

Role of the functional SYNTAX score in evaluating multivessel coronary artery disease

The SYNTAX score (SS) was recently introduced to overcome the limitation of coronary angiography in the interpretation of multivessel coronary artery disease (MVD). The SS is an angiography-based scoring system that describes lesion complexity and correlates with clinical outcomes. However, angiographic assessment of MVD often over- or underestimates the functional significance of MVD. A fractional flow reserve-guided SS, termed the functional SS (FSS), which is obtained by counting only ischemia-provoking lesions, can overcome this limitation. Compared with the classic SS, the FSS has better reproducibility and prognostic value, and it increases the proportion of patients with MVD who fall into the lowest risk for adverse events after percutaneous coronary intervention. Therefore, the selection of target vessels, the method for revascularization and the determination of prognosis in patients with MVD are improved by calculating the FSS in daily practice.

KEYWORDS: coronary angiography • coronary artery bypass
• coronary artery disease • fractional flow reserve • prognosis • stent

Multivessel coronary artery disease (MVD) is one of the unresolved complex lesion subsets in the current era of interventional cardiology. Historically, coronary artery bypass grafting (CABG) has been the preferred method of revascularization in patients with MVD. However, as a result of the recent drug-eluting stent (DES) revolution, a large and growing number of patients with MVD are undergoing percutaneous coronary intervention (PCI) [1–4].

The SYNERgy between percutaneous intervention with TAXus DES and cardiac surgery (SYNTAX) Score (SS) is a comprehensive angiographic scoring system for risk stratification of patients with MVD undergoing contemporary revascularization [5,6]. It has been shown to stratify risk for both early and late outcomes in patients with MVD [2,3,7,8]. However, the SS is inherently limited because it is angiography-based [9]. Recent studies have shown that many angiographically significant lesions are not hemodynamically significant and stenting these stenoses results in worse outcomes. The SS weighs equally all epicardial lesions of greater than 50% stenosis, despite the fact that some may not be physiologically significant (i.e., not responsible for myocardial ischemia). The FAME study demonstrated that fractional flow reserve (FFR) measurement can be used as guidance to decrease rates of major adverse cardiac events (MACE) in patients with MVD compared with angiography-guided

PCI [10–12], presumably by focusing intervention on ischemia-producing lesions only. A recent sub-study from the FAME trial demonstrated that an FFR-guided functional SS (FSS) can better discriminate risk for adverse events in patients with MVD undergoing PCI than the classic SS [13]. In this article, we will review revascularization methods for patients with MVD and the role of the SS and FSS in evaluating patients with MVD.

How to treat MVD: prior to the SYNTAX trial

Although there has been a dramatic improvement in devices and percutaneous techniques for the treatment of complex stenoses, CABG remains the reference standard approach for revascularizing patients with MVD [14,15].

Historical data from trials comparing PCI with stent implantation and surgical revascularization revealed no differences in terms of mortality and myocardial infarction (MI), but a more favorable outcome has been observed in the CABG arm regarding repeat revascularization [2,3,16]. However, in these initial randomized PCI versus CABG studies, fewer than 10% of patients screened were actually enrolled.

The ERACI II compared bare-metal stent (BMS) implantation with CABG in symptomatic patients with MVD [16]. At the 5-year follow-up, patients initially treated with PCI had similar survival and freedom from non-fatal

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MI compared with CABG (92.8 vs 88.4% and 97.3 vs 94%, respectively; $p = 0.16$). Freedom from repeat revascularization procedures was significantly lower with PCI compared with CABG (71.5 vs 92.4%; $p = 0.0002$). Freedom from MACE was also significantly lower with PCI compared with CABG (65.3 vs 76.4%; $p = 0.013$).

The ARTS II study compared the efficacy of sirolimus-eluting stent implantation with the two historical arms of ARTS [3]. The 5-year major adverse cardiac and cerebrovascular event (MACCE) rate in ARTS II (27.5%) was significantly higher than ARTS I CABG (21.1%; $p = 0.02$), and lower than in ARTS I BMS (41.5%; $p < 0.001$). Although the re-intervention rates in the PCI group were still higher than those of the CABG group, this was counterbalanced by a higher incidence of death/stroke and MI in the CABG group.

Fueled by these promising results, the SYNTAX trial was performed. It was a multicenter, randomized study designed to evaluate the optimal revascularization treatment for all-comer patients with *de novo* three-vessel disease

and/or left main disease by randomizing patients to either PCI with paclitaxel-eluting stents or surgery [2]. The 1-year rate of MACCE among patients with three-vessel disease in the absence of left main coronary artery disease (CAD) was significantly increased in the PCI group as compared with the CABG group (19.2 vs 11.5%; $p < 0.001$) (FIGURE 1), as was the rate of repeat revascularization (14.6 vs 5.5%; $p < 0.001$). The rate of death from any cause, stroke, or MI in this subgroup was similar with PCI and CABG (8.0 and 6.6%, respectively; $p = 0.39$). However, at 3 years in the same group, not only MACCE (CABG 18.8% vs PCI 28.8%; $p < 0.001$), but also the rates of the composite safety end point (death/stroke/MI 10.6 vs 14.8%; $p = 0.04$) was higher in the PCI arm. These results are consistent with previous registries reporting a survival advantage and a marked reduction in the need for repeat revascularization with CABG in comparison with PCI in patients with more severe CAD [17]. In general, CABG has the advantages of longer durability and more complete revascularization, regardless of the morphology of the obstructing atherosclerotic lesions [18]. However,

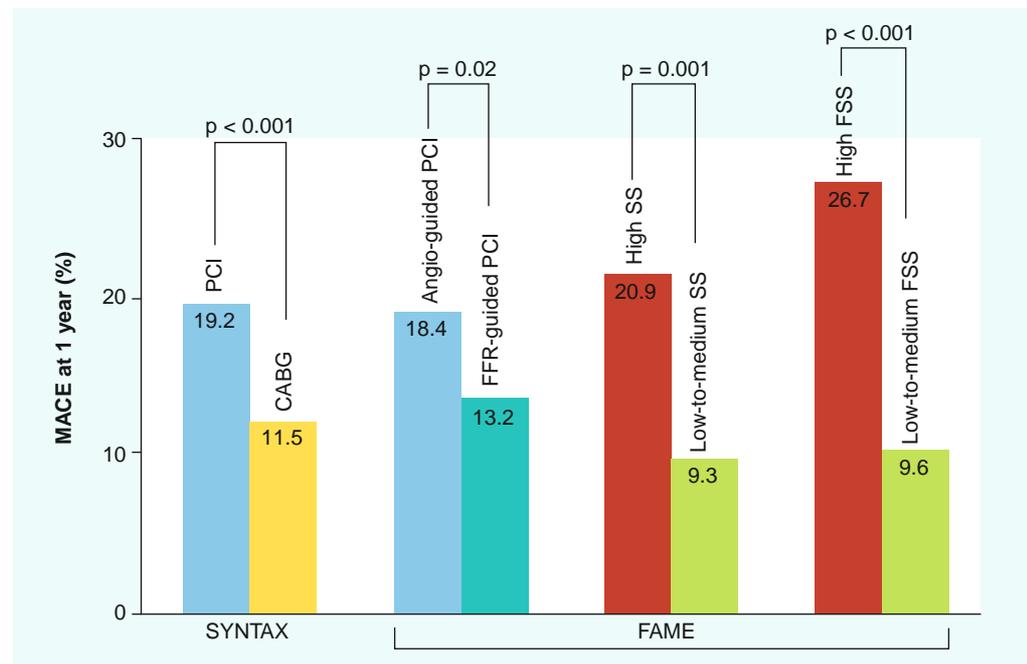


Figure 1. 1-year major adverse cardiac events according to the trials. The MACE rate was similar in the SYNTAX PCI group (three-vessel disease without left main disease) and the FAME angio-guided PCI group. MACE was slightly greater in the FAME FFR-guided PCI group compared with the SYNTAX CABG group. However, when the SS was applied to the FAME study, the difference in the MACE rate between the highest SS and lower SS groups was quite large, and the low and medium SS group who underwent PCI had similar outcomes when compared with the SYNTAX CABG group. This change was also observed by calculating the FSS. CABG: Coronary artery bypass grafting; FFR: Fractional flow reserve; FSS: Functional SYNTAX score; MACE: Major adverse cardiac event; PCI: Percutaneous coronary intervention; SS: SYNTAX score. Data taken from [2,10,13].

we also have to remember that the very long-term durability of CABG has not been compared with DES as the data are currently unavailable.

Although DES significantly decrease the rate of restenosis compared with BMS and have demonstrated promising results regarding high risk populations with complex lesions [19–21], new concerns including the long-term safety and efficacy of DES have been raised, as a consequence of increased risk of late thrombosis and a late catch-up phenomenon [22,23]. Furthermore, the cost-effectiveness of DES in MVD has been raised [24,25]. All of the studies comparing PCI with DES to CABG performed PCI based on angiographic guidance. The FAME trial demonstrated that PCI guided by angiography alone results in a greater number of stents placed in functionally nonsignificant stenoses. In these cases, the patient suffers the early and late risks of PCI without accruing any benefit from relief of ischemia [10,12,26]. More judicious selection of target lesions and/or patients may make possible similar outcomes after PCI as compared with CABG in patients with MVD.

The role of the SS

In the SYNTAX study, a new scoring system called the SS was introduced in an attempt to better risk stratify patients and inform decision regarding PCI versus CABG for achieving optimal revascularization [5]. The SS is an angiographic scoring system based on coronary anatomy and lesion characteristics, such as presence of total occlusion, bifurcation or trifurcation, angle and involvement of branch vessels, calcification, lesion length, ostial location, tortuosity and presence of thrombus. The SS not only quantifies lesion complexity, but also predicts early and late outcomes after PCI in patients with three-vessel disease and/or left main disease [2,6,8,27]. From the diagnostic angiogram, each coronary lesion producing $\geq 50\%$ diameter stenosis in vessels ≥ 1.5 mm is scored separately and added together to provide the overall SS. From the SYNTAX study, three tertiles of SS were established: a low score defined as ≤ 22 , an intermediate score as 23–32 and a high score as ≥ 33 [5].

The 1-year rate of MACCE in the PCI group in the SYNTAX study was significantly higher among patients with high SS (23.4%) as compared with those with low scores (13.6%) or intermediate scores (16.7%; $p = 0.002$ for high vs low scores; $p = 0.04$ for high vs intermediate scores) [2]. In contrast, in the CABG group, the rate of MACCE was similar among patients

with low, intermediate and high scores (14.7, 12.0 and 10.9%, respectively; $p > 0.05$). There was a significant interaction between SS and treatment group ($p = 0.01$); patients with low or intermediate scores in the CABG group and in the PCI group had similar rates of MACCE, whereas among patients with high scores, the event rate was significantly increased in the PCI group. A similar result was observed at 3-year follow-up [17]. Patients with 3-vessel disease with a SS in the lowest tertile exhibited similar 3-year MACCE rates between treatment arms (CABG 22.2% vs PCI 25.8%; $p = 0.45$). In those patients with intermediate or high SS, the rate of MACCE was significantly higher after PCI (intermediate score: CABG 16.8% vs PCI 29.4%; $p = 0.003$; high score: CABG 17.9% vs PCI 31.4%; $p = 0.004$) (FIGURE 2). This finding suggests that a percutaneous approach should be avoided in patients with high or intermediate SS.

The value of the SS was validated by several subsequent studies. The SS was applied to 1292 lesions in 306 patients who underwent PCI for three-vessel disease in the ARTS II trial. When compared with the lowest tertile group (SS < 16 ; 5-year MACE-free rate: 80.1%), both the intermediate (SS: 16–24) and high (SS > 24) tertile groups demonstrated a lower MACE-free survival rate (intermediate: 70.1%, log-rank $p = 0.02$; high: 67.1%; $p = 0.001$) [3]. The SS also had a role in the risk stratification of 1707 all-comer patients undergoing PCI in the LEADERS trial [27]. There was a lower 1-year MACE-free survival in the highest tertile of the SS; 92.2% in low SS (≤ 8), 91.1% in mid SS (> 8 and ≤ 16) and 84.6% in high SS (> 16), respectively ($p < 0.001$). Similar results were observed in the RESOLUTE all-comers study as the rate of MACE at 1-year was significantly higher in patients in the highest SS tertile [28]. Recently, the largest assessment of the SS in 6508 patients treated with PCI from seven contemporary coronary stent trials was performed by an independent academic research organization and confirmed the ability of the SS to identify patients who are at highest risk of adverse events, irrespective of clinical presentation [29]. Because of these findings, the SS can have a role in patients with any degree of CAD. Recent guidelines have recommended using the SS to decide whether a patient with MVD is appropriate for PCI or CABG [14].

An important limitation of using the SS is that anatomy-based scoring systems have been shown to have a lower ability to predict mortality, when compared with scoring systems using

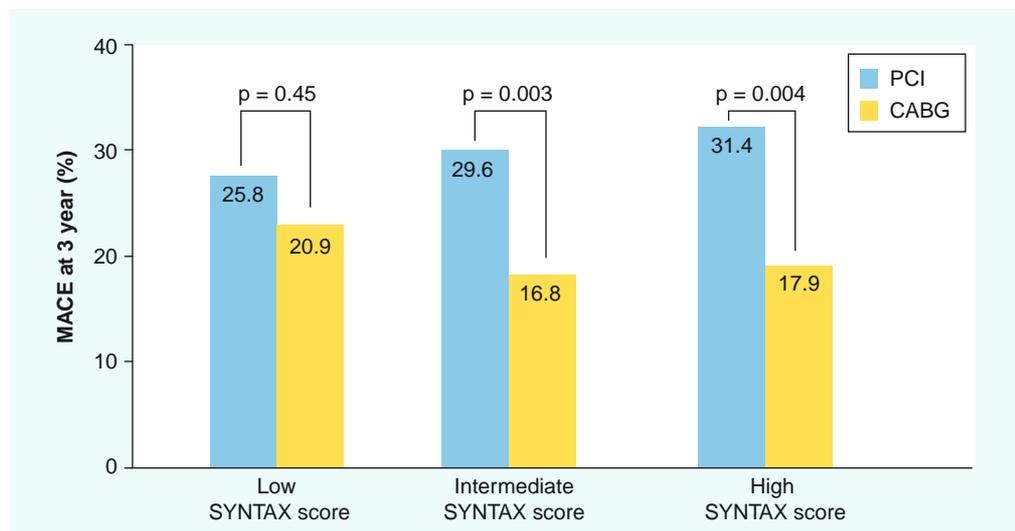


Figure 2. 3-year outcomes in three vessel disease subgroup of SYNTAX trial according to SYNTAX score tertile. Patients with three-vessel disease with a SYNTAX score in the lowest tertile exhibited similar 3-year MACE and cerebrovascular event rates between treatment arms (CABG 22.2% vs PCI 25.8%; $p = 0.45$). In those patients with intermediate or high SYNTAX score, the rate of MACE and cerebrovascular event was significantly higher after PCI (intermediate score: CABG 16.8% vs PCI 29.4%; $p = 0.003$; high score: CABG 17.9% vs PCI 31.4%; $p = 0.004$). CABG: Coronary artery bypass grafting; MACE: Major adverse cardiac event; PCI: Percutaneous coronary intervention. Data taken from [17].

clinical characteristics [30]. The ability to predict outcomes can be improved by adding clinical variables, as is the case in the euroSCORE, the ACEF score, the Mayo Clinic Risk Score or the clinical SS [31–34]. However, despite a continuous effort to detect new and progressively more sophisticated markers of prognosis in patients with CAD, implementation of complicated risk stratification algorithms in the clinical setting remains problematic [35], and the use of too many individual variables may reduce the overall accuracy of data [36].

FFR-guided PCI for MVD

FFR, measured with a coronary pressure wire, is an accurate and lesion-specific index for determining the functional significance of a particular stenosis. FFR takes into account the myocardial distribution of a vessel and the presence of collaterals [37–39]. Assessing the functional significance of nonculprit coronary lesions after culprit lesion intervention in patients with acute coronary syndrome is critical, as increasing stent length or number is associated with worse outcomes [40,41]. Determining the physiological significance of each lesion is challenging with noninvasive or invasive imaging techniques [42–46]. Although nuclear perfusion imaging and other noninvasive stress imaging modalities are generally accurate in patients with single-vessel disease, they are significantly less accurate in patients

with MVD [42]. Coronary angiography is not reliable for assessing the functional significance of moderate (50–80% narrowed) single stenoses, let alone multiple or complex abnormalities [45,46]. Intravascular ultrasound (IVUS) in MVD patients generally shows diffuse disease of varying degrees of severity along the coronary artery and is unable to provide functional information of distinct lesions [44,47]. These findings were supported by our previous study, which included 167 consecutive patients with intermediate coronary lesions evaluated by FFR or IVUS (FFR-guided, 83 lesions vs IVUS-guided, 94 lesions) [44]. Although baseline percent diameter stenosis and lesion length were similar in both groups, the IVUS-guided group underwent revascularization therapy significantly more often (91.5 vs 33.7%; $p < 0.001$). No significant difference was found in MACE between the two groups (3.6% in FFR-guided PCI vs 3.2% in IVUS-guided PCI). However, FFR assessment for multiple lesions is invasive, can be time consuming in some cases and demands systemic injection of vasodilator pharmacotherapy. The technical aspect of FFR measurement and interpretation is also important, especially in multiple lesions in the same vessel and in bifurcation lesions. For example, in the setting of tandem lesions, it is important to measure FFR with the sensor beyond both lesions. If the FFR is not ischemic, then no further intervention is

necessary. If it is ischemic then a slow pullback should be performed to identify which lesion is responsible for most of the pressure gradient. The more significant lesion should be stented and then FFR should be measured again. If the FFR remains ischemic, the second lesion should be stented.

Recent studies have shown that stenting functionally nonsignificant coronary stenoses does not improve outcome [10,26,44,48], and optimal medical treatment results in similar outcomes [49]. In the DEFER study [26], event-free survival at 5 years was not different between the DEFER and perform groups who had $\text{FFR} \geq 0.75$ (80 and 73%, respectively; $p = 0.52$), but was significantly worse in the Reference group with $\text{FFR} < 0.75$ (63%; $p = 0.03$). The composite rate of cardiac death and acute MI in the Defer, Perform and Reference groups was 3.3, 7.9 and 15.7%, respectively ($p = 0.21$ for Defer vs Perform group; $p = 0.003$ for the Reference vs both other groups).

The FAME study was a multicenter trial designed to compare two strategies for performing PCI in 1005 patients with MVD [10]. All patients were randomly assigned to angiography-guided PCI (497 patients) or FFR-guided PCI (509 patients). Patients assigned to angiographic guidance underwent stenting of all indicated lesions with DES. In patients assigned to FFR guidance, FFR was measured in each vessel

with at least one stenosis and stents were placed only if the FFR was ≤ 0.80 . MACE occurred in 91 patients (18.3%) in the angiography group and in 67 (13.2%) in the FFR group ($p = 0.02$) at 1 year (FIGURE 1) [10]. At 2-year follow-up, death or MI occurred in 12.9% of the angiography-guided patients and in 8.4% of the FFR-guided patients ($p = 0.02$) [12]. These results support the evolving strategy of revascularization of ischemic lesions and medical treatment of nonischemic lesions in patients with MVD.

FSS

Although the SS quantifies lesion complexity and predicts early and late clinical outcomes after PCI in patients with MVD, it can also under- or over-estimate the severity of a significant number of lesions because it is based on angiographic information.

In a recent study, we introduced the FSS, which is determined by recalculating the SS after counting only ischemia-producing lesions with $\text{FFR} \leq 0.80$. We found that the FSS shifted many apparently high-risk patients into a lower risk group. In addition, it was more reproducible than the SS and a better predictor of outcomes in patients with MVD undergoing PCI [13]. The SS and FSS were prospectively collected in 497 patients enrolled in the FFR-guided arm of the FAME trial. Approximately 23% of patients in the highest SS tertile moved to

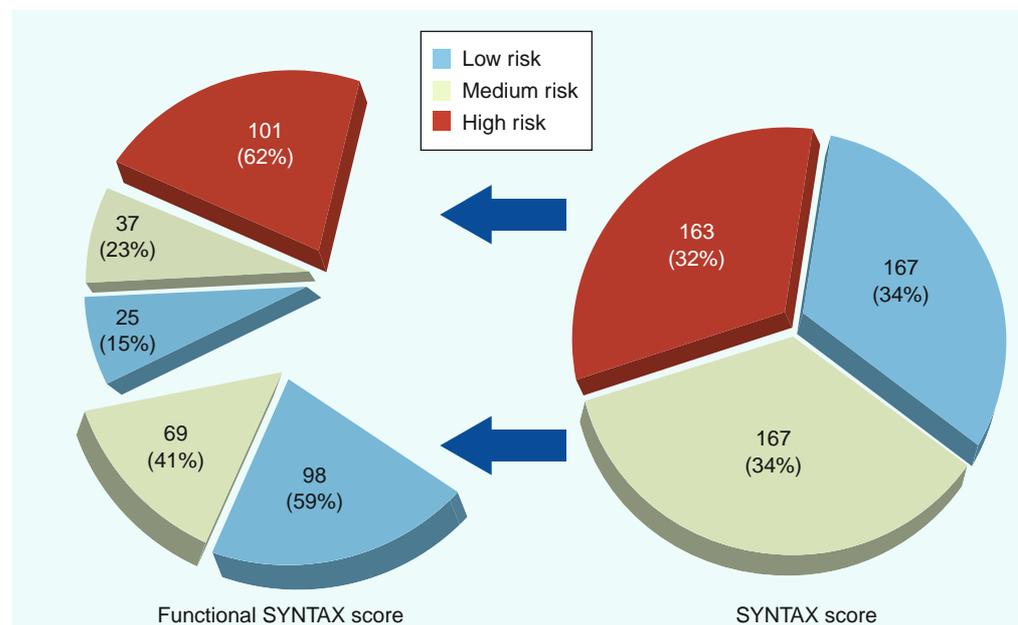


Figure 3. Proportional changes between scoring systems. By using the stratified scores of the SYNTAX score (SS) tertile, 23% of patients in the highest SS tertile moved to the middle group, 15% of the highest tertile moved to the lowest group and 59% of patients in middle SS tertile moved to the lowest group after calculating the functional SS. Data taken from [13].

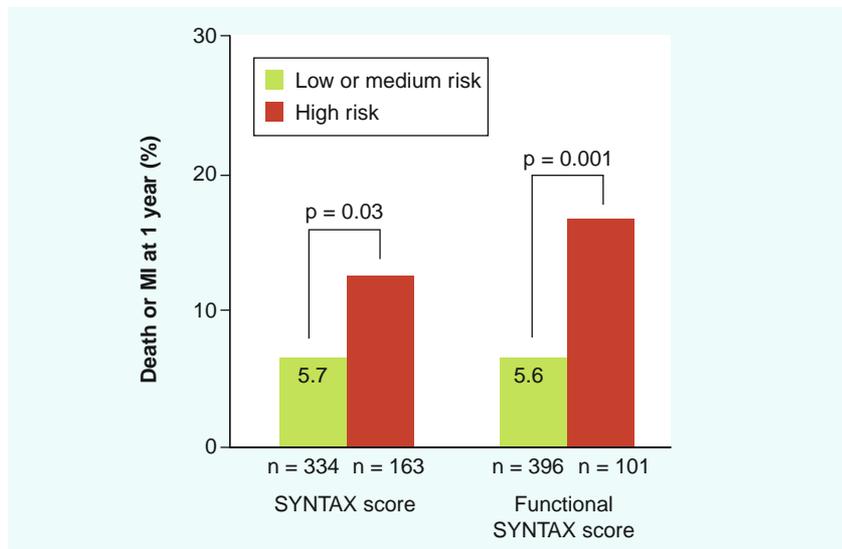


Figure 4. Death or myocardial infarction rate at 1-year. The rate of death or MI was increased in the highest-risk SYNTAX score (SS) group; the difference between death or MI was even greater when comparing the low or medium risk functional SS groups to the highest risk functional SS group. MI: Myocardial infarction. Data taken from [13].

the middle group, 15% of the highest tertile moved to the lowest group and 59% of patients in middle SS tertile moved to the lowest group. 32% of all patients moved from a higher risk SS group to lower risk groups by calculation of the FSS (FIGURE 3). Death or MI occurred 15.8% in the highest FSS group and 5.6% in lower FSS groups ($p = 0.001$) (FIGURE 4). The rate of MACE was 26.7% in the highest FSS group and 9.6% in lower FSS groups ($p < 0.001$) (FIGURE 1). The area under the ROC curve for 1-year MACE was greater with the FSS than with the SS (Harrell's C of FSS, 0.677 vs SS, 0.630; $p = 0.02$). FSS demonstrated a better predictive accuracy for MACE compared with SS (integrated discrimination improvement of 1.94%; $p < 0.001$). Finally, the inter- and intra-observer variability of the FSS was better than that for the SS.

Clinical application of FSS

To optimize outcomes in patients undergoing PCI for MVD, the ability to identify those patients and lesions at highest risk of undesired events is very important. With this in mind, the FSS may be an important tool for risk stratification. The FSS can help to more accurately stratify the risk in each patient with multivessel CAD. The MACE rate of the patients who moved from the highest SS tertile to a low or medium risk group based on the FSS, was significantly lower when compared with those patients who remained in the highest risk group (11.3 vs

26.7%; $p = 0.028$). It means that the patients who moved to a lower risk group are located in a high-risk group angiographically, but in a lower risk group functionally. Their prognosis is similar to patients who started in the lower risk group based on the angiogram alone. This change was driven, in large part, by the conversion of angiographic three-vessel CAD to functional one- or two-vessel CAD. In a FAME subanalysis [11], of all stenoses with an angiographic severity of 50 to 70%, only 35% were functionally significant by FFR. Even in more severe stenoses between 71 and 90% angiographic stenosis severity, a full 20% did not induce reversible MI as established by an FFR value above the ischemic threshold. By first measuring FFR, patients with apparent three-vessel disease can be converted to one- or two-vessel disease. In this manner, the number of low and medium risk patients with MVD in whom percutaneous revascularization can be recommended is increased. A representative case is shown in FIGURE 5. Although the SS of this case is 33, the FSS is only 12. This patient with angiographic three-vessel disease falls in the highest risk SS group, and CABG is the recommended method for revascularization. However, by adding functional information using the FSS, the patient is only actually in the medium-risk group, and therefore PCI can be considered for revascularization.

In FIGURE 1, outcomes between SYNTAX and FAME trials, which included patients with MVD and analyzed into tertile risk groups, are described. Although direct comparison of these two trials is impossible due to the different degree of coronary disease [2,13], the MACE rate looks similar in the SYNTAX PCI group and the FAME angio-guided PCI group. MACE was slightly greater in the FAME FFR-guided PCI group compared with the SYNTAX CABG group. However, when the SS was applied to the FAME study, the difference in the MACE rate between the highest SS and lower SS groups was quite large and the low and medium SS group who underwent PCI had similar outcomes when compared with the SYNTAX CABG group. This change was also observed by calculating the FSS. Because the patients with the highest FSS had the worst outcome after PCI, surgical revascularization should be considered in this group to hopefully improve outcomes.

A major limitation of the work performed to date on the FSS is that it is retrospective. It remains unclear whether and to what extent our findings can be reproduced in a different

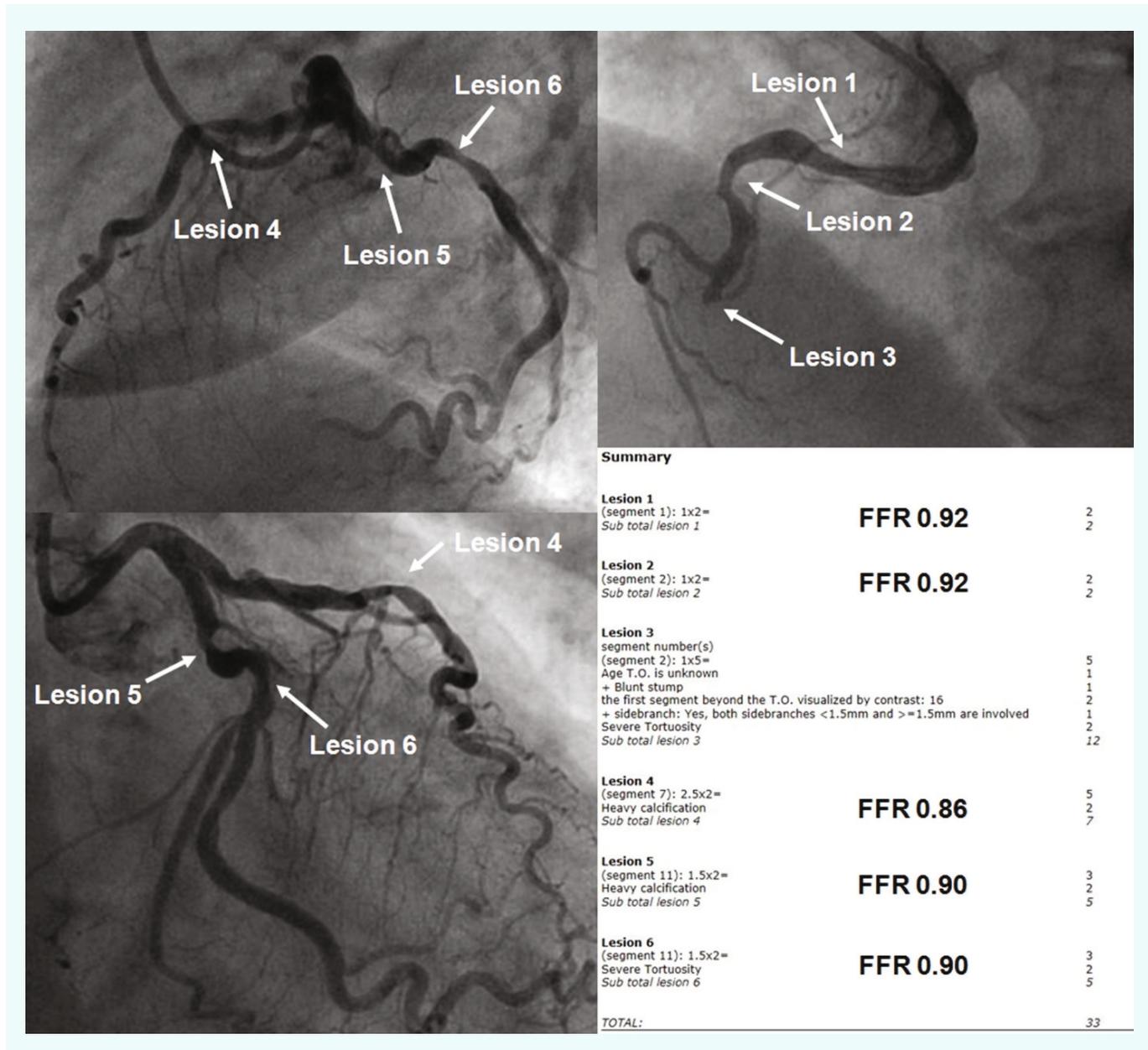


Figure 5. SYNTAX and functional SYNTAX score in three-vessel disease. The SYNTAX score (SS) of this three-vessel disease is 33. However, when using FFR to determine the functional SS, it is only 12. Although this patient falls into the highest risk group based on the SS, by adding functional information using functional SS, the patient moves to a lower risk group and percutaneous coronary intervention can be considered for revascularization of mid-right coronary total occlusive lesion. FFR: Fractional flow reserve.

group of patients with extensive CAD. Similarly, more data are required to clarify whether the slightly better performance of the FSS observed in this study justifies its use in clinical practice compared with the classic SS or conventional ACC/AHA classification system.

Future perspective

A new paradigm for performing PCI only on physiologically significant lesions based on FFR assessment and medically treating functionally

insignificant lesions, even if angiographically significant, has been introduced. The FSS is a new mechanism for further defining which MVD patients will benefit most from PCI as compared with CABG. The next step in establishing this new paradigm is to perform a prospective trial comparing an FSS-guided approach to PCI in patients with MVD with traditional CABG surgery. It may be that with this approach PCI performs as well as CABG in this challenging patient population.

Executive summary

How to treat multivessel coronary artery disease

- Coronary artery bypass graft is a reference standard approach for multivessel coronary artery disease (MVD).
- Coronary artery bypass graft has a lower rate of repeat revascularization, and a similar rate of death or myocardial infarction. Selection of target lesions or patients is important for percutaneous coronary intervention (PCI) in MVD.

The role of the SYNTAX score

- SYNTAX score (SS) is a new anatomical scoring system for MVD.
- SS quantifies lesion complexity and predicts early or late outcomes after PCI in MVD.

Fractional flow reserve-guided PCI for MVD

- Stenting in coronary stenoses, without demonstrating their physiologic significance, does not improve outcome.
- Treatment based on fractional flow reserve in addition to angiography can decrease adverse cardiac events in MVD.

New anatomical & functional scoring system: functional SS

- Functional SS (FSS) is determined by recalculating the SS after counting only ischemia-producing lesions with fractional flow reserve ≤ 0.80 .
- FSS has better reproducibility and prognostic value in patients with MVD undergoing PCI.

Clinical application of FSS

- Increase the number of lower risk patients with MVD in whom PCI can be recommended.
- Significant implications on decision making regarding the choice of revascularization strategy in MVD.

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