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Short communication

Impact of major infections on 10-year mortality after revascularization in patients with complex coronary artery disease

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ABSTRACT

Background: The significant interaction between major infection and 5-year mortality after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) for complex coronary artery disease (CAD) was observed previously. However, the very long-term outcomes beyond 5 years remains unclear.

Methods and results: This is a subgroup analysis of the SYNTAX Extended Survival (SYNTAXES) trial, which is the extended follow-up of the randomized SYNTAX trial comparing PCI versus CABG in patients with three-vessel disease (3VD) or left-main CAD (LMCAD). Out of 1517 patients enrolled in the SYNTAX trial with available survival status from 5 to 10 years, 140 patients had experienced major infections and survived at 5 years (major infection group). From 5 to 10 years, the mortality of major infection group was 19.8% whereas the mortality of no major infection group was 15.1% ($p = 0.157$). After the adjustment of other clinical factors, the risk of mortality from 5 to 10 years did not significantly differ between major infection and no major infection groups (HR: 1.10; 95% CI: 0.62–1.96; $p = 0.740$). When stratified by the presence or absence of periprocedural major infections, defined as a major infection within 60 days after index procedure, there was also no significant difference in 10-year mortality between two groups (30.8% vs. 24.5%; $p = 0.057$).

Conclusions: Despite the initial association between major infections and 5 years mortality, postprocedural major infection was not evident in the 10 years follow-up, suggesting that the impact of major infection on mortality subsided over time beyond 5 years.

Trial registration:
SYNTAXES ClinicalTrials.gov reference: NCT03417050
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1. Introduction

Recently the incidence and impact on 5-year mortality of infections after coronary artery bypass graft (CABG) surgery versus percutaneous coronary intervention (PCI) for three-vessel or left main coronary artery disease in the randomized SYNTAX trial [1] have been reported. In 1800 patients randomized, CABG was associated with higher incidence of major infection than PCI whereas major infections were independently associated with all-cause mortality at 5 years.

In the same randomized cohort, the follow-up was extended up to 10 years to collect the survival status of the patients. The main results of this extended follow-up (SYNTAXES) were reported elsewhere [2]. The objective of this sub-study is to update with this new information the impact of major infections on 10-year mortality in patients with left main and/or three-vessel disease undergoing PCI or CABG.

2. Methods

The design and methods used in the SYNTAX trial and SYNTAXES extended follow-up were published elsewhere [2,3]. Briefly, the SYNTAX trial was a multicenter (85 European or American sites), multinational, open-label, randomized controlled trial between PCI and CABG in patients with three-vessel disease (3VD) and/or left-main coronary artery disease (LMCAD), with nested registries of CABG and PCI. The SYNTAXES was the extended follow-up of the randomized cohort of SYNTAX trial for survival status. The post-hoc adjudication of the infection was performed independently by clinical adjudication committee according to CDC/NHSN criteria [4]. Patients were stratified according to the status of the major infection in the first five years after randomization. If the patients experience any major infections in the first five years, patients were classified as a major infection group. Kaplan-Meier method is used to estimate the cumulative rates of events and log-rank test was performed to examine the differences between groups. The incidence of mortality from 5 to 10 years was assessed using the unadjusted Cox proportional hazards model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

For exploratory purpose, 10-year mortality was assessed also in patients stratified by the presence or absence of periprocedural major infections, defined as a major infection within 60 days after index procedure.

3. Results

In the SYNTAX trial, 1800 patients were randomized to PCI (903 patients) and CABG (897 patients). Among them, 186 patients experienced major infections up to 5 years with 141 (75.8%) occurring within 60 days after the index procedure (periprocedural major infection, **Online** Fig. 1). Baseline characteristics according to the study arm and occurrence of major infections up to 5 years were previously described [1]. Complete 5-year follow-up data were available in 1676 patients (CABG arm: 89.7%; PCI arm: 96.5%).

Out of 1517 patients with available survival status from 5 to 10 years, 140 patients (9.2%; 29 in PCI and 111 in CABG) had experienced major infections and survived at 5 years (major infection group) with 109 (77.8%) being periprocedural major infections (**Online** Fig. 1).

Median follow-up time was 11.5 (interquartile range: 10.4–12.2) years. From 5 to 10 years, the mortality occurred in 229 patients (15.6%). The mortality occurred in 27 patients of major infection group and 202 patients of no major infection group (19.8% vs. 15.1%; HR: 1.34; 95% CI: 0.89–2.00; $p = 0.157$, Fig. 1A **and** Table 1). Cox regression analysis demonstrated that after the adjustment of other clinical factors, the risk of mortality from 5 to 10 years did not differ between major infection and no major infection groups (HR: 1.10; 95% CI: 0.62-1.96; p = 0.740, Table 1). There was no interaction between treatment arm (p for interaction = 0.564), suggesting that this finding was consistent in CABG and PCI arm. Ten-year mortality risks according to the types of

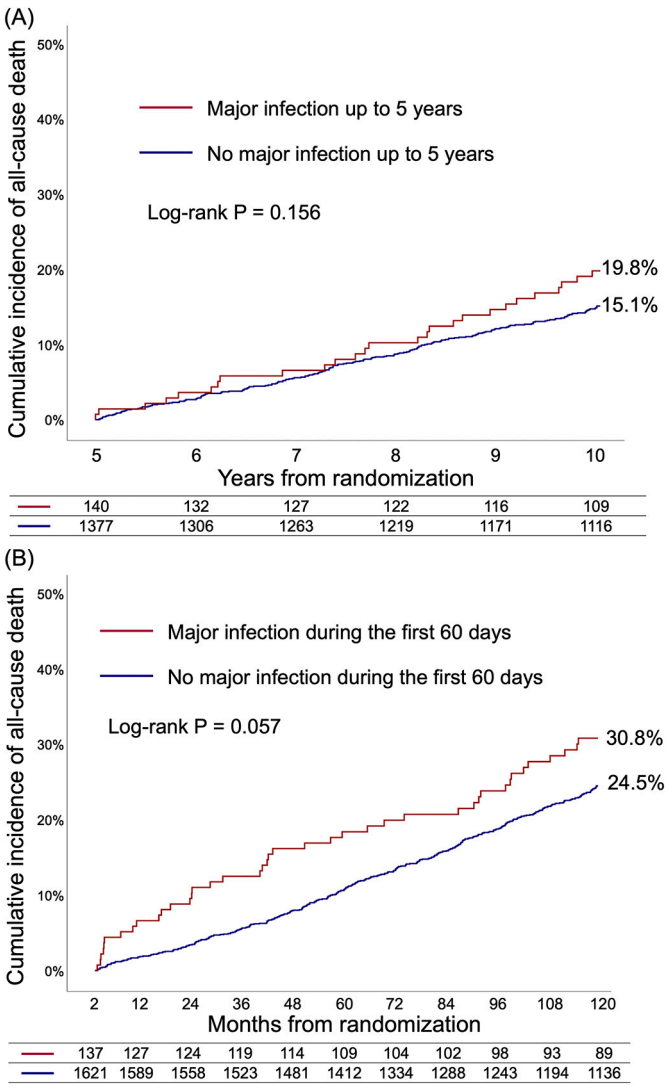

Fig. 1. Cumulative incidence of all-cause death up to 10 years in patients with or without major infections.
(A) Landmark analysis from 5 to 10 years in patients who had experienced major infection up to 5 years. (B) Landmark analysis from 60 days to 10 years stratified by the presence or absence of periprocedural major infections within 60 days from index procedure.

Table 1
Hazard risks in all-cause death from 5 to 10 years among patients with major infection up to 5 years over those without.

	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	P value	P value for interaction
Overall	1.34 (0.89–2.00)	0.157	1.10 (0.62–1.96)	0.740	–
PCI	2.23 (1.13–4.40)	0.021	0.71 (0.17–2.98)	0.635	0.564
CABG	1.19 (0.71–1.97)	0.510	1.17 (0.60–2.27)	0.642	

Adjusted covariates are age, sex, BMI, diabetes, creatinine clearance <60 ml/min, peripheral vascular disease, chronic obstructive pulmonary disease, left ventricular ejection fraction, EuroSCORE, SYNTAX score, and study arm (only for Overall).
PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; HR: hazard ratio; CI: confidence interval.

major infections are shown in **Online** Table 1.

In the exploratory analysis of periprocedural major infections, out of overall 1800 patients, 1758 patients with available follow-up data from 2 to 120 months were analyzed (**Online** Fig. 1). In this specific analysis, periprocedural major infections occurred in 137 patients (16 in PCI and 121 in CABG). There was also no significant difference in 10-year mortality risk between periprocedural major infection versus no-major infection group overall (30.8% vs. 24.5%; HR: 1.36; 95% CI: 0.99–1.88; $p = 0.058$, Fig. 1B **and** Table 2). When stratified by revascularization mode (Table 2), in the PCI arm the periprocedural major infection was associated with a significantly increased crude mortality risk. However, after adjustment for confounders, the periprocedural major infection was not an independent predictor of all-cause death from 60 days to 10 years both in PCI and CABG arm.

4. Discussions

The major findings of the current extended report of the SYNTAX study with stratification of patients with major infections were: 1) the initial association between major infections and 5 years mortality was not significant in the extended follow-up from 5 to 10 years; 2) this observation remained unchanged after adjustment for possible confounders; and 3) the periprocedural major infection did not significantly increase 10-year mortality risk.

The previous study of the SYNTAX trial on the major infections demonstrated that the major infection occurring in periprocedural phase and mid- to long-term follow-up (5 years) has impact on 5-year mortality of the patients undergoing PCI or CABG for complex coronary disease, when the infection status was considered as a time-dependent variable [1]. In that analysis, not only periprocedural major infection but also late/very-late major infections were associated with mortality at 5 years,

The current analysis demonstrated that at 10 years follow-up, the association between post-procedural infections and long-term mortality subsided after 5 years and was not statistically significant at 10 years. In addition, the majority (75.8%) of major infections occurred within 60 days after the index procedure. This suggests that the post-procedural major infections could contribute to the early- or mid-term mortality, however, once the infection process has been cured, then the occurrence of major infections may no longer affect the long-term survival, irrespective of the type of infections. In other words, patients who had experienced major (periprocedural) infections but had been cured do not necessarily require an intensive long-term follow-up and could receive the local standard of care. Due to the limited number of patients with a history of major (periprocedural) infections in the current study, this hypothesis should be confirmed in large pooled data, ideally with very long-term follow-up.

4.1. Limitations

The infection status was not collected beyond 5 years. Therefore, the status of major infection was not included as time-dependent factor in the Cox regression analysis to assess the adjusted mortality risk between 5 and 10 years. Due to the non-prespecified post-hoc nature of the study, potential bias derived from unobserved confounders might affect the results.

4.2. Conclusion

Despite the initial association between major infections and 5 years mortality, major infections after PCI or CABG were not significant in the 10 years follow-up, suggesting that the impact of major infection on mortality subsided over time beyond 5 years.

Table 2
Hazard risks in all-cause death from 2 to 120 months in patients with or without periprocedural major infection.

	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	P value for interaction
Overall	1.36 (0.99–1.88)	0.058	1.36 (0.87–2.14)	0.182	–
PCI	3.40 (1.80–6.41)	<0.001	1.51 (0.60–3.82)	0.387	0.827
CABG	1.23 (0.84–1.80)	0.299	1.48 (0.86–2.56)	0.156	

Hazard ratios were calculated in patients with periprocedural major infection (defined as major infection within 60 days after index procedure) over those with no periprocedural major infection.
Adjusted covariates are listed in Table 1.
Abbreviations as in Table 1.

Disclosures

Dr. Serruys reports personal fees from Biosensors, Micel Technologies, Sinomedical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work.

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Dr. Morice is CEO and shareholder of CERC, a CRO not involved in this trial, and is minor shareholder of Electroducer.

Dr. Kappetein report to work as employee of Medtronic, outside the submitted work.

All other authors have no conflict of interest to declare.

Author statement

Masafumi Ono gathered, analyzed and interpreted data, wrote the first draft of the article and contributed to all revisions.

Patrick W. Serruys and **Yoshinobu Onuma** designed the study, gathered and interpreted data and contributed to all revisions.

Michael J. Mack, David R. Holmes, Marie-Claude Morice, Arie Pieter Kappetein, Daniel J.F.M. Thuijs, Thilo Noack, Friedrick W. Mohr, and **Piroze M. Davierwala** designed the study, gathered and interpreted data and contributed to critical revision of the manuscript.

Massimo Mancone interpreted data and contributed to revisions.

Hideyuki Kawashima and Hironori Hara gathered, cleaned data and contributed to revision of the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.08.013.

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