

High SYNTAX Score and Long-Term Outcome Following Percutaneous Coronary Intervention with Drug-Eluting Stents: Insights from the LEADERS Trial

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Abstract

In the quest to quantify the different coronary anatomical and lesion characteristics in a comprehensive, yet simple way, the SYNTAX score was initially designed. Thereafter, the SYNTAX score was liberally employed to predict Major Adverse Cardiac Events (MACE) following percutaneous coronary intervention of multivessel coronary artery disease at varying periods of follow-up. Ultimately, the SYNTAX score was used for risk stratification of patients in the LEADERS trial (Limus Eluted from A Durable versus ERodable Stent coating), at one- and two-year follow-up. Eventually, the authors concluded that “the SYNTAX score when applied to an all-comers patient population allows for prospective risk stratification of patients undergoing PCI up to two years follow-up. In addition, the SYNTAX score appears to separate the performance of devices in high-risk patient groups”. Nevertheless, after reappraisal of published data from the SYNTAX score substudy of the LEADERS trial at two-year follow-up, we came up with the conclusion: the higher rate of early stent thrombosis in the Sirolimus-Eluting Stent (SES) group may explain the higher rates of cardiac death and clinically-indicated target vessel revascularization with SES during the first month after the index procedure, both were responsible for the early divergence of the MACE curves between the two stent arms during the first month of follow-up, which was the prime driver of higher MACE with SES versus Biolimus-Eluting Stent (BES) at 12-month and 24-month follow-up; yet, the higher rate of myocardial infarction in the BES group early during the first month remains unclear.

Keywords: SYNTAX score; Drug-eluting stents; Outcome

Assessment of lesion complexity has long been one of the chief interests of interventional cardiologists, not only for prediction of procedural success and potential periprocedural complications of Percutaneous Coronary Intervention (PCI), but also for balancing the weight of risk/benefit for the different alternative revascularization strategies. In the quest to quantify the different coronary anatomical and lesion characteristics in a comprehensive, yet simple way, the SYNTAX score was initially designed [1,2]. Thereafter, the SYNTAX score was liberally employed to predict Major Adverse Cardiac Events (MACE) following PCI of multivessel coronary artery disease at varying periods of follow-up [3,4]. In the ARTS-II study, for instance, patients with SYNTAX score in the highest tertile had significantly more MACE as compared with those in the lower tertiles (HR 3.5; CI 1.7-7.4; $p=0.0001$); actually, the SYNTAX score was an independent predictor of a 4-fold increase in MACE [4]. The SYNTAX score was then adopted even more widely to predict periprocedural Myocardial Infarction (MI) in patients undergoing elective PCI for left main coronary disease, long lesions, and bifurcation lesions [5]. Ultimately, the SYNTAX score was used for risk stratification of patients in the LEADERS trial (Limus Eluted from A Durable versus ERodable Stent coating), at two points of follow-up [6,7].

The LEADERS trial was a multi-center randomized controlled trial comparing two members of the limus-eluting stent family in an ‘all-comer’ population: a second generation biodegradable polymer Biolimus-Eluting Stent (BES) and a first-generation durable polymer Sirolimus-Eluting Stent (SES). In the original comparison, the former proved non-inferior to the latter regarding the occurrence of the primary endpoint: a composite of cardiac death, MI, and clinically-indicated Target Vessel Revascularization (TVR) at 12-month follow-up [8]. The SYNTAX score was prospectively collected for 1,397 out of a total of 1,707 patients, and its prognostic value for predicting MACE was reported at one- and two-year follow-up [6,7]. Analysis was carried out by stratifying clinical outcomes based on three SYNTAX score tertiles: low ≤ 8 , mid $8 < \leq 16$, and high > 16 . Initially, at one-year follow-up, patients in the highest SYNTAX score tertile had a significantly

higher rate of cardiac death, TVR, MACE and a trend for higher MI [6]. At two-year follow-up, the rate of MACE was 18.4%, 12.0% and 9.4% in the high, mid, and low tertiles, respectively ($p < 0.01$). There was a significantly higher rate of cardiac death in patients in the high tertile (7% high versus 2.4% mid versus 1.8% low; $p < 0.001$). Within the high tertile, the rate of cardiac death was significantly lower in the BES group as compared with the SES group (4.7% versus 9.6%, $p = 0.046$). Eventually, the authors concluded that “the SYNTAX score when applied to an all-comers patient population allows for prospective risk stratification of patients undergoing PCI up to two years follow-up. In addition, the SYNTAX score appears to separate the performance of devices in high-risk patient groups” [7].

Reappraisal of published data from the SYNTAX score substudy of the LEADERS trial at two-year follow-up would, nevertheless, depict a rather diverse landscape. First, a careful look at the time-to-event curves stratified by the SYNTAX score will disclose that the divergence of the MACE curves occurred in the first 12 months (chiefly in the first 3 months), whereas from 12 to 24 months, the curves of the 3 tertiles continue almost parallel to each other. Similarly, the difference in cardiac death was noted in the first 12 months (again chiefly in the first 3 months), whereas from 12 to 24 months, almost no difference was noted. In the same way, the excess of clinically indicated TVR occurred mainly during the first 6 months. Furthermore, there was a high rate of

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MI and clinically indicated TVR (most probably driven by the excess early MI) during the initial 2 weeks in the high, and mid tertiles.

Second, a closer look at the time-to-event curves for patients in the high SYNTAX score tertile treated with BES versus SES, likewise, reveals that the differences in MACE and cardiac death (both in favor of BES) occurred mainly during the first 12 months, after which the curves continue virtually parallel to each other. More interestingly, the rate of clinically-indicated TVR was significantly higher with SES versus BES during the first 12 months only (chiefly driven by an amazingly high rate of TVR with SES in the first 2 weeks), whereas during the period from 12 to 24 months, it was actually higher in the BES arm, speaking of a late catch-up phenomenon regarding TVR associated with BES as compared with SES in the high SYNTAX score tertile. Moreover, the rates of MI were exceptionally high during the first 2 weeks in both arms (more with BES) in the high SYNTAX score tertile.

Third, further analysis of the curves of Stent Thrombosis (ST) for patients in the high SYNTAX score tertile treated with BES versus SES would raise more intriguing concerns. The rate of definite (and that of definite/probable) ST was remarkably higher with SES versus BES during the initial 2 weeks following the index procedure; thereafter the curves continue nearly parallel to each other till 24-month follow-up, denoting that the difference in ST in the high SYNTAX score tertile was restricted to early ST, whilst late and very late ST in that tertile were almost similar between the 2 stent arms. In this respect, the rates of early ST (both definite and definite/probable) were rather high in both stent arms: nearly 4% with SES, and nearly 2% with BES. Nevertheless, whereas the rate of MI during the first month in the SES arm with high SYNTAX score (roughly 4%) matched that of early ST associated with SES, the MI rate during the first month in the BES arm with high SYNTAX score (roughly 5.5%) was far exceeding that of early ST in that arm.

Taken at face value, the message distilled from the time-to-event curves of the SYNTAX score substudy of the LEADERS trial at two-year follow-up seems rather straightforward: in an all-comers population, the SYNTAX score allowed for prospective risk stratification of all-comer patients undergoing PCI up to one year follow-up, whereas after one year, there was no further divergence of the MACE curves stratified by the SYNTAX score tertiles. Additionally, and equally important, in the high SYNTAX score tertile, the higher rate of MACE in the SES group as compared with the BES group was largely driven by higher rates of cardiac death and clinically-indicated TVR in that group (MI rates were actually higher in the BES arm). We can also assume that the high

rates of MI and clinically-indicated TVR early during the first month in the high SYNTAX score tertile were mostly driven by high rates of early ST (both definite and definite/probable) in both stent arms. Finally, we can reasonably come up with the following conclusion: in the high SYNTAX score tertile, the higher rate of early ST in the SES group may explain the higher rates of cardiac death and clinically-indicated TVR associated with SES during the first month after the index procedure, both were responsible for the early divergence of the MACE curves between the two stent arms during the first month of follow-up, which was the prime driver of higher MACE associated with SES versus BES in the high SYNTAX score tertile at 12-month and 24-month follow-up; yet, the higher rate of MI in the BES group with high SYNTAX score early during the first month (despite a lower rate of early ST in that group) remains largely unclear.

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