

Application of SYNTAX and its Derivative Scores in the Selection of Revascularization Strategies for Complex Coronary Heart Disease

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ABSTRACT

Complex coronary heart disease (CHD) has become a hot spot in medicine due to its complex coronary anatomy, variable clinical factors, difficult hemodynamic reconstruction, and limited effect of conservative drug treatment. Identifying complex CHD and selecting optimal treatment methods have become more scientific as revascularization technology has improved, and coronary risk stratification scores have been introduced. SYNTAX and its derivative scores are decision-making tools that quantitatively describe the characteristics of coronary lesions in patients based on their complexity and severity. The SYNTAX and its derivative scores could assist clinicians in rationalizing the selection of hemodynamic reconstruction treatment strategies, and have demonstrated outstanding value in evaluating the prognosis of patients with complex CHD undergoing revascularization treatment. The authors in this article summary the practical application of SYNTAX and its derivative scores in complex CHD in order to deepen the understanding of the relationship between the choice of different revascularization strategies and SYNTAX and its derived scores in complex CHD and provide a further reference for clinical treatment of complex CHD.

Key words: complex coronary heart disease; revascularization strategies; SYNTAX and its derivative scores

INTRODUCTION

Cardiovascular disease has a high morbidity and mortality rate worldwide^[1]. With the improvement of revascularization technology, the expansion of surgical indications for percutaneous coronary intervention (PCI), and the revision of coronary lesion risk stratification scores, revascularization treatment strategies are gradually replacing conservative pharmacological treatment as the preferred therapeutic modality to treat complex coronary heart disease (CHD). However, it is well known that revascularization therapy is not appropriate for all patients with complex coronary

artery disease (CAD). To ensure maximum clinical benefit for patients, we must clarify the beneficiary population of revascularization strategies and individually assess the long-term prognosis of patients under different treatment strategies. Fortunately, after repeated validation in numerous clinical trials over a long period, an objective measure of complex coronary lesions and disease severity, the Synergy Between PCI with Taxus and Cardiac Surgery (SYNTAX) and its derivative scores, has been developed. It has been recommended to guide the rationalization of coronary revascularization strategies and the evaluation of the long-term prognosis of patients with complex CAD treated with different revascularization strategies^[2,3]. The SYNTAX and its derivative scores are currently used in clinical settings such as left main coronary artery and coronary multi-vessel lesions, acute coronary syndrome, cerebral infarction, and cardiogenic shock due to their

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ability to accurately demonstrate the characteristics of multi-vessel lesions in CAD and their satisfactory discriminatory ability for adverse cardiovascular events. In this review, we expand on the clinical application of SYNTAX and its derivative scores, including anatomical SYNTAX score, clinical SYNTAX score, SYNTAX score II, residual SYNTAX score, functional SYNTAX score, and SYNTAX score III, to deepen our understanding of the SYNTAX score.

Anatomical SYNTAX score

The anatomical SYNTAX score was developed in the context of the SYNTAX trial, which was designed to compare the likelihood of major adverse cardiovascular and cerebrovascular events (MACCE) 1 year after left main coronary artery or three-vessel disease treated with different revascularization modalities to find the best revascularization guideline. The trial used an anatomical SYNTAX score, which can accurately quantify the complexity of coronary lesions based on coronary angiography results, with higher scores indicating more complex lesions and worse disease prognosis^[4]. Their 1-year postoperative follow-up study revealed that the risk of MACCE is significantly lower in the coronary artery bypass graft (CABG) group than in the PCI group (12.4% vs. 17.8%, $P = 0.002$). The incidence of MACCE in the PCI group increases with increasing anatomical SYNTAX score grade (13.6% vs. 16.7% vs. 23.4%), whereas the incidence of MACCE in the CABG group (13.6% vs. 12.0% vs. 10.9%) is very similar regardless of the anatomical SYNTAX score subgroups. For lesion types of three-vessel disease or left main CAD, the incidence of MACCE (19.2% vs. 11.5%, $P < 0.001$) and revascularization of multivessel lesions (14.6% vs. 5.5%, $P < 0.001$) are higher in the PCI group than that in the CABG group, but there is no significant difference between the two groups in the left main coronary artery lesion subgroup study (13.7% vs. 15.8%, $P = 0.44$)^[5]. The results of their 5-year follow-up study showed that the risk of MACCE is significantly higher in the PCI group compared to the CABG group (37.3% vs. 26.9%, $P < 0.0001$), where the risk of MACCE is significantly higher in the medium and high anatomical SYNTAX score subgroups of the PCI group compared to the subgroups of the CABG group (36.0% vs. 25.8%, $P = 0.008$; 44.0% vs. 26.8%, $P < 0.0001$), and the results are identical to the 1-year follow-up study^[6], revealing the superiority of the anatomical SYNTAX score in the prognostic

evaluation of different revascularization strategies. In contrast, subsequent follow-up studies on the anatomical SYNTAX score at 4 months^[7], 4 years^[8], and 10 years^[9] after revascularization in complex CHDs and the applied studies on the anatomical SYNTAX score were used in different types of lesions and myocardial infarction (MI) in complex CHDs, such as the left main coronary artery^[8,10], three-vessel disease^[9], ST-segment elevation myocardial infarction (STEMI)^[7,11], non-STEMI (NSTEMI)^[12], and others. All preceding studies confirmed the accuracy of the anatomical SYNTAX score in identifying high-risk complex coronary arteries and its effectiveness in aiding the decision-making about revascularization. However, the limitations of the anatomical SYNTAX score referring to coronary anatomic parameters unidirectionally and ignoring their clinical risk variables were also identified. Furthermore, several follow-up studies, such as the meta-analysis of Sabatine *et al.*^[13] incorporating other two 10-year follow-up studies in which patients with left main coronary artery lesions were treated with different revascularization strategies, known as the MAIN-COMPARE trial^[14] and the PRECOMBAT trial^[15], concluded that there was no significant difference in all-cause mortality after PCI and CABG in patients with different anatomical SYNTAX scores and further exposed the limitations of the anatomical SYNTAX score. Therefore, SYNTAX derivative scores are made available for clinical use to optimize the SYNTAX scoring system and improve clinicians' accuracy and rationality in selecting treatment strategies for complex coronary lesions.

Clinical SYNTAX score

The clinical SYNTAX score, developed by Garg *et al.*^[16], was used for the first time in the ARTS-II study in 2010 to assess complex coronary risk stratification. The clinical SYNTAX score was calculated in the ARTS-II study using the formula: clinical SYNTAX score = anatomical SYNTAX score $\times$ age, creatinine, and ejection fraction (ACEF) score. The ACEF score has been validated in numerous trials and can predict the risk of death in cardiac surgery^[17]. The ARTS-II study enrolled 512 patients into the low, medium, and high clinical SYNTAX score groups. The high clinical SYNTAX score group has the highest 1-year and 5-year revascularization and mortality rates of patients with complex CHD^[16]. Since then, the clinical SYNTAX score has gradually been used to guide selecting a revascularization strategy for complex CHD. The clinical

SYNTAX score is more accurate than the anatomical SYNTAX score in predicting all-cause mortality after revascularization for complex CHD^[18,19]. A follow-up study of 460 complex CHD patients with STEMI and multiple vessel diseases found that the clinical SYNTAX score was superior to the anatomical SYNTAX score in predicting the occurrence of long-term adverse events after CABG for complex CAD, but the study also found a deficiency of the low-to-moderate level clinical SYNTAX score in assessing the long-term prognosis of complex CHD treated with different revascularization regimens^[20]. To address these limitations, researchers conducted a 2-year follow-up study in 512 STEMI patients, proposed the Logistic Clinical SYNTAX score (LCSS) concept, and concluded that the LCSS has significant discrimination and acceptable calibration in predicting all-cause mortality^[21]. Furthermore, it has been demonstrated through continuous improvement of SYNTAX-derived scores and subsequent studies that the clinical SYNTAX score has better predictive performance than the residual SYNTAX score for all-cause mortality 2 years after revascularization for complex CAD, whereas its predictive power for revascularization is the opposite^[22]. Compared to the clinical SYNTAX score, the SYNTAX score II demonstrated more accurate predictive performance in predicting all-cause mortality after complex CAD revascularization^[18]. Therefore, the clinical applications of the SYNTAX score have been limited, and more optimized SYNTAX-derived scores have been developed gradually.

SYNTAX score II

To overcome the anatomical SYNTAX score's limitation of ignoring individual variation, the clinical variables, such as age, sex, ejection fraction, creatinine clearance, peripheral vascular disease, and chronic obstructive pulmonary disease, are introduced in the SYNTAX score II, which greatly improves the score system's efficiency in predicting post-revascularization risk for complex CAD^[23,24]. In 2017, He *et al.*^[25] used the SYNTAX score II to predict the risk of death following the left main coronary artery PCI. The result showed that The SYNTAX score II was an independent risk factor for predicting the risk of death after PCI [hazard ratio (HR): 1.5, 95% confidence interval (CI): 1.05–2.32, $P = 0.03$]. Moreover, they found that the long-term mortality rates after PCI in the low, medium, and high SYNTAX score II groups were 2.4%, 3.4%, and 11.6%, respectively ($P < 0.0001$)^[25], which was con-

sistent with the findings of Xu *et al.*^[26]. In addition, the SYNTAX score II can not only predict adverse events at 1 year^[27], 4 years^[26,28], 5 years^[29-31], and 10 years^[31] after revascularization for complex CHD, such as major adverse cardiovascular events (MACE)^[31,32], MACCE^[24,27], no-reflow phenomenon^[33], all-cause mortality^[26,31], and others, but it also has a significant predictive value in a variety of hemodynamic settings, such as left main coronary artery^[25,28,29,34], multiple vessel diseases^[29,30,34], acute coronary syndrome^[27,33], cerebral infarction^[35], and cardiac valve disease^[36], and so on. Yang *et al.*'s study also confirmed that the SYNTAX score II has a higher predictive value for revascularization in complex CAD than the anatomical SYNTAX score [risk ratio (RR): 2.65, 95% CI: 1.05–6.73, $P = 0.04$]^[32]. The SYNTAX score II has a better predictive ability and wider application for all-cause mortality and MACCE after revascularization for complex CAD than the anatomical SYNTAX score, clinical SYNTAX score, residual SYNTAX score, and SYNTAX revascularization index, among others^[18]. The SYNTAX score II is widely used for its unique advantages in revascularization guidance and prognostic assessment of complex CAD.

Residual SYNTAX score

Although the long-term prognosis of patients who present with complex CAD and undergo partial revascularization is inferior to that of complete revascularization, such as higher MACE and reinfarction rates^[37,38], given that not all complex CADs are amenable to complete revascularization, the partial revascularization is also applicable in complex CAD. The residual SYNTAX score is a tool developed to quantify residual lesion stenosis and residual ischemic load after partial revascularization for complex CAD. The residual SYNTAX score counted the residual lesion vessels with diameters > 1.5 mm and $> 50\%$ stenosis after PCI for complex CAD^[39]. One study that evaluated the impact of the residual SYNTAX score on the 1-year outcome of PCI in patients with multi-vessel disease found that when the residual SYNTAX score was > 5 points, the area under the curve (AUC) for MACE 1-year after surgery in patients with incomplete revascularization for complex CAD was 0.769 ($P < 0.001$), with a sensitivity of 75% and a specificity of 2%^[40], indicating that the residual SYNTAX score was an independent predictor of adverse ischemic events 1-year after incomplete revascularization. The findings agreed with those of G  n  reux *et al.*'s study (all-cause mortality HR: 1.05, 95%CI:

1.02–1.09, $P = 0.006$)^[41]. According to Génereux *et al.*, it is significant when the residual SYNTAX score is > 8.0 ^[41]. Furthermore, in the 2-year^[17] and 5-year^[38] follow-up studies of patients with incomplete revascularization^[17,41,42], the residual SYNTAX score was a better predictor of postoperative cardiac mortality, MI, revascularization, and MACCE than the anatomical SYNTAX score. A follow-up study discovered the value of the residual SYNTAX score in predicting 10-year all-cause mortality in patients. Furthermore, a SYNTAX extended survival study revealed that patients undergoing incomplete revascularization with a residual SYNTAX score > 8 had a significantly higher 10-year all-cause mortality compared to complete revascularization, whereas there was no significant difference in 10-year all-cause mortality in patients undergoing incomplete revascularization with a residual SYNTAX score ≤ 8 compared to complete revascularization^[43]. Moreover, another study that combined residual SYNTAX score and functional score confirmed the importance of the residual functional SYNTAX score (representing the sum of residual SYNTAX scores of residual vessels with a quantitative flow ratio ≤ 0.80 after PCI) in assessing motility improvement after PCI^[44]. In conclusion, the residual SYNTAX score can be used to evaluate the prognosis of residual lesions after revascularization, allowing clinicians to make more informed treatment decisions.

Functional SYNTAX score

The functional SYNTAX score introduces the Fractional Flow Reserve (FFR), a functional evaluation index, which allows the SYNTAX score to assess vessel lesions from coronary angiography more objectively and accurately than the anatomical SYNTAX score. The FFR is defined as the ratio of the mean coronary pressure at the distal end of the coronary stenosis (P_d) to the mean aortic pressure at the coronary ostia (P_a) at the left ventricular peak diastolic filling, and a ratio ≤ 0.8 can be used as a cutoff value for determining the lesion, reflecting the relationship between the entire coronary circulation and blood flow, and has been proven to accurately detect MI, which is of great significance for the formulation of cardiac surgical treatment strategies^[23]. A 1-year follow-up study of 497 patients undergoing FFR-guided PCI found that the functional SYNTAX score not only reduced the risk threshold compared to the anatomical SYNTAX score but also effectively differentiated the risk of MACE after FFR-guided PCI among the low, intermediate, and high functional

SYNTAX score groups (9.0%, 11.3%, and 26.7%, respectively), implying that the functional SYNTAX score had a higher predictive value for MACE than the anatomical SYNTAX score (*Harrell's C*: 0.677 vs. 0.630, $P = 0.02$)^[45]. Thus, the functional SYNTAX score has unique potential for predicting the efficacy of revascularization therapy for complex CHD. However, because the cost and time required for FFR-testing are high, and the invasive procedure cannot guarantee that the coronary arteries are not damaged, which patients do not readily accept, the functional SYNTAX score is challenging to be popularized in clinical practice.

A Chinese research team developed a new non-invasive coronary artery function evaluation index, caFFR, to overcome the drawbacks of FFR testing's high technical requirements and the high-cost requirements of using pressure guidewires and vasodilators. The caFFR is based on conventional angiographic images for three-dimensional coronary artery reconstruction, the flow velocity is calculated using the thrombolysis in the MI frame counting method, and the FFR is calculated using an optimized computational pressure-flow dynamics model. It is now used in clinical settings^[46,47]. The FLASH FFR study^[47] found that caFFR-guided FSS (FSScaFFR) is more cost-effective, safer, faster, and more accurate than invasive FFR in assessing coronary artery severity. Furthermore, FSScaFFR outperforms the anatomical SYNTAX score in predicting ventricular tachycardia/ventricular fibrillation after acute MI^[48]. In addition, to overcome the limitations of invasive FFR, researchers have also investigated another method of coronary artery function assessment that does not require adenosine-induced congestion and pressure guidewire measurement—quantitative flow ratio (QFR), which is in good agreement with FFR and has been successfully incorporated into coronary artery function evaluation. The QFR-guided functional SYNTAX score (calculated only for lesions with $QFR \leq 0.8$) was found to be more accurate than the anatomical SYNTAX score in predicting 2-year composite endpoint events and MACE^[49,50].

The proposed functional SYNTAX-derived score mentioned above invariably confirms that the functional SYNTAX score has a higher predictive value than the anatomical SYNTAX score in predicting adverse events after different revascularization treatments for complex CAD, but it also fully exposes the shortcomings of the invasive functional SYNTAX score, providing a new vision for scholars to actively explore a non-invasive

SYNTAX-derived score that is safer, cheaper, more reasonable, more applicable, and more effective.

Non-invasive SYNTAX score and SYNTAX score III

Coronary computed tomography angiography (CCTA) and computed tomography-derived FFR (FFRct) have gradually evolved as an emerging technology for diagnosing stable CAD in recent years, with the popularization of CCTA and the development of deep machine learning technology based on artificial intelligence algorithms^[51]. The CCTA-based SYNTAX score (CCTA-SS) was found to be in good agreement with the conventional coronary angiography-based SYNTAX score (CAG-SS) in the study^[52], which was also confirmed in the SYNTAX III REVOLUTION trial^[53]. In this trial, the combination of functional SYNTAX score with clinical characteristics and comorbidities is designated as SYNTAX score III^[54], potentially strengthening the radiologist's position in non-invasive imaging treatment decisions for CAD. Furthermore, in terms of consistency, FFRct can be very similar to invasive FFR^[23]. FFRct is a technique that applies computational fluid dynamics to CCTA imaging to calculate the simulated fractional flow reserve^[55]. It uses computer technology to simulate the principles of fluid dynamics. Unlike invasive FFR, caFFR, and QFR calculations based on coronary angiography, FFRct not only saves cost but also greatly reduces the damage to coronary arteries from invasive operations, improves patient acceptance, and is safer, more economical, and more convenient. At the same time, the FFRct method significantly mitigates the disadvantage of CCTA-SS, which cannot effectively identify coronary arteries with significant calcification, causing coronary stenosis to be overestimated, and it effectively compensates for CCTA-SS's inability to assess the relationship between coronary artery lesions and myocardial blood supply in patients^[56,57]. In comparison to CCTA-SS, FFRct better predicts MACE, improves diagnostic accuracy, and the calculated value of FFRct is similar to the functional SYNTAX score^[58,59]. Another study confirmed that non-invasive FFRct was significantly associated with invasive FFR at the same time (FFRct *AUC*: 0.90, 95%*CI*: 0.87–0.94)^[60], and it can be used in the risk stratification assessment of cardiac surgery. However, the FFRct-guided functional SYNTAX score, on the other hand, is also susceptible to various factors such as collateral circulation and microvascular lesions, which can interfere with FFRct accuracy due to image artifacts, and has the disadvan-

tage of complex arithmetic methods and long analysis time. Numerous prospective clinical studies are needed to validate the value of the FFRct-guided functional SYNTAX score in the prognostic assessment of complex coronary revascularization.

Summary and perspective

To summarize, coronary angiographic techniques have been the first choice to guide the selection of different treatment strategies for CAD, but they cannot objectively evaluate the long-term outcome after CABG/PCI treatment for complex CAD. Therefore, an anatomical SYNTAX score was generated, which can help clinicians make better treatment decisions for complex CAD. The anatomical SYNTAX score could be used to systematically describe and objectively quantify the anatomical characteristics of coronary lesions, but it was found to have some inherent flaws in subsequent research. SYNTAX-derived scores, such as the clinical SYNTAX score, LCSS, SYNTAX score II, residual SYNTAX score, functional SYNTAX, and residual functional SYNTAX score, have gradually emerged to this end. They have a high predictive value for the risk of adverse events following CABG/PCI for complex CAD. However, because of the invasive nature of this type of score, scholars have proposed non-invasive SYNTAX score, SYNTAX score III, and other non-invasive SYNTAX-derived scores in recent years (**Fig. 1**). It makes the individualized assessment of complex coronary lesions safer and easier, more applicable, accurate, and cost-effective for clinicians.

The treatment of patients with complex CHD is difficult. The standard conservative medication treatment can no longer meet the needs of patients in terms of quality of survival and life cycle, but not all patients are candidates for revascularization therapy. Therefore, coronary risk stratification methods such as the SYNTAX score and its derivative scores are being developed to systematically quantify the lesion characteristics of a patient's coronary arteries and individually assess the beneficiary population and long-term prognosis of revascularization strategies to achieve optimal patient benefit. This paper integrates various research results on the SYNTAX score and its derivative scores by summarizing the advantages and disadvantages of the SYNTAX score and its derivative scores. This confirms the significance of the SYNTAX score and its derivative scores in clinical decision-making in complex CHD and highlights the application value of SYNTAX

score II in other SYNTAX derivative scores. However, with the publication of new medical materials and the advancement of medical technology, their permanent applicability for long-term prognostic assessment of revascularization still needs to be verified in many prospective randomized controlled trials and long-term follow-ups.

Conflict of interest

All authors have no conflict of interest to disclose.

Authors' contributions

Zhang YX contributed to conception and design of the

article; Zhang YX and Zeng RR collected data; Zhang YX and Yang Y analyzed the data; Zhang YX and Shen Y contributed to manuscript writing. All authors reviewed and confirmed the manuscript.

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Figure 1. The evolution of the SYNTAX score and its variants.

ACC/AHA: American College of Cardiology/American Heart Association; ACEF: age, creatinine, and ejection fraction score = age (years) /ejection fraction (%) + 1 (if creatinine ≥ 2 mg/dl); FFR: Fractional Flow Reserve; CrCl: creatinine clearance rate; EF: ejection fraction; BMI: body mass index; LM: left main coronary artery; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; FFRct: computed tomography-driven FFR.

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中文摘要

SYNTAX 及其衍生评分被应用于复杂冠心病选择血运重建策略的研究进展

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摘要

复杂冠心病因其冠状动脉解剖结构复杂、临床因素多变、血运重建难度大、药物保守治疗效果有限等特点，近年来成为医学研究领域的热点。而随着血运重建技术的日臻完善和冠状动脉危险分层评分的引入，使得复杂冠心病的识别和最佳治疗方式的选择更加科学化。作为一种新兴的冠状动脉危险分层评分工具，SYNTAX 及其衍生评分基于冠状动脉血管病变的复杂性及严重性，定量描述冠状动脉的病变特点，以辅助临床医师合理选择冠状动脉血运重建治疗的策略。本文总结了 SYNTAX 及其衍生评分在复杂冠心病中的应用情况，期望能加深临床医师对复杂冠心病不同血运重建策略抉择的认识，为复杂冠心病的救治提供参考。

关键词：复杂冠心病；血运重建策略；SYNTAX 及其衍生评分