Circulation: Cardiovascular Interventions

RESEARCH LETTER

Prospective Multicenter Randomized All-Comers Trial to Assess the Safety and Effectiveness of the Ultra-Thin Strut Sirolimus-Eluting Coronary Stent Supraflex

Two-Year Outcomes of the TALENT Trial

Chao Gao, MD; Norihiro Kogame, MD; Faisal Sharif, MD, PhD; Pieter C. Smits, MD, PhD; Pim Tonino MD, PhD; Sjoerd Hofma, MD, PhD; Raul Moreno, MD; Anirban Choudhury, MD; Ivo Petrov, MD; Angel Cequier, MD; Antonio Colombo, MD; Upendra Kaul, MD, PhD; Azfar Zaman, MD; Robbert J. de Winter, MD, PhD; Yoshinobu Onuma, MD, PhD; Patrick W. Serruys, MD, PhD

Outcomes with the current second-generation drug eluting stents, although outstanding, have plateaued and remained steady over the past decade.[1] To further improve event-free survival, drug eluting stents with ultra-thin struts have been introduced. Compared with the thin strut drug eluting stents, stents with ultra-thin struts have the theoretical advantages of accelerating endothelialization, reducing vascular injury, and improving device deliverability.[2]

The Supraflex is a sirolimus-eluting metallic stent (Sahajanand Medical Technologies, Surat, India) with biodegradable polymeric matrix coating. The novelty of the Supraflex is its uniformly 60 μm strut thickness, irrespective of the diameter of the stents, ranging from 2.0 to 4.5 mm.[3] This is at variance with the Orsiro stent, which has a strut thickness of 60 μm in the small stent size platform (2.25–3.0 mm) but 80 μm in the large stent size platform (3.5–4.0 mm).

The TALENT trial (Thin Strut Sirolimus-Eluting Stent in All Comers Population vs Everolimus-Eluting Stent)[4] is a prospective, multicenter, single-blinded, all-comers, randomized controlled trial, allocating patients in a 1:1 ratio to either Supraflex or Xience everolimus-eluting stent (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02870140). Twenty-three sites in Europe enrolled patients from October 21, 2016, to July 3, 2017. Previously, the TALENT trial has showed noninferiority of Supraflex as compared with Xience in terms of device-oriented composite end point (a composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization [CI-TLR]) at 12 months. However, it is still unknown whether these outcome results persisted in the long term. We here present the 2-year results of the TALENT trial.

All patients provided written informed consent to participate in the study. The study protocol of TALENT trial was approved by institutional ethics committees of participating institutions and central regulatory bodies for each of the center and was conducted according to the Declaration of Helsinki and Good Clinical Practice. The data that support the findings of this study are available from the corresponding author upon reasonable request. Time-to-event outcomes are compared using the log-rank test. A 2-sided P value <0.05 was considered as statistically significant.

Two-year follow-up information was available in 97.8% (704/720) of patients in the Supraflex arm and in 98.6% (705/715) of patients in the Xience arm. Comparisons of the clinical end points are presented in the Table. At 2 years, in the intention to treat data set, device-oriented composite end point occurred in 49 (6.9%) patients treated with

Key Words: death ■ drug-eluting stent ■ sirolimus ■ stents

Correspondence to: Patrick W. Serruys, MD, PhD, National University of Ireland, Galway (NUIG), PO University Rd, Galway, H91 TK33, Ireland. Email patrick.w.j.c.serruys@gmail.com

For Sources of Funding and Disclosures, see page 368.

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

Nonstandard Abbreviations and Acronyms

CI-TLR	clinically indicated target lesion revascularization

Supraflex and 56 (7.9%) patients treated with Xience (*P*=0.491). Frequencies of cardiac death (9 [1.3%] versus 11 [1.6%], *P*=0.659), target vessel myocardial infarction (21 [3.0%] versus 27 [3.8%], *P*=0.382), and CI-TLR (33 [4.7%] versus 37 [5.3%], *P*=0.627) were not significantly different for both stent type. The rate of definite/probable ST was also not different between the Supraflex and XIENCE arms (8 [1.1%] versus 9 [1.3%], *P*=0.813).

The per-protocol population set consists of all patients who have been randomized to a treatment group, and who have received only the assigned study stent. Because the per-protocol analysis comparing the 1-year results showed a significantly lower CI-TLR rate in the Supraflex arm (1.2%) than in the Xience arm (3.1%), we investigated whether this difference persisted or accrued beyond 1 year. At 2-year follow-up, in the per-protocol data set, device-oriented composite end point occurred in 36 (5.5%) patients treated with Supraflex and 49 (7.2%) patients treated with Xience (*P*=0.223). Frequencies of cardiac death (9 [1.4%] versus 11 [1.6%], *P*=0.736), target vessel myocardial infarction (17 [2.6%] versus 26 [3.8%], *P*=0.216), and CI-TLR (21 [3.3%] versus 30 [4.5%], *P*=0.267) were all numerically lower in the Supraflex arm, but without reaching statistically significant differences compared with the Xience arm.

The main finding of our analyses is that the use of the Supraflex showed sustained efficacy and safety at 2-year, as compared with the Xience.

The fact that the rate of nontarget vessel revascularization is numerically lower in the Xience arm at 2-year has to be acknowledged. On one hand, nontarget vessel revascularization is not directly related to the allocated study device, and on the other hand, the study did not have the adequate sample size for any secondary end points. Therefore, we believe this observation is largely due to play of chance. In the second-year outcome, although in the per-protocol data set, the rate of CI-TLR was still numerically lower in the Supraflex arm than in the Xience arm, it did not reach a statistical significance. A longer-term follow-up is still needed to investigate whether Supraflex might show a lower CI-TLR rate as compared with Xience.

The current analyses have limitations. First, the study did not have the adequate statistical power for any itemized end points due to the relatively small sample size. Moreover, taking into account the observational nature of the analysis, there was no formal correction for multiple testing.[5] Therefore, these results should be interpreted cautiously and as hypothesis-generating only.

ARTICLE INFORMATION

Affiliations

Department of Cardiology, Xijing hospital, Xi'an, China (C.G.). Department of Cardiology, Radboud University, Nijmegen, the Netherlands (C.G.). Department of Cardiology, National University of Ireland Galway (C.G., F.S., Y.O., P.W.S.). Amsterdam UMC, University of Amsterdam, the Netherlands (N.K., R.J.d.W.). Maasstad Ziekenhuis, Rotterdam, the Netherlands (P.C.S.). Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands (P.T.). Medical Centre Leeuwarden, the Netherlands (S.H.). Cardiology Department, La Paz University Hospital, Madrid, Spain (R.M.). Department of Cardiology, University Hospital of Wales, Cardiff, United Kingdom (A. Choudhury). Acibadem City Clinic Cardiovascular Center, Sofia, Bulgaria (I.P.). University Hospital of Bellvitge, Barcelona, Spain (A. Cequier). Division of Interventional Cardiology, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy (A. Colombo). Academics and Research, Batra Hospital and Medical Research Center, New Delhi, India (U.K.). Freeman Hospital, Newcastle University, and Newcastle upon Tyne Hospitals NHS Trust, Newcastle, United Kingdom (A.Z.). NHLI, Imperial College London, United Kingdom (P.W.S.).

Acknowledgments

We would like to thank MarieAngele Morel, Anita van der Wal, and Maurice Vorage from Cardialysis for their intellectual and managerial contribution.

Sources of Funding

This study was sponsored by the European Cardiovascular Research Institute (ECRI), and supported with an unrestricted grant from Sahajanand Medical Technologies (India). ECRI funded the independent research organization Cardialysis for site management, safety reporting, data management, end point adjudication, database management, and statistical analyses. The study funders had no role in trial design, data collection, analysis, interpretation of the data, preparation, approval, or making a decision to submit the article or publication.

Disclosures

Dr Zaman reports speaker fees from Sahajanand Medical Technologies and speaker and consulting fees from Abbott Vascular. Dr Kogame reports grant from DalCor Pharmaceuticals, Hamilton Health Sciences Corporation, Population Health Research Institute, and Bayer, and personal fees from Pfizer and AstraZeneca, outside the submitted work. Dr Onuma is a member of the Advisory Board of Abbott Vascular. Dr Serruys reports personal fees from Biosensors, personal fees from Medtronic, personal fees from Micel Technologies, personal fees from Sinomedical Sciences Technology, personal fees from Philips/Volcano, personal fees from Xeltis, personal fees from HeartFlow, outside the submitted work. The other authors report no conflicts.

REFERENCES

1. Chichareon P, Katagiri Y, Asano T, Takahashi K, Kogame N, Modolo R, Tenekecioglu E, Chang CC, Tomaniak M, Kukreja N, et al. Mechanical properties and performances of contemporary drug-eluting stent: focus on the metallic backbone. *Expert Rev Med Devices*. 2019;16:211–228. doi: 10.1080/17434440.2019.1573142
2. Iglesias JF, Muller O, Heg D, Roffi M, Kurz DJ, Moarof I, Weilenmann D, Kaiser C, Tapponnier M, Stortecky S, et al. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial. *Lancet*. 2019;394:1243–1253. doi: 10.1016/S0140-6736(19)31877-X
3. Modolo R, Chichareon P, Kogame N, Asano T, Chang CC, de Winter RJ, Kaul U, Zaman A, Spitzer E, Takahashi K, et al. A prospective multicentre randomised all-comers trial to assess the safety and effectiveness of the thin-strut sirolimus-eluting coronary stent SUPRAFLEX: rationale and design of the Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent (TALENT) trial. *EuroIntervention*. 2019;15:e362–e369. 10.4244/EIJ-D-18-00499
4. Zaman A, de Winter RJ, Kogame N, Chang CC, Modolo R, Spitzer E, Tonino P, Hofma S, Zurakowski A, Smits PC, et al; TALENT trial investigators. Safety and efficacy of a sirolimus-eluting coronary stent with ultrathin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial. *Lancet*. 2019;393:987–997. doi: 10.1016/S0140-6736(18)32467-X
5. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, Devereaux PJ, Thabane L. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol*. 2017;46:746–755. doi: 10.1093/ije/dyw320

Table. Clinical Outcomes at 24 Months After Stent Implantation (Intention-to-Treat Basis)

Outcome	Supraflex SES (N=720)	Xience EES (N=715)	Difference (95% CI)	*P* value
TLF (DoCE)	6.9% (49)	7.9% (56)	−1.0% (−3.7% to 1.7%)	0.49
PoCE	15.5% (110)	13.1% (93)	2.4% (−1.3% to 6.0%)	0.20
TVF	8.3% (59)	8.9% (63)	−0.6% (−3.5% to 2.4%)	0.71
Components of composite end points				
Death	2.5% (18)	3.0% (21)	−0.4% (−2.1% to 1.3%)	0.64
Cardiac death	1.3% (9)	1.6% (11)	−0.3% (−1.5% to 0.9%)	0.66
MI	4.4% (31)	5.0% (35)	−0.6% (−2.8% to 1.6%)	0.62
Q-wave	0.7% (5)	0.9% (6)	−0.1% (−1.1% to 0.8%)	0.77
Non-Q-wave	3.8% (27)	4.2% (30)	−0.4% (−2.5% to 1.6%)	0.69
TV-MI	3.0% (21)	3.8% (27)	−0.9% (−2.8% to 1.0%)	0.38
Q-wave	0.6% (4)	0.9% (6)	−0.3% (−1.2% to 0.6%)	0.53
Non-Q-wave	2.5% (18)	3.1% (22)	−0.6% (−2.3% to 1.1%)	0.52
Non-TV MI	1.4% (10)	1.1% (8)	0.3% (−0.9% to 1.5%)	0.63
Q-wave	0.1% (1)	0.0% (0)	0.1% (−0.1% to 0.4%)	0.32
Non-Q-wave	1.3% (9)	1.1% (8)	0.2% (−1.0% to 1.3%)	0.80
All revascularization	12.4% (87)	9.7% (68)	2.7% (−0.5% to 6.0%)	0.11
TL revascularization	6.1% (43)	5.7% (40)	0.4% (−2.0% to 2.9%)	0.73
Clinically indicated	4.7% (33)	5.3% (37)	−0.6% (−2.8% to 1.7%)	0.63
nonclinically indicated	1.7% (12)	1.0% (7)	0.7% (−0.5% to 1.9%)	0.25
TV revascularization	7.4% (52)	7.0% (49)	0.4% (−2.3% to 3.1%)	0.77
Clinically indicated	6.3% (44)	6.4% (45)	−0.1% (−2.7% to 2.4%)	0.90
Nonclinically indicated	1.7% (12)	1.6% (11)	0.2% (−1.2% to 1.5%)	0.84
Non-TV revascularization	7.9% (55)	4.4% (31)	3.5% (0.9% to 6.0%)	0.01
Stent thrombosis				
Definite	1.0% (7)	1.1% (8)	−0.1% (−1.2% to 0.9%)	0.80
Acute (0–1 days)	0.1% (1)	0.0% (0)	0.1% (−0.1% to 0.4%)	0.32
Subacute (2–30 days)	0.1% (1)	0.3% (2)	−0.1% (−0.6% to 0.3%)	0.56
Late (31–360 days)	0.4% (3)	0.4% (3)	0.0% (−0.7% to 0.7%)	0.99
Very late stent thrombosis (after 360 days)	0.3% (2)	0.4% (3)	−0.1% (−0.8% to 0.5%)	0.66
Definite or probable	1.1% (8)	1.3% (9)	−0.1% (−1.3% to 1.0%)	0.81
Acute (0–1 days)	0.1% (1)	0.0% (0)	0.1% (−0.1% to 0.4%)	0.32
Subacute (2–30 days)	0.3% (2)	0.3% (2)	−0.0% (−0.6% to 0.5%)	0.99
Late (31–360 days)	0.4% (3)	0.6% (4)	−0.1% (−0.9% to 0.6%)	0.70
Very late stent thrombosis (after 360 days)	0.3% (2)	0.4% (3)	−0.1% (−0.8% to 0.5%)	0.66

DoCE indicates device-oriented composite end point; EES, everolimus-eluting stent; MI, myocardial infarction; PoCE, patient-oriented composite end point; SES, sirolimus-eluting stent; TLF, target lesion failure; TVF, target vessel failure; and TV-MI, target vessel myocardial infarction.