2.60)	0.96	1.23 (0.40-3.84)	0.72
Hospitalization for heart failure	14 (17%)	56 (10%)	2.54 (1.41-4.60)	0.002	2.66 (1.25-5.63)	0.01
	Urinary tract infection (n = 59)	*No urinary tract infection* (n = 585)				
MACE	5 (8.5%)	121 (21%)	0.46 (0.19-1.14)	0.09	0.72 (0.23-2.31)	0.58
All-cause mortality	2 (3.4%)	40 (6.8%)	0.58 (0.14-2.41)	0.45	1.37 (0.17-10.81)	0.77
Nonfatal myocardial infarction	4 (6.8%)	44 (7.5%)	1.07 (0.39-2.98)	0.90	2.99 (0.67-13.44)	0.15
Hospitalization for heart failure	2 (3.4%)	68 (12%)	0.32 (0.08-1.29)	0.12	0.88 (0.20-3.77)	0.86

Table 4
Predictors of major adverse cardiovascular events (MACE)

Variable	Univariate analysis		Multivariate analysis	
	HR (90% CI)	p value	HR (90% CI	p value
Age (years)	1.08 (1.02-1.14)	0.007	1.07 (0.99-1.15)	0.10
Female gender	0.88 (0.61-1.26)	0.47		
Body mass index (kg/m^2)	0.99 (0.96-1.02)	0.56		
Diabetes mellitus	1.79 (1.25-2.58)	0.002	1.14 (0.66-1.95)	0.64
Hypertension	0.81 (0.51-1.28)	0.36		
Dyslipidemia	1.11 (0.78-1.59)	0.57		
Known coronary artery disease	1.39 (0.97-1.98)	0.07		
Prior percutaneous coronary intervention	0.96 (0.67-1.38)	0.64		
Prior coronary bypass	1.86 (1.24-2.78)	0.003	1.91 (1.15-3.19)	0.01
Prior stroke	0.98 (0.60-1.59)	0.92		
Peripheral arterial disease	1.23 (0.69-2.18)	0.48		
Atrial fibrillation	1.31 (0.92-1.88)	0.14		
Congestive heart failure	1.79 (1.15-2.78)	0.01	1.43 (0.79-2.60)	0.24
Chronic obstructive pulmonary disease	1.74 (1.04-2.91)	0.04	1.35 (0.60-3.00)	0.47
Left ventricular ejection fraction	0.97 (0.96-0.98)	<0.001	0.97 (0.95-0.98)	<0.001
Acute coronary syndrome at presentation	1.09 (0.69-1.73)	0.71		
Chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73^2)	2.16 (1.15-4.04)	0.02	0.93 (0.39-2.21)	0.87
In-hospital infection	1.33 (0.90-1.96)	0.15	1.41 (0.84-2.38)	0.20

least in part to worse clinical outcomes. To what extent the increased risk is related to the high burden of comorbidities and the poor baseline health status of patients suffering infectious complications or the acute infectious event per se remains largely unknown.[11]

A few limitations merit consideration. Although a large cohort of consecutive elderly patients who underwent PCI was included in the study, the analysis is limited by the single center, retrospective design precluding adjudication of events. Although the impact of both pre-existing infections and those occurring after PCI was differentially investigated, cause and effect relation between in-hospital infections and acute myocardial infarction cannot be established in an observational study. Given the lack of detailed information on early clinical signs of infection, differentiation between community-acquired and nosocomial infections was precluded. Further, unmeasured confounding factors may have affected the outcome measures despite the covariates incorporated into the multivariate models. Although adjustment for bleeding events did not affect the observed associations, we cannot rule out completely that bleeding events may have affected the results.

In conclusion, this study demonstrates that the prevalence of concomitant infectious diseases in elderly (≥80 years) patients who underwent PCI is high, with increased rates observed in women. The high rate of concomitant infections, along with the observed association between pulmonary infections and worse outcomes, underlines the importance of infection prevention in frail elderly patients. Future studies are needed to define measures for infection prevention in high-risk patients with coronary artery disease who underwent PCI.

Disclosures

The authors have no conflicts of interest to disclose.

Author Agreement/Declaration

We certify that all authors have seen and approved the final version of the manuscript being submitted. The article is the authors' original work, has not received previous publication and is not under consideration for publication elsewhere.

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