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Authors: Henning Kelbæk, M.D, DMSc; Robert Yeh, M.D; Thomas Engstrøm, M.D, DMSc; Franz-Josef Neumann, M.D; Patrick W Serruys, M.D, PhD; Stephan Windecker, M.D, PhD; Jorge Belardi, M.D; Shubin Qiao, M.D; Bo Xu, MBBS; Minglei Liu, PhD; Sigmund Silber, M.D

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Five-year clinical outcomes for the Resolute zotarolimus-eluting stent in total coronary occlusions

Henning Kelbæk[1], MD, DMSc; Robert Yeh[2], MD; Thomas Engstrøm[3], MD, DMSc; Franz-Josef Neumann[4], MD; Patrick W Serruys[5], MD, PhD; Stephan Windecker[6], MD, PhD; Jorge Belardi[7], MD; Shubin Qiao[8], MD; Bo Xu[8], MBBS; Minglei Liu[9], PhD; Sigmund Silber[10], MD

[1]Department of Cardiology, Zealand University Hospital, Roskilde, Denmark; [2]Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [3]Department of Cardiology, The Heart Centre, Rigshospitalet, University of Copenhagen, Denmark; [4]Department of Cardiology and Angiology II, University Heart Center, Bad Krozingen, Germany; [5]Thorax Center, Erasmus Medical Center, Rotterdam, The Netherlands; [6]Department of Interventional Cardiology, Bern University Hospital, Bern Switzerland; [7]Division of Cardiology, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina; [8]Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China; [9]Coronary and Structural Heart, Medtronic PLC, Santa Rosa, California, USA; [10]Department of Cardiology, Isar Heart Center, Munich, Germany.

Short title: 5-year outcomes with chronic total occlusions

Corresponding author:

Henning Kelbæk, MD, DMSc

Department of Cardiology, Zealand University Hospital,

Sygehusvej 10, 4000 Roskilde, Denmark;

E-mail: hkelbaek@dadlnet.dk

Disclosures

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Abstract

Aims: Reports of long-term outcomes of patients treated with drug-eluting stents in total coronary occlusions are limited. We analyzed clinical outcomes of patients treated with the zotarolimus-eluting Resolute stent (R-ZES) implanted in total coronary versus non-occluded lesions.

Methods and results: Patients treated with R-ZES and included in 4 trials (RESOLUTE All Comers, RESOLUTE International, RESOLUTE China RCT, and RESOLUTE China Registry) were pooled and divided in 3 groups: patients with chronic total occlusions (CTO), patients with total occlusions that had occurred recently (rec-TO), and patients without total occlusions (non-TO). Clinical outcomes at 5-years were analyzed. Of 5,487 patients treated with R-ZES in these trials, 8.0% had CTO's, 8.5% rec-TO's and 83.5% non-TO's. Patients had a mean age of 62.8 years, approximately 25% were female and 30% diabetics. TLF was similar in the 3 groups at 5 years (TLF was 13.2%, 12.5% and 13.3% in the CTO, rec-TO and non-TO groups, respectively, p=0.96). Stent thrombosis tended to occur more frequently for rec-TO compared to CTO and non-TO patients (2.6% vs 1.2% and 1.3%, respectively, p=0.11).

Conclusions: In this large population of patients who had R-ZES implanted, 5-year clinical outcomes were similar whether or not the stents were implanted in total occlusions.

Key words: ACS / NSTE-ACS; Chronic coronary total occlusion; Drug-eluting stent; Stable angina

Condensed Abstract:

Clinical outcomes of patients treated with the zotarolimus-eluting Resolute stent (R-ZES) implanted in total coronary versus non-occluded lesions were analyzed. Patients treated with R-ZES and included in 4 trials (RESOLUTE All Comers, RESOLUTE International, RESOLUTE China RCT, and RESOLUTE China Registry) were pooled and divided in 3 groups: patients with chronic total occlusions (CTO), with recent total occlusions (rec-TO), and without total occlusions (non-TO). Target lesion failure was similar in the 3 groups at 5 years. In this large population of patients with R-ZES implanted, 5-year clinical outcomes were similar whether or not the stents were implanted in total occlusions.

Abbreviations

Not totally occluded = non-TO

Occluded recently = rec-TO

Percutaneous coronary intervention = PCI

Chronic total occlusions = CTO

Drug-eluting stent = DES

Resolute zotarolimus-eluting stent = R-ZES

Randomized Controlled trial = RCT

Target lesion failure = TLF

Target lesion revascularization = TLR

Target vessel failure = TVF

Stent thrombosis = ST

Target vessel myocardial infarction = TVMI

Introduction

Patients with occluded coronary arteries may have clinical symptoms ranging from stable angina to acute coronary syndromes. Whereas lesions that are not totally occluded (non-TO) in addition to those occluded recently (rec-TO) rarely represent technical challenges unless containing a heavy thrombus burden, percutaneous coronary intervention (PCI) in those with chronic total occlusions (CTO) is obtained with varying technical success (1). Implantation of a drug-eluting stent (DES) improves outcomes including the occurrence of restenosis in patients with coronary total occlusions (2,3), despite a higher occurrence of stent strut malapposition (4). We have previously reported favorable 2-year outcomes in patients with both CTO and rec-TO in comparison with those with non-TO lesions treated with the Resolute zotarolimus-eluting stent (R-ZES) (5). We found the incidence of stent thrombosis highest in patients with rec-TO probably due to a higher level of thrombogenicity in these patients often presenting with acute coronary syndromes.

The R-ZES has previously been demonstrated to be clinically safe and effective compared with other drug-eluting stents (6-9). However, reports of long-term outcomes in patients with recanalized total occlusions appear to be limited, especially with the use of second-generation DES. Patients with rec-TO often have acute coronary syndrome, and from a patient population of 2 trials we have previously reported a slightly higher occurrence of stent thrombosis in patients treated with PCI and R-ZES implantation for rec-TO when compared with both patients with CTO and those without an occlusion (5). Based on the patient-level pooled data from 4 prospective trials and registries, our study aimed at assessing long-term safety and efficacy of 2nd generation R-ZES in the treatment of CTO lesions.

Methods

Study designs and populations

Our data are derived from the RESOLUTE All-Comers trial, the RESOLUTE International trial, the RESOLUTE China Randomized Controlled trial (RCT) and the RESOLUTE China Registry, all registered with ClinicalTrials.gov, numbers NCT00617084, NCT00752128, NCT01334268 and NCT01243749, respectively. All trials evaluated clinical outcomes of patients with significant coronary artery disease treated with PCI including R-ZES implantation with annual clinical follow-up.

RESOLUTE All Comers is a randomized multicenter trial primarily evaluating clinical outcomes up to 5 years after implantation of R-ZES versus an everolimus-eluting stent in an unselected cohort of patients representing a variety of coronary artery disease (n=2,292) (5,10). A fraction of the patients (20%) had a 13- month coronary angiography performed. The RESOLUTE International trial is a world-wide multicenter observational registry of clinical outcomes of unselected patients 3 years after implantation of R-ZES (n=2,349) (11,12). RESOLUTE China RCT is a randomized trial comparing 5-year clinical outcomes of an all-comer Chinese patient population, who have either a R-ZES or a paclitaxel-eluting stent implanted (n=400). The study included coronary angiography at 9 months (13). RESOLUTE China Registry is a multicenter observational registry study of clinical outcomes from unselected patients, who have R-ZES implanted and followed for 5 years (n=1,800) (14).

Procedures

Patients were treated with dual antiplatelet therapy for at least 6 months according to current international guidelines. PCI was performed in accordance with local standard techniques aiming to cover (≥ 2 mm on each side of) the culprit lesion from healthy-to-healthy vessel with stent with a finalizing residual diameter of <25% by post-dilatation using non-compliant balloons.

All patients were included after written consent, and the local ethics committees approved the respective studies, that were all conducted in accordance with the Declaration of Helsinki.

Endpoints and definitions

CTO was defined as a total occlusion with TIMI grade 0 blood flow with estimated duration of at least 3 months prior to the index procedure. Rec-TO was defined as a recently (<3 months prior to PCI) occluded lesion with TIMI 0 blood flow. The RESOLUTE All Comers study did not collect timing of CTO, so patients with a total occlusion were included in the CTO group if they had no recent myocardial infarction and in the rec-TO group if they had a recent myocardial infarction. Patients in all studies who were not categorized as CTO or rec-TO were considered non-TO.

The primary endpoint of the present analysis was target lesion failure (TLF) defined as the composite of cardiac death, target vessel myocardial infarction (TVMI) and target lesion revascularization (TLR) recorded at follow-up. Secondary endpoints included the components of the primary endpoint and the rate of definite and probable stent thrombosis. Independent site monitoring was performed in all studies, and clinical events committees adjudicated the endpoints.

Deaths were considered cardiac unless an unequivocal noncardiac cause was documented. Target vessel MI was defined as an MI clearly not located in a nontarget vessel, and TLR and target vessel revascularization as clinically-driven PCI or coronary artery bypass grafting of the culprit lesion or

vessel. Definite and probable stent thromboses were adjudicated in accordance with the Academic Research Consortium (15).

Statistical analysis

Data from patients that had R-ZES implanted in the 2 randomized trials and data from all patients included in the 2 registries were pooled. The pooled data were divided in 3 groups according to the presence and duration of a total coronary occlusion.

Categorical data among groups were compared using the Chi-square test, and continuous variables with Student's t-test. Survival curves were created using Kaplan-Meier estimates, and the log-rank test was used for comparisons between groups. A 2-tailed p-value <0.05 was considered significant.

Results

Of the 6,841 patients included in the four trials, 5,487 had at least one R-ZES implanted. Among the lesions treated with R-ZES implantation 436 (8.0%) were CTOs, 467 (8.5%) were rec-TOs, and 4,584 (83.5%) were non-TOs. Three-year follow-up data were available for 97% of patients in the RESOLUTE International trial, and 5-year data were available in 98% of patients in the remaining trials.

Baseline demographic and angiographic data of the patients and procedures are presented in **Tables 1 and 2**. Non-TO patients were slightly older with fewer stents implanted (especially compared to the CTO group). The majority of rec-TO patients had acute coronary syndromes (78.4%) and fewer cardiac risk factors except for diabetes. The non-TO group had significantly less lesions treated per

patient and a significantly smaller total stent length per patient compared to the rec-TO and non-TO groups. Otherwise no relevant differences were found among the 3 groups.

At 5-year follow-up, there were no differences in the incidence of the primary endpoint (**Figure 1**) or its components (**Figure 2**) between the 3 groups: TLF at 5 years was 13.2% for CTO, 12.5% for rec-TO and 13.3% for non-TO patients (p=0.96). There was also no difference between groups in secondary endpoints measured at 5 years (**Table 3**). Most stent thromboses occurred relatively early. The rate of stent thrombosis leveled off after 12 months and was generally low with a non-significant numerically higher incidence occurring in the patient group with recently occluded vessels (p=0.11, **Figure 3**).

Discussion

Patients treated with R-ZES in their recanalized CTO lesions had low 5-year rates of the primary endpoint of target vessel failure (TVF), despite longer stent length, smaller stent diameter and higher mean number of implanted stents, and as an unexpected finding, we were able to report almost identical TVF rates in patients with CTO and non-TO. Treatment of CTOs with R-ZES was safe with a very low 5-year rate of stent thrombosis (ST), that was almost identical to that of patients without CTO. The rates of cardiac death and TVMI were also low and did not differ significantly in patients with CTO vs. patients with non-TO. Probably due to the thrombogenic environment, rec-TO patients, mostly in the setting of acute coronary syndrome (3/4 of the patients in this group), had low albeit numerically higher rates of ST compared to patients in the CTO and non-TO group.

Although the safety of PCI treatment including implantation of DES in patients with acute occlusion of a large coronary artery presenting with ST-segment elevation myocardial infarction has

been investigated in long-term follow up trials (16,17), treatment of patients with coronary occlusions of longer duration remains a matter of debate. Only a small number of randomized comparisons of clinical outcomes between patients treated with optimal medical therapy versus CTO revascularization have been performed (18-20).

Randomized studies comparing DES and bare-metal stent implantation in recently occluded coronary arteries or chronic total coronary occlusions are also scarce (2,21,22), as the initial pivotal trials of DES did not include patients with complex lesions. Because of the high rate of restenosis in patients who had a bare metal stent implanted, especially in total occlusions, the use of DES in recanalized total occlusions would be expected to provide a considerable advantage by reducing the risk of restenosis and the need for repeat revascularization. Later registries including first- and second-generation DES have confirmed the safety and efficacy of stents in recanalizing total coronary occlusions.

The rate of stent thrombosis in this analysis was low, considering the fact that all studies contributing to the pooled results included unselected patient populations. We have recently reported favorable outcomes of patients who had R-ZES implanted in all-comer patients and in patients with total coronary occlusions (5,7). In patients with total occlusions the rate of definite and probable stent thrombosis was higher in patients with recent occlusions, interpreted as a consequence of an increased thrombogenic nature of these lesions. This trend is seen in the present trial, although it did not reach statistical difference (**Figure 3**).

The present study describes long-term outcomes of patients with a variety of clinical conditions treated with R-ZES and compares patient outcome in those treated for non-occluded versus occluded target lesions. Both the level of TLF and the occurrence of ST reported in our study, especially late ST, are considerably lower than long-term reports after implantation of first-

generation DES in all-comer populations (23,24). This reduction may reflect that the excessive inhibition of neointimal growth seen after implantation of first-generation stents causing delayed vascular healing was modulated by introduction of new DES. The balance between complete neointimal stent strut coverage and hyperplasia has been optimized during the years using stents with thinner struts and altered drugs and drug release characteristics. So, while previous studies of first-generation DES have reported a constant occurrence of ST up to 10 years after PCI, the leveling off of ST with time as demonstrated in the present study may represent an effect of the above described combination of both an improved stent design including altered drug kinetics and thinner stent struts in comparison with the original DES (25,26). The impact of a biodegradable polymer, originally created to reduce the risk of ST, is still a matter of debate, because long-term follow up of patient cohorts with these stents implanted are still outstanding (27).

There is recent evidence of a lack of association between interrupted dual antiplatelet therapy and development of ST with the use of newer DES (28,29). However, because of the very low level of ST observed in the present study, we are unable to draw any conclusion about an association or lack of connection between ST and interrupted antiplatelet therapy. Indeed, shortening of the duration of dual antiplatelet therapy seems safer after implantation of newer DES compared with those of first-generation DES.

Limitations

The current analysis was not prespecified. The RESOLUTE International trial followed patients up to 3 years whereas the other 3 trials followed patients to 5 years. All patients in the RESOLUTE China RCT and 20% of those in RESOLUTE All-comers had angiographic follow up at 9-13 months.

Because we only report clinical outcomes in patients with recanalized vessels, our clinical outcome results cannot be extrapolated to a general population of patients with CTO. On the other hand, the total stent length in our CTO patients (median length 42 mm) indicates that the lesions were not simple to treat.

Our results originate from pooled data from 2 randomized trials and 2 registries, all of which had independent monitoring, that was probably most thorough in the randomized trials, especially with regard to screening of patients for eligibility. Enrollment in the RESOLUTE All comers trial was close to 50% of all patients treated with PCI at the participating centers, and we expect this percentage to have been even higher in the remaining 3 studies, especially the registries. So, patients were not entirely treated by experienced operators. Still, a certain selection bias towards a favourable outcome in the overall enrollment cannot be ruled out, and our results should be interpreted accordingly. In addition, more research is warranted to focus on the impact of zotarolimus versus other –limus drugs on the beneficial outcome in patients with occluded coronary arteries treated with PCI.

As previously mentioned, incomplete revascularization of patients with CTO is associated with an increase in future events, especially new or repeat revascularizations. We were not able to report the more patient-oriented endpoint of all-cause mortality, or any myocardial infarction and revascularization, known to occur approximately twice as often as our primary endpoint of TLF.

Conclusions

Long-term TLF was similar in patients with both rec-TO and CTO lesions compared with patients with non-TO lesions, suggesting that R-ZES implantation is safe and effective in patients with total occlusions.

Impact on daily practice

Our results indicate that patients who have their occluded coronary artery recanalized and the Resolute Zotarolimus-eluting stent implanted have the same long-term clinical outcome compared with those who have this stent implanted in non-occluded vessels. Whether this applies to all new-generation coronary stents is unknown.

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Figure Legends

Figure 1: Cumulative incidence to 5 years for target lesion failure.

*CTO: chronic total occlusion; †Rec-TO: recent total occlusion; ‡Non-TO: No occlusion; TLF: target lesion failure.

Figure 2: Cumulative incidence to 5 years for: **A)** Cardiac death or target vessel myocardial infarction; **B)** Target vessel revascularization

*CTO: chronic total occlusion; †Rec-TO: recent total occlusion; ‡Non-TO: No occlusion.

Figure 3: Cumulative incidence to 5 years for stent thrombosis (definite/probable)

*CTO: chronic total occlusion; †Rec-TO: recent total occlusion; ‡Non-TO: No occlusion.

Table 1: Baseline characteristics

	CTO group* (N=436)	**Rec-TO group*** (N=467)	**Non-TO*** (N=4584)	p-value (CTO vs Non-TO)	p-value (Rec-TO vs Non-TO)
Age (years)	60.8±11.2	60.0±11.6	63.3±10.9	<0.001	<0.001
Female gender	17.2	24.6	23.6	0.002	0.61
Diabetes mellitus	26.1	26.6	28.9	0.22	0.28
Insulin dependent	4.6	4.9	6.2	0.19	0.29
Hypertension	64.7	57.6	68.5	0.10	<0.001
Hyperlipidemia	52.1	48.6	56.5	0.08	0.001
Current smoker	30.3	45.8	27.2	0.16	<0.001
Prior myocardial infarction	37.7	33.5	29.4	<0.001	0.06
Prior percutaneous coronary intervention	20.9	10.3	25.7	0.03	<0.001
Acute coronary syndrome	47.0	78.4	53.3	0.01	<0.001

*Data presented as % or mean ± standard deviation.

CTO: chronic total occlusion; Rec-TO: recent total occlusion; Non-TO: No occlusion.

Table 2: Angiographic characteristics

	CTO group* (N=436)	**Rec-TO group*** (N=467)	**Non-TO*** (N=4584)	p-value (CTO vs Non-TO)	p-value (Rec-TO vs Non-TO)
Reference vessel diameter (mm)	2.9±0.5	2.9±0.5	2.9±0.5	0.19	0.15
Number of lesions treated/patient	1.6±0.8	1.5±0.8	1.4±0.7	<0.001	0.01
Total stent length/patient (mm)	53.9±35.9	41.3±28.2	33.4±22.1	<0.001	<0.001
Vessel location (patient level)					
Left anterior descending	51.6	48.2	56.2	0.06	<0.001
Left circumflex	27.1	26.6	27.5	0.86	0.67
Right coronary artery	50.7	45.0	30.8	<0.001	<0.001
Left main	0.9	1.5	2.6	0.03	0.15

*Data presented as % or mean ± standard deviation.

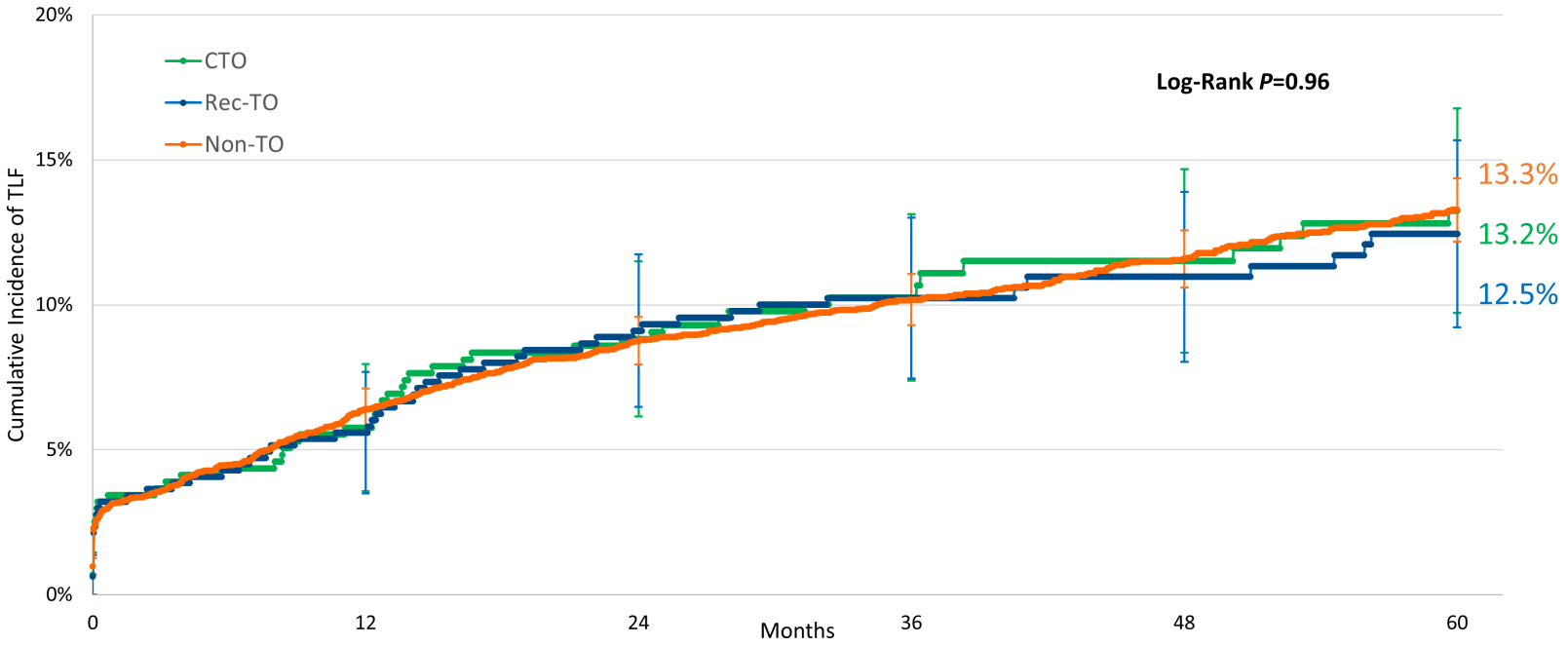
CTO: chronic total occlusion; Rec-TO: recent total occlusion; Non-TO: No occlusion.

Table 3: Clinical outcomes to 5 years

	CTO group* (N=436)	**Rec-TO group*** (N=467)	**Non-TO*** (N=4584)	p-value (CTO vs Rec-TO vs Non-TO)
Target lesion failure	13.2 (51)	12.5 (53)	13.3 (535)	p=0.96
Cardiac Death	5.3 (21)	5.1 (19)	4.8 (179)	p=0.64
Target vessel myocardial infarction	4.2 (17)	3.2 (14)	4.3 (185)	p=0.54
Target lesion revascularization	5.8 (21)	6.9 (29)	6.5 (254)	p=0.70
Target vessel revascularization	7.0 (26)	9.1 (36)	8.8 (343)	p=0.52
Stent thrombosis (definite/probable)	1.2 (5)	2.6 (11)	1.3 (55)	p=0.11

*Data presented as percentage of cumulative incidence of events calculated by Kaplan Meier method with log-rank p-values (# of events)

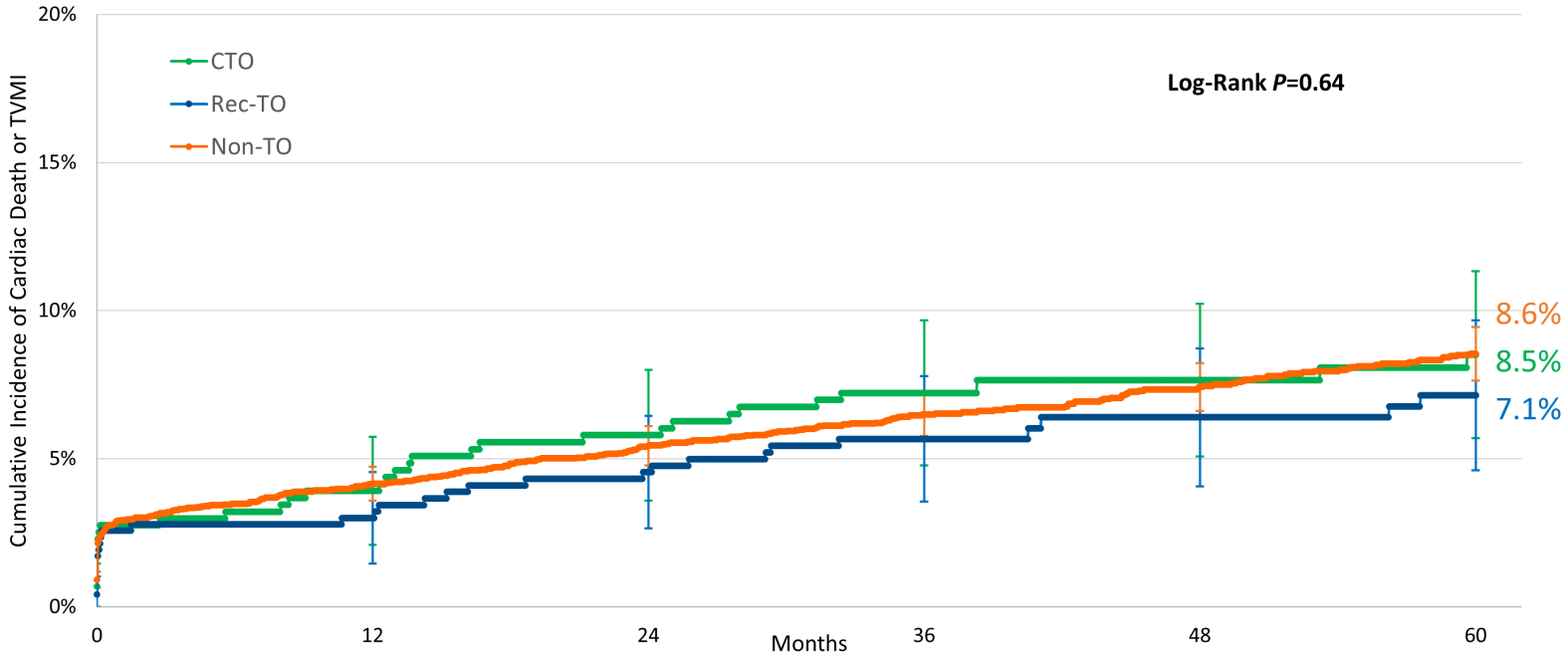
CTO: chronic total occlusion; Rec-TO: recent total occlusion; Non-TO: no occlusion.



Number at risk

CTO	436	433	403	384	351	207
Rec-TO	467	464	434	410	355	240
Non-TO	4584	4537	4213	4040	3612	2180

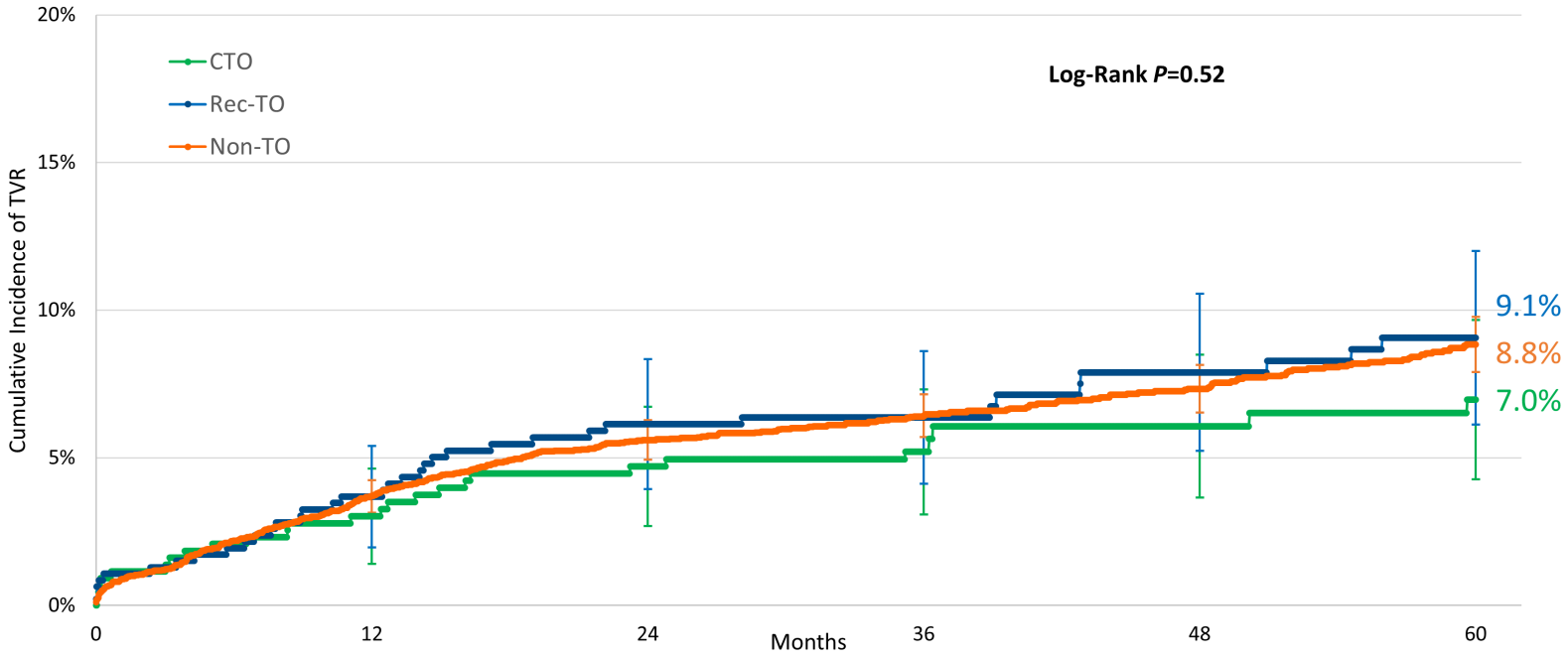
A



Number at risk

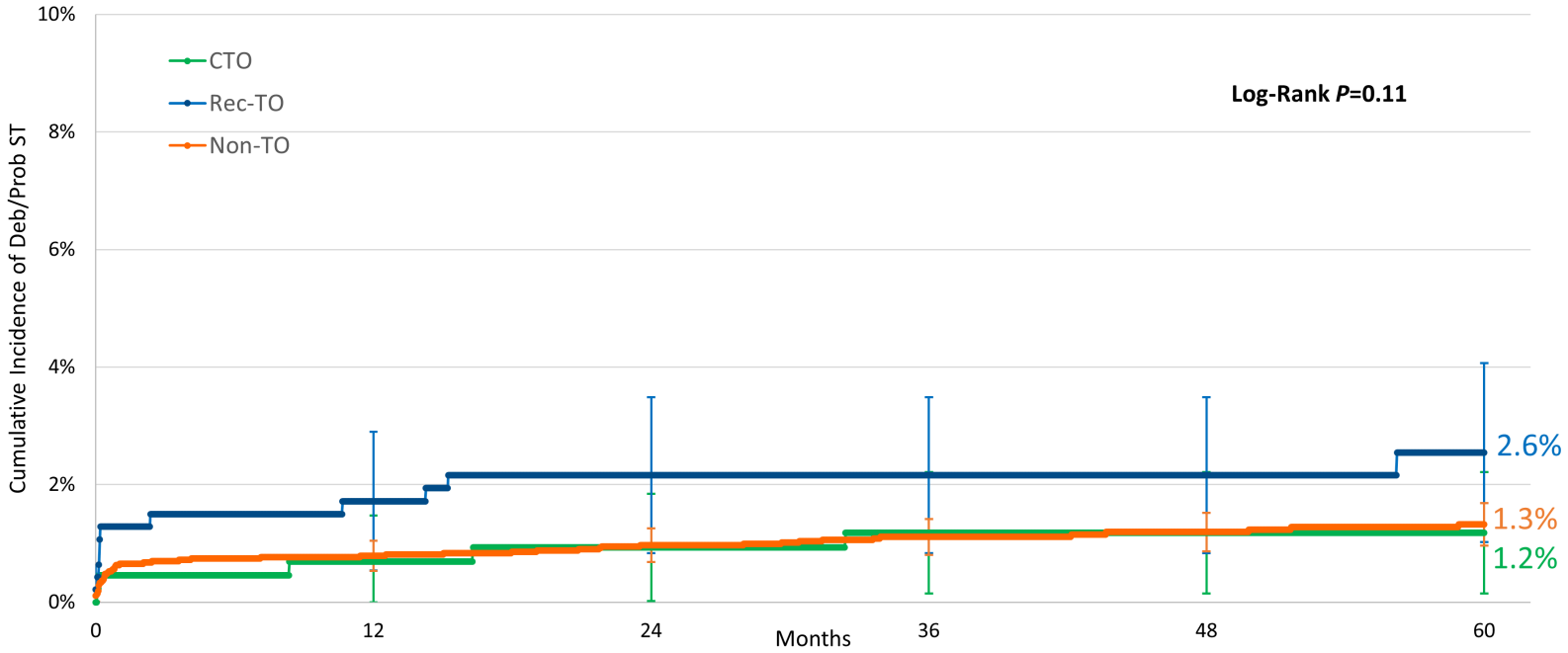
CTO	436	433	411	397	363	215
Rec-TO	467	465	445	430	373	254
Non-TO	4584	4540	4315	4188	3749	2263

B



Number at risk

CTO	436	436	410	390	354	211
Rec-TO	467	466	440	416	360	237
Non-TO	4584	4577	4286	4094	3655	2202



Number at risk

CTO	436	436	421	407	371	220
Rec-TO	467	466	452	437	379	256
Non-TO	4584	4577	4422	4302	3855	2322