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Short-Term and Long-Term Clinical Impact of Stent Thrombosis and Graft Occlusion in the SYNTAX Trial at 5 Years

Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial

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Objectives The aim of this study was to report the short-term and long-term clinical impact of stent thrombosis (ST) and graft occlusion (GO) in the final 5-year outcomes of the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial.

Background The clinical effect of newer-generation drug-eluting stents and operative factors in complex coronary artery disease is uncertain.

Methods The incidence of 5-year ST and GO, and their association with clinical outcomes, were analyzed in the randomized percutaneous coronary intervention and coronary artery bypass graft cohorts. ST and GO were defined by the SYNTAX protocol definitions (clinical presentation with acute coronary syndrome and angiographic/pathological evidence), the Academic Research Consortium (ARC) definition for ST, and the newly devised "ARC-like" definition of GO (i.e., definite, probable, or possible GO).

Results At 5 years, 871 of 903 patients (96.5%) in the percutaneous coronary intervention cohort and 805 of 897 patients (89.7%) in the coronary artery bypass graft cohort completed follow-up. As compared with other vessel locations, protocol ST (72 lesions) occurred more frequently in the left main (14 of 72; 19%) and proximal coronary vasculature (37 of 72; 51%) and protocol GO (41 lesions) with grafts anastomosed to the distal right coronary artery (17 of 41; 42%). The incidence of 5-year ARC definite ST and ARC-like definite GO did not significantly differ (7% [n = 48] vs. 6% [n = 32], log rank p = 0.34); landmark analyses indicated significantly increased ARC definite ST within 30 days (3% [n = 19] vs. 1% [n = 6], log rank p = 0.033) but not >30 days to 5 years (4.2% [n = 29] vs. 4.5% [n = 26], log rank p = 0.78). At presentation, ARC definite ST (n = 48) and ARC-like definite GO (n = 32) were adjudicated to be linked to 4 (8%) and 0 deaths, respectively. At 5 years, ARC definite ST (n = 48) and ARC definite/probable ST (n = 75) were associated with 17 (17 of 48, 35.4%; median days to death: 0 days; interquartile range: 0 to 16 days; maximum: 321 days) and 31 (31 of 75, 41.3%; median: 0 days; interquartile range: 0 to 9 days; maximum: 721 days) cardiac deaths, respectively. At 5 years, ARC-like definite GO (n = 32) and ARC-like definite/probable GO (n = 53) were associated with 0 and 12 (12 of 52, 23.1%; median: 0 days; interquartile range: 0 to 14 days; maximum: 257 days) cardiac deaths, respectively.

Conclusions Although the incidence of ST and GO was similar at 5 years, the clinical impact of ST appeared greater, with a negative impact on short-term to long-term mortality. (J Am Coll Cardiol 2013;62:2360–9) © 2013 by the American College of Cardiology Foundation

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The final 5-year reporting of the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial showed that coronary artery bypass graft (CABG) surgery remained the standard of care for patients with complex (left main or 3-vessel) coronary artery disease compared with percutaneous coronary intervention (PCI) with first-generation drug-eluting stents (1,2). In subjects with lesser complex coronary artery disease undergoing PCI, using the anatomic SYNTAX Score to assess coronary artery complexity (3) or the SYNTAX Score augmented with clinical factors (SYNTAX Score II), (4,5) were shown to be an acceptable alternative to CABG.

The clinical impact of stent thrombosis (ST) and graft occlusion (GO) in the SYNTAX trial is unreported. The purpose of the study was to report the incidence, timing, predictors, and clinical impact of ST and GO in the SYNTAX trial.

Methods

The SYNTAX trial is a randomized, prospective, multicenter, "all-comers" trial investigating subjects with unprotected left main coronary artery (ULMCA) disease (isolated or associated with 1-, 2-, or 3-vessel disease) or de novo 3-vessel disease and has previously been described (1,2). In total, 1,800 subjects were randomized on a 1:1 basis to either PCI with Taxus Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Massachusetts) or CABG.

An independent clinical events committee (CEC), including cardiologists, cardiac surgeons, and a neurologist, reviewed all the primary clinical endpoints and ST/GO events. All deaths were subdivided into cardiovascular and noncardiovascular deaths by the CEC. Cardiac deaths were classified as related or unrelated to a cardiac procedure by the CEC.

ST and GO. Because the SYNTAX trial began before publication of the Academic Research Consortium (ARC) definition, (6) the SYNTAX trial instigated a protocol definition for ST and GO (Table 1). Subsequently, the ARC criteria (6) for ST were implemented and reported by a separate CEC (see the Acknowledgments section). To allow comparisons of ARC ST events to GO, "ARC-like" definitions were formulated for GO (i.e., definite, probable, or possible GO) using adapted ARC definitions (Table 1).

Abbreviations and Acronyms

ARC = Academic Research Consortium
CABG = coronary artery bypass graft
CEC = clinical events committee
GO = graft occlusion
KM = Kaplan-Meier
LAD = left anterior descending artery
LIMA = left internal mammary artery
MI = myocardial infarction
PCI = percutaneous coronary intervention
RIMA = right internal mammary artery
ST = stent thrombosis
ULMCA = unprotected left main coronary artery

Table 1 SYNTAX Protocol and ARC/ARC-Like Definitions of ST and GO

Stent Thrombosis	Graft Occlusion
SYNTAX protocol definition The occurrence of any of the following: 1. Clinical presentation of acute coronary syndrome with ST confirmed by angiography, multi-slice CT, or autopsy a. Angiographic documentation of a complete occlusion (TIMI flow grade 0 or 1) of a previously successfully treated artery (TIMI flow gade 2 to 3 immediately after stent placement and diameter stenosis ≤30) and/or b. Documentation by angiography, multi-slice CT, or autopsy of flow-limiting thrombus or complete luminal obstruction within or adjacent to a previously successfully treated lesion 2. Q-wave MI in the territory of one or more of the treated vessels (LAD, LCX, RCA) within the first 30 days (acute or subacute)	SYNTAX protocol definition The occurrence of any of the following: 1. Clinical presentation of acute coronary syndrome with GO confirmed by angiography, multi-slice CT, or autopsy a. Angiographic documentation of occlusion (TIMI flow grade 0 or 1) of a vascular graft and/or b. Documentation by angiography, multi-slice CT, or autopsy of flow-limiting thrombus or complete luminal obstruction within a bypass graft or a flow limiting thrombus adjacent to the anastomosis of previously bypassed coronary artery 2. Q-wave MI in the territory of one or more of the treated vessels (LAD, LCX, RCA) within the first 30 days (acute or subacute)
ARC definite ST 1. Angiographic or pathological confirmation of partial or total thrombotic occlusion within the peri-stent region and at least one of the following additional criteria: a. Acute ischemic symptoms b. Ischemic electrocardiographic changes c. Elevated cardiac biomarkers	ARC-like definite GO* 1. SYNTAX protocol definition as stated in the preceding text
ARC probable ST 1. Any unexplained death within 30 days of stent implantation 2. Any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST	ARC-like probable GO† 1. Any unexplained death within 30 days of graft 2. Any MI that is related to documented acute ischemia in the territory of the anastomosed graft without angiographic confirmation of GO
ARC possible ST 1. Any unexplained death beyond 30 days	ARC-like possible GO‡ 1. Any unexplained death beyond 30 days

*The definitions of protocol GO and ARC-like definite GO were identical. †Because subjects had left main or de novo 3-vessel disease, it was assumed that an MI in any of the 3-vessel territories for 3-vessel disease or the left coronary system for unprotected left main coronary artery disease without subsequent angiographic confirmation of graft patency was classified as probable GO. ‡ARC possible GO was identical to ARC-like possible ST.

ARC = Academic Research Consortium; CT = computed tomography; GO = graft occlusion; MI = myocardial infarction; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; ST = stent thrombosis; TIMI = Thrombolysis in Myocardial Infarction.