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CLINICAL RECOMMENDATIONS ON ASIAN POPULATIONS

Practical Application of Coronary Physiologic Assessment

Asia-Pacific Expert Consensus Document: Part 2

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ABSTRACT

Coronary physiologic assessment is performed to measure coronary pressure, flow, and resistance or their surrogates to enable the selection of appropriate management strategy and its optimization for patients with coronary artery disease. The value of physiologic assessment is supported by a large body of clinical data that has led to major recommendations in all practice guidelines. This expert consensus document aims to convey practical and balanced recommendations and future perspectives for coronary physiologic assessment for physicians and patients in the Asia-Pacific region, based on updated information in the field that includes both wire- and image-based physiologic assessment. This is Part 2 of the whole consensus document, which provides theoretical and practical information on physiologic indexes for specific clinical conditions and patient statuses. (JACC: Asia 2023;3:825–842) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CFR = coronary flow reserve

DAPT = dual antiplatelet therapy

DCB = drug-coated balloon

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

IMR = index of microcirculatory resistance

INOCA = ischemia with no obstructive coronary artery

NHPR = nonhyperemic pressure ratios

PCI = percutaneous coronary intervention

CLINICAL APPLICATION OF CORONARY PHYSIOLOGY IN SPECIAL CONDITIONS

LEFT MAIN AND BIFURCATION LESIONS. Bifurcation lesions consist of the proximal main vessel, distal main vessel, and side branch, and each segment has distinct characteristics in vessel size, perfusion territory, and plaque distribution.[1-3] Angiography has limitations in assessing coronary bifurcation lesions,[4,5] some accounting for the discordance between anatomic stenosis severity and the functional significance in bifurcation lesions. To circumvent such limitations, physiologic assessment for bifurcation lesions is strongly recommended in cases of intermediate or ambiguous bifurcation lesions. Fractional flow reserve (FFR) or nonhyperemic pressure ratio (NHPR) can also be used for procedural guidance of bifurcation percutaneous coronary intervention (PCI), particularly to monitor the result of a provisional intervention strategy (**Table 1**).[6-9]

The concept of physiology-based approaches for bifurcation lesions is shown in **Figure 1**. Application of physiologic assessment before PCI for the main vessel is generally similar to nonbifurcation lesions, but special attention is required for the side branch. First, further assessment or intervention is needed only in clinically relevant branches. A study using coronary computed tomography (CT) angiography reported that only 21% of non-left main side branches subtended more than 10% of the myocardium.[1] Second, the physiologic index measured in the side branch before the main vessel PCI is influenced by the upstream stenosis. Therefore, careful pullback pressure tracing is needed to localize the segment of significant pressure step-up when the side branch FFR or NHPR is significant. Finally, as plaque shift or carina shift occur during main vessel stent implantation, preintervention physiologic assessment of the side branch cannot predict the functional significance of jailed side branches reliably.[2,3,10]

Physiology index-guided intervention is safe and effective in jailed side branches after main branch stent implantation. Previous studies showed that the FFR-guided side branch intervention strategy resulted in similar clinical outcomes with the angiography-guided side branch intervention strategy with less PCI for side branches.[7,8,11] However, even for the jailed side branches, operators should assess the cost-to-benefit ratio as well as the procedural risk before the physiologic assessment. physiologic index-guided side branch intervention is most effective in short ostial lesions, and its effectiveness and procedural risk can vary depending on the lesion length, the presence of a distal lesion, the degree of calcification, and the vessel tortuosity.

Although most bifurcation lesions can be treated by the provisional 1-stent technique, the initial 2-stent technique can still be an effective option for coronary true bifurcation lesions with extensive plaque involving large side branches.[12,13] physiologic assessment after bifurcation stenting can give additional information on the adequacy of PCI by detecting the residual ischemia left behind.[14] However, intravascular imaging-guided optimization of the stented segment is more practical and important in cases treated with 2-stent techniques.

Distal left main disease is a special form of bifurcation lesion, with the side branch usually covering a significant territory of myocardium.[1,15] The discordance between angiographic and physiologic severity in the left main disease has been reported to be more frequent with different features compared with other lesions (**Figure 2**).[16-18] Several studies reported favorable outcomes of FFR- or NHPR-guided revascularization strategy in left main disease (Supplemental Table 1).[16,19-26] Lee et al[9] assessed the long-term outcomes of a jailed left circumflex coronary artery after left main crossover stenting according to the FFR value and reported that a low FFR was an independent predictor of adverse clinical events at 5 years (HR: 6.49, 95% CI: 1.37-30.73). All these studies support the use of FFR and NHPR in the assessment and treatment of left main bifurcation lesions. Measurement of physiologic indexes and their

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TABLE 1 Previous Studies Evaluating the FFR- or NHPR-Guided Revascularization Strategies in Side Branch Lesions

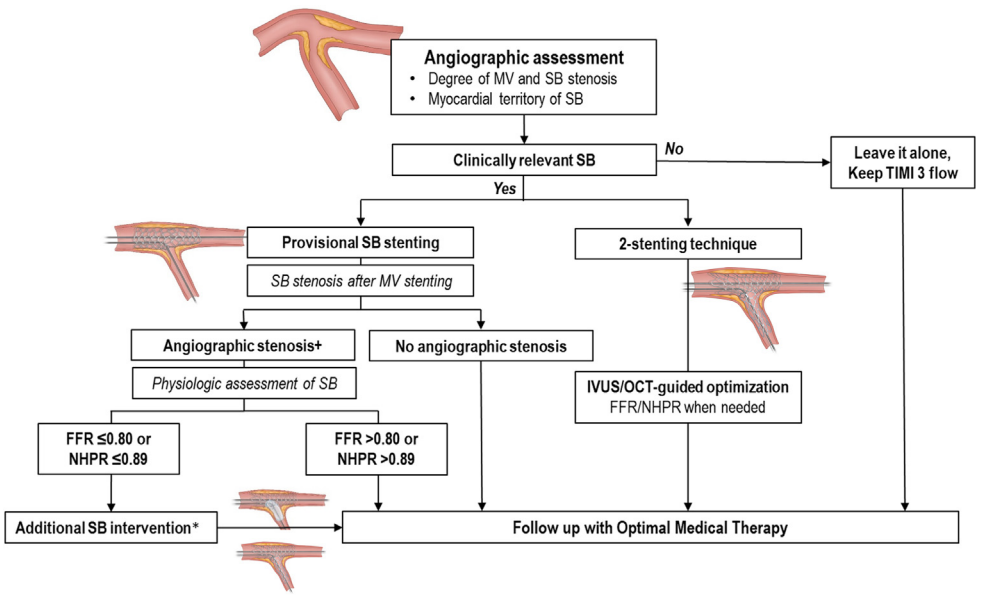
First Author (Ref. #) (Year)	Study Population	Outcomes	Main Results
Koo et al[7] (2008)	110 patients treated by provisional bifurcation treatment strategy Side branch intervention for FFR <0.75	Follow-up side branch FFR and clinical outcomes including cardiac death, myocardial infarction, target-vessel revascularization	Side branch FFR was maintained during follow-up until 6 months with (0.86 ± 0.05 to 0.84 ± 0.01, $P = 0.40$) and without side branch angioplasty (0.87 ± 0.06 to 0.89 ± 0.07, $P = 0.10$). Clinical outcomes were comparable with conventional treatment group (4.6% vs 3.7%, $P = 0.70$).
Chen et al[8] (2015)	320 patients randomized to angiography-guided and FFR-guided provisional side branch intervention	1-y rate of major adverse cardiac events (cardiac death, myocardial infarction, and target-vessel revascularization)	Side branch intervention was performed in 63.1% and 56.3% in angiography-guided and FFR-guided groups, respectively. The rate of 1-year major adverse cardiac event was 18.1% in both groups ($P = 1.00$).
Shaheen et al[11] (2018)	50 patients with coronary bifurcation lesions equally divided into iFR-guided group and conventional group	6-mo follow-up for postoperative ejection fraction and clinical outcomes	No significant differences between iFR-guided and conventional groups regarding post-PCI left ventricular ejection fraction ($P = 0.90$), heart failure class ($P = 0.89$), or post-PCI angina ($P = 0.066$)
Lee et al[9] (2019)	83 patients with left main to left anterior descending coronary artery simple crossover stenting FFR in jailed left circumflex artery	5-y rate of target-lesion failure	The low FFR group (≤0.80) had a significantly higher rate of target lesion failure than the high FFR group (33.4% vs 10.7%; HR: 4.09, 95% CI: 1.15-14.52).

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; NHPR = nonhyperemic pressure ratio; PCI = percutaneous coronary intervention.

interpretation is technically more demanding in left main lesions. Therefore, physiologic index-guided left main intervention requires the operator to have sufficient experience in both physiologic assessment and left main PCI.

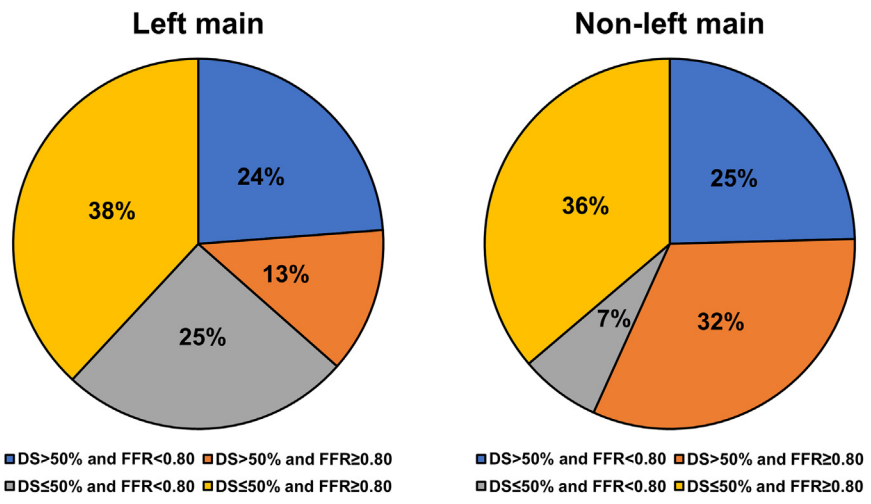
TANDEM LESIONS. In the presence of tandem lesions, FFR assessment of individual stenosis is sometimes challenging because of the crosstalk phenomenon among stenoses.[27] The crosstalk phenomenon is caused by the relative hemodynamic interdependence of stenoses that is especially prominent under hyperemic conditions. Therefore, measuring FFR again after stenting the lesion with the largest pressure step-up is required to assess the

FIGURE 1 Physiologic Approach for Coronary Bifurcation Lesions



Based on the previous evidence, treatment strategy flow of coronary bifurcation intervention based on angiographic, physiologic, and imaging assessments is suggested. Reprinted with permission from the Central Illustration in *J Am Coll Cardiol Intv.* 2022;15(13):1297-1309.
FFR = fractional flow reserve; IVUS = intravascular ultrasound; MV = main vessel; NHPR = nonhyperemic pressure ratio; OCT = optical coherence topography; SB = side branch.

FIGURE 2 Discordance Between Anatomic and Physiologic Severity in Coronary Bifurcation Lesions



Discordance between angiographic and physiologic severities has been reported in about 30% to 40% of coronary stenosis. The distribution of mismatch (angiographic diameter stenosis >50% and FFR ≥0.80, orange) and reverse mismatch (diameter stenosis ≤50% and FFR <0.80, gray) is different between left main disease and non-left main disease. The reverse mismatch was more frequently observed in left main disease than in non-left main disease. DS = diameter stenosis; FFR = fractional flow reserve.

functional significance of the remaining lesions in clinical practice. In contrast, NHPR has potential benefit in tandem lesions, as interstenosis crosstalk can be theoretically minimized in resting conditions because of a relatively narrow range of changes in resting coronary flow.[28] Recent studies have shown that instantaneous wave-free ratio (iFR) pullback can predict the hemodynamic consequences of stenting in tandem and diffuse lesions.[29,30] The concept of predicting functional results using iFR pullback is also available with other NHPRs, such as resting full-cycle ratio or diastolic pressure ratio (Table 2).[31] These findings suggest that NHPR-guided procedural planning and revascularization may lead to appropriate planning of PCI in tandem lesions. There are 2 limitations of this approach that physicians should recognize in daily practice. First, coronary blood flow after PCI is sometimes unpredictable, which may affect the reliability of post-PCI NHPR values.[32,33] It is reported that the hemodynamic interdependence of NHPRs can be similar to that seen with FFR when the degree of serial coronary stenoses is very severe.[34] Second, this concept does not include the residual pressure gradient across the treated segment. Kawase et al[35] reported that residual post-PCI iFR pressure gradient across the implanted stent was an independent risk factor of the mismatch in the

TABLE 2 Prediction of Post-PCI Physiologic Results Based on Pre-PCI FFR or NHPRs

First Author (Ref. #)	Year	Number of Lesions	Physiologic Index	Difference Between Predicted and Observed Values
Pijls et al[27]	2000	32[a]	FFR	11% error[b]
Nijjer et al[29]	2014	32[a]	iFR	0.016 ± 0.004
Kikuta et al[30]	2018	168[a]	iFR	0.011 ± 0.004
Kawase et al[35]	2018	71	iFR	0.036 ± 0.037
Omori et al[31]	2020	50	iFR	0.018 ± 0.028
		50	dPR	0.036 ± 0.037
		50	RFR	0.014 ± 0.037

[a]Tandem or diffusely diseased lesions. [b]Without coronary occlusive pressure correction.
dPR = diastolic pressure ratio; RFR = resting full-cycle ratio; other abbreviations as in Table 1.

TABLE 3 Studies Evaluating the Reliability of FFR Measurements in Nonculprit Lesions

First Author/Study (Ref. #)	Year	Study Design	AMI Type	STEMI/NSTEMI, n	Time From Index PCI to FFR	Findings
Ntalianis et al[151]	2010	Observational registry	STEMI and NSTEMI	75/26	35 ± 4 days	Mean value of FFR did not change between acute and follow-up. FFR declined from >0.80 to <0.75 at follow-up in 2 patients
WAVE study[152]	2017	Observational registry	STEMI	50/0	5-8 days	The iFR and FFR values of nonculprit lesions did not change significantly between the index and staged procedure
Choi et al[153]	2018	Observational registry	STEMI and NSTEMI	34/66	Not available	Changes in FFR and iFR for the nonculprit stenosis of AMI patients were not significantly different from those in stable coronary disease patients.
Van der Hoeven et al[41]	2019	Cohort analysis of randomized clinical trial	STEMI	73/0	1 month	FFR of nonculprit lesions decreased at 1 month follow-up, but iFR was unchanged
DANAMI-3-PRIMULTI[43]	2015	Randomized	STEMI	314[a]/0	2 days (IQR: 2-4 days)	FFR-guided complete revascularization significantly reduces repeat revascularization
COMPARE-ACUTE[44]	2017	Randomized	STEMI	295[a]/0	83% during index procedure, 17% during same admission	FFR-guided complete revascularization significantly reduces repeat revascularization
FLOWER-MI[46]	2021	Randomized	STEMI	586[a]/0	2.6 ± 1.4 days	FFR-guided complete revascularization was not better than angiography-guided strategy
FRAME-AMI[48]	2022	Randomized	STEMI and NSTEMI	265/297	60% at index PCI and 40% at staged PCI during same hospitalization Median length of hospital stay, 3.0 days (IQR: 2.0-4.0 days)	FFR-guided noninfarct-related artery lesions revascularization was superior to angiography-guided revascularization regarding the risk of death, myocardial infarction, or repeat revascularization

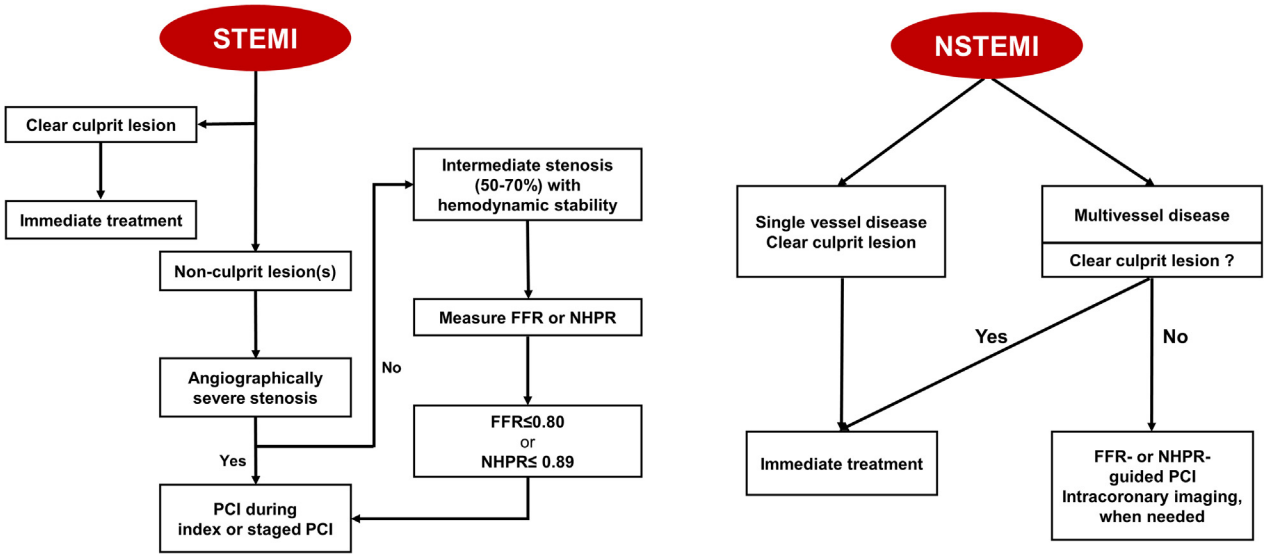
[a]Patients randomized to FFR-guided intervention of nonculprit lesions.

NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

iFR prediction. Incorporating residual NHPR values across the stented segment into the predicted NHPR values improved the accuracy of NHPR prediction (Supplemental Figure 1).

NONCULPRIT LESIONS IN ACUTE CORONARY SYNDROME. The benefit of PCI in patients with acute coronary syndrome (ACS) has been clearly demonstrated.[36] Recent guidelines support complete revascularization following treatment of the culprit lesion in ST-segment elevation myocardial infarction (STEMI),[37,38] As multivessel coronary artery disease is present in up to 50% of patients with ACS, management of the nonculprit lesion is a frequent and important clinical issue. Although FFR of nonculprit lesions is believed to be accurate even in the setting of acute myocardial infarction, there remain concerns that generalized microvascular dysfunction may result in underestimation of lesion severity, especially when the infarct size is large.[39,40] NHPRs, conversely, were shown to be more sensitive in identifying significant lesions in the acute setting, albeit at risk of more unnecessary interventions because of overestimation of the functional lesion severity attributed to the generally increased coronary flow in the setting of an acute myocardial infarction (AMI).[41,42] Table 3 summarizes recent studies evaluating the reliability of FFR measurements in nonculprit lesions. Two early studies—the DANAMI-3-PRIMULTI (Complete Revascularization vs Treatment of the Culprit Only in Patients With ST-Elevation and Multivessel Disease) (N = 627) and COMPARE-ACUTE (Fractional Flow Reserve Guided Primary Multivessel Percutaneous Coronary Intervention to Improve Guideline Indexed Actual Standard of Care for Treatment of ST-elevation Myocardial Infarction in Patients With Multivessel Coronary Disease) (N = 885)—demonstrated the superiority of an FFR-guided treatment of nonculprit lesions during primary angioplasty.[43,44] In a substudy of the COMPARE-ACUTE trial, Piroth et al[45] reported that the event risk was linearly and inversely associated with the FFR values of deferred nonculprit lesions. However, the recent FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction) trial (N = 1,171) could not demonstrate the superiority of an FFR-guided

FIGURE 3 Physiologic Assessment of Nonculprit Lesion in Patients With ACS

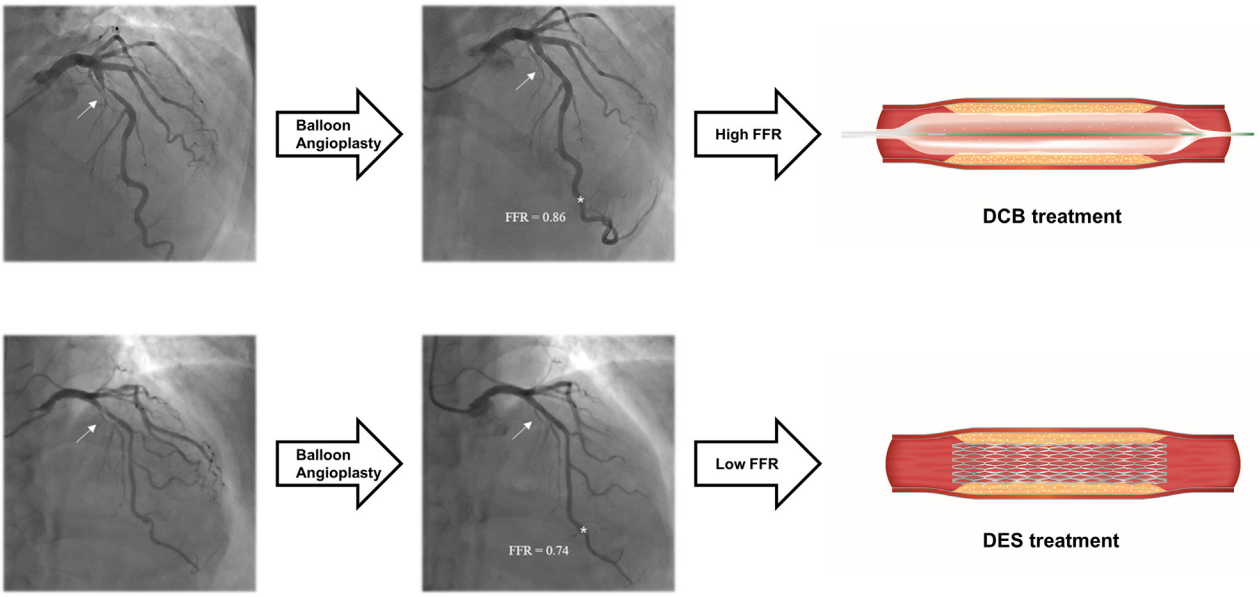


Based on the previous evidence, treatment strategy flow of nonculprit lesion treatment in patients with acute coronary syndrome based on invasive physiologic assessment is suggested. ACS = acute coronary syndrome; FFR = fractional flow reserve; NSTEMI = non-ST-segment elevation myocardial infarction; NHPR = nonhyperemic pressure ratio; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

strategy over an angiography-guided strategy.[46] In this study, staged intervention of the nonculprit lesion was performed in >95% of patients. The wide CIs of estimate effects suggest that the study was underpowered for definitive interpretation. In addition, peri-procedural myocardial infarction, which was a part of the primary endpoint, was higher in the FFR group despite less PCI than in the angiography group. The largest randomized trial addressing the intervention of nonculprit lesions in STEMI to date is the COMPLETE (Complete vs Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI) trial (N = 4,041). This study was virtually an angiography-guided trial, as 99% of nonculprit lesions did not fulfill the criteria for FFR (>2.5 mm diameter and 50% to 69% angiographic stenosis).[47] Hence, there remain uncertainties regarding the role of routine FFR use in guiding complete revascularization following primary PCI for the culprit lesion. A more recent FRAME-AMI (FFR vs Angiography-Guided Strategy for Management of Acute Myocardial Infarction With Multivessel Disease) trial randomized 563 patients with AMI and noninfarct-related artery lesions to either FFR- or angiography-guided (>50% by visual estimation) PCI strategies.[48] During the median follow-up of 3.5 years, the primary endpoint occurred in 18 of 284 patients in the FFR-guided PCI and 40 of 278 patients in the angiography-guided PCI group (7.4% vs 19.7%, HR: 0.43, 95% CI: 0.25-0.75). Compared with the angiography group, the FFR group used a lower number of stents in noninfarct-related artery lesions (0.9 ± 0.9 vs 1.3 ± 0.7; $P < 0.001$) and a lower total amount of contrast agent. Among patients with unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI), the benefit of physiologic assessment is well established in the presence of multivessel disease.[49,50] The FAME (Fractional Flow Reserve vs Angiography for Multivessel Evaluation) trial (N = 1,005) showed the superiority of FFR in multivessel PCI, with approximately one-third (32%) of patients in the study having unstable angina or NSTEMI. The heterogeneity of benefits of FFR use in patients with or without ACS was not observed.[51]

In summary, the advantage of physiologic index-guided revascularization in patients with STEMI has been demonstrated in intermediate stenosis, in which a reduction in stent use would reduce the incidence of stent-related complications. In the less extreme spectrum of ACS, invasive physiologic indices can be helpful in identifying the target lesion for PCI. It is also important to remind that intracoronary imaging can be helpful in identifying the culprit lesion of ACS

FIGURE 4 **FFR-Guided Drug-Coated Balloon Treatment for De Novo Coronary Artery Disease**



Based on the previous evidence, drug-coated balloon treatment can be performed safely and effectively after successful balloon angioplasty with physiology guidance. DCB = drug-coated balloon; DES = drug-eluting stent(s); FFR = fractional flow reserve.

or the target lesion for PCI. Figure 3 summarizes the practical approach to the physiologic assessment of nonculprit lesions in patients with ACS.

INVASIVE PHYSIOLOGIC ASSESSMENT IN DRUG-COATED BALLOON ANGIOPLASTY. A drug-coated balloon (DCB) locally delivers the drug into the vessel after balloon angioplasty to inhibit restenosis, and its benefit in in-stent restenosis lesions has been clearly documented. However, concerns over acute vessel closure and a lack of practical guidance for a successful balloon angioplasty result before DCB treatment have hampered their use for de novo lesions, especially in large vessels. Therefore, physiologic assessment for defining the appropriateness of balloon angioplasty to enable the operators to guide whether to perform DCB treatment or stent implantation may be a promising option.

In the era of balloon angioplasty, Bech et al[52] demonstrated that patients with residual diameter stenosis ≤35% and postangioplasty FFR ≥0.90 had excellent clinical outcomes. This cutoff can be lower for DCB treatment with its antiproliferative effects.[53,54] A recent expert consensus document suggested the angiographically successful angioplasty before DCB as residual stenosis diameter ≤30% and < type C dissection.[55] However, previous studies that compared the angiographic stenosis severity and FFR after balloon angioplasty showed a significant discordance between the 2 methods.[53,54] This finding is expected, considering the limitations of angiography in assessing the complex local hemodynamic and structural milieu in the setting of post-balloon angioplasty. In clinical follow-up studies, DCB treatment in cases with post-balloon angioplasty FFR ≥0.75 showed comparable outcomes with those with stent implantation.[53,54,56] These results suggest that FFR-guided DCB treatment may be helpful in the selection of an appropriate candidate for DCB and reduce the number of stents implanted. Although the definitive physiologic threshold to define optimal post-DCB treatment has not been identified, the Third Report of the International DCB Consensus Group suggested criteria of postangioplasty FFR value of >0.80 in addition to residual stenosis ≤30% and no flow-limiting dissection for DCB-only PCI strategy.[55] An iFR-guided DCB treatment strategy also showed safety and efficacy in de novo coronary lesions.[57] An angiography-based physiologic assessment can be an alternative method to FFR or NHPR.

In summary, the evidence to date suggests that physiology-guided DCB treatment strategy may reduce the risk of acute vessel closure and stent implantation (Figure 4). However, further research and randomized controlled trials are still needed to clarify

the role of invasive physiologic assessment in guiding DCB angioplasty.

CORONARY PHYSIOLOGIC ASSESSMENT IN THE PRESENCE OF AORTIC STENOSIS. Assessment for the functional significance of coronary stenosis is sometimes needed to determine the treatment strategy in patients with severe aortic stenosis before surgical or transcutaneous aortic valve replacement. Coronary physiologic assessment is helpful in guiding clinical decision making in patients with severe aortic stenosis and the use of hyperemic agents has been reported to be safe in the presence of aortic stenosis.[58-64] However, interpreting the results from these measurements can be challenging because of the following reasons. Aortic stenosis causes an increase in coronary microcirculatory resistance because of structural and functional changes within the myocardium.[65] The effect of vasodilatory agents such as adenosine is attenuated by activation of the sympathetic and renin-angiotensin-aldosterone systems.[58,64,66-68] Because of decreased hyperemic blood flow and lower pressure gradient across lesions, FFR tends to be higher and can be falsely negative, as evidenced by higher FFR levels before transcutaneous aortic valve replacement compared with that after transcutaneous aortic valve replacement.[58,59,64] However, based on the small change of FFR after transcutaneous aortic valve replacement, an FFR >0.85 is unlikely to be falsely negative.[59] In contrast, an FFR ≤0.80 is indicative of the functional significance of the target lesion. NHPRs have been proposed as a potential substitute for FFR in the presence of aortic stenosis. NHPRs do not require hyperemia and rely mostly on measurements during the diastolic phase when the aortic valve is closed. Coronary blood flow at rest is not reduced because of aortic stenosis, and the NHPRs are therefore not likely to cause false negative results.[63,69] However, resting blood flow can increase in patients with severe aortic stenosis because of increased left ventricular oxygen demand and left ventricular hypertrophy and higher afterload.[60,64,70] This can cause variable NHPR values and possible false positive results that are only detectable with remeasurement several months after transcutaneous aortic valve replacement.[63,71,72] Several studies have shown that using a lower ischemic cutoff value of ≤0.82 for iFR results in an excellent positive predictive value.[60,69,73,74] One study showed that other NHPRs, such as diastolic pressure ratio or diastolic hyperemia-free ratio, correlated well with iFR, suggesting that all NHPRs could be used interchangeably in patients with aortic stenosis.[75]

Until now, the studies available to guide the use of invasive physiologic assessment in patients with severe aortic stenosis have been limited by a relatively small sample size. CT or angiography-based physiologic assessment is a promising option but also requires further studies before its clinical application.[76,77] The consensus group eagerly awaits larger studies reporting clinical outcomes for further guidance.

CORONARY PHYSIOLOGIC ASSESSMENT IN MYOCARDIAL DISEASE. Recent studies have expanded the role of invasive physiologic assessment to diagnosis and prognostication of patients with the myocardial disease. Because myocardial disease primarily involves the microcirculatory system, measuring coronary flow reserve (CFR) and microcirculatory resistance can serve as a surrogate marker of severity of disease or degree of myocardial damage. In this regard, there have been several studies that adopted invasive physiologic assessment in evaluating patients with cardiac amyloidosis or heart transplantation.[78-83]

The Physiologic Assessment of Microvascular Function in Patients with Cardiac Amyloidosis registry prospectively enrolled patients with biopsy-confirmed cardiac amyloidosis and evaluated the prognostic implication of index of microcirculatory resistance (IMR) in addition to the revised staging system.[78] In this study, patients with IMR ≥40 showed a significantly higher risk of death than those with IMR <40 (55.6% vs 11.9%, HR: 6.31, 95% CI: 1.34-29.83). The model using the revised staging system and IMR showed significantly increased discrimination and reclassification abilities than the model with the revised staging system alone. Supplemental Figure 2 demonstrates representative cases showing the physiologic indexes in cardiac amyloidosis patients.

There have been several studies supporting the prognostic role of invasive physiologic indexes in heart transplant patients.[79-83] Two studies retrospectively evaluated prognostic impact of IMR in predicting the risk of acute allograft rejection within 1 year[81] or a composite of cardiac allograft vasculopathy, all-cause death, and retransplantation during a mean follow-up of 4.5 years.[80] Lee et al[79] conducted a prospective study with scheduled invasive physiologic assessment at 1 month and 2 years from heart transplantation. In this study, IMR measured early after heart transplantation was associated with a risk of acute cellular rejection, and an IMR ≥15 was highly predictive of the occurrence of acute cellular rejection

TABLE 4 Endotypes of INOCA

Endotypes	Features	Diagnosis
Coronary microvascular disease	Structural or functional abnormalities in the microvascular system A limitation in the vasodilatory ability and absolute conductance ability of the microvascular system Associated with risk factors of cardiovascular disease, ventricular hypertrophy, or cardiomyopathies	Based on invasive physiologic assessment: • FFR >0.80 or NHPR >0.89 • CFR <2.0-2.5 • IMR >25U or HMR >2.5 mm Hg/cm/s
Epicardial vasospastic angina	Hyper-reactive response of the epicardial coronary segment to vasoconstrictive stimuli	Based on provocation test using ergonovine or acetylcholine: • Ischemic symptom during provocation test • A transient total or subtotal coronary artery occlusion • Ischemic ECG changes (ST-segment depression or elevation ≥0.1 mV) in at least 2 contiguous leads
Microvascular vasospastic angina	Spasm of vascular smooth muscle cells in prearteriolar vessels and arterioles	Based on the provocation test using acetylcholine: • Ischemic symptom during provocation test • Without significant epicardial artery constriction during provocation test • Ischemic ECG changes (ST-segment depression or elevation ≥0.1 mV) in at least 2 contiguous leads
Masked diffuse disease	Coronary angiography can underestimate diffuse coronary atherosclerosis Invasive physiologic assessment and/or intravascular coronary imaging can reveal hidden coronary atherosclerosis	Based on invasive physiologic assessment: • FFR ≤0.80 or NHPR ≤0.89 with gradual step-up during pullback tracing Based on intravascular imaging studies

CFR = coronary flow reserve; ECG = electrocardiogram; HMR = hyperemic microvascular resistance; IMR = index of microcirculatory resistance; INOCA = ischemia with nonobstructive coronary artery disease; other abbreviations as in Table 1.

during 2 years of follow-up after heart transplantation. Similar results were also shown by patient-level pooled analysis of different patient populations.[82,83] These data support the potential role of microvascular assessment with CFR and IMR to detect earlier changes in diseased myocardial structure and prognostication of future development of the more severe form of myocardial damage. Another important finding was that the presence of an epicardial coronary stenosis at 1 year, defined by FFR ≤0.80 or evidence of multivessel disease, was a strong predictor of long-term death at 10 years.[82] As there are several limitations of noninvasive tests, the invasive physiologic assessment might be 1 of the potential diagnostic tools for patients with the primary myocardial disease. Nevertheless, given its invasive nature, further research is required to adopt invasive physiologic assessment in daily practice for this purpose.

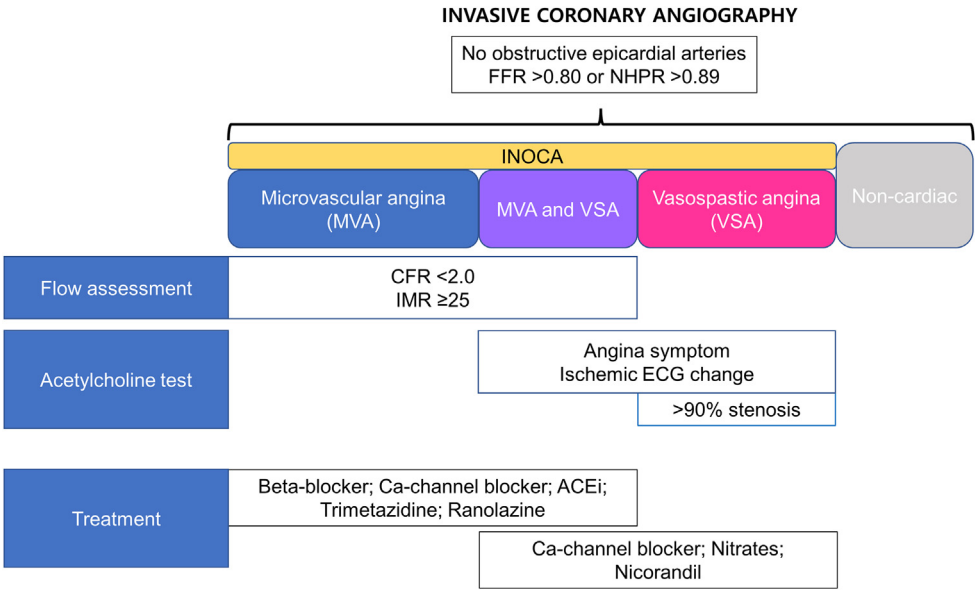
PHYSIOLOGIC ASSESSMENT FOR ISCHEMIA WITH NO OBSTRUCTIVE CORONARY ARTERY

Ischemia with no obstructive coronary artery (INOCA) is defined as clinically evident myocardial ischemia without significant stenosis in the epicardial coronary arteries. Previously, some patients with INOCA had been diagnosed as suffering from noncardiac pain and were often ignored in clinical practice. However, recent studies have shown that INOCA is not benign and can cause recurrent angina, impaired quality of life, repeated hospitalization, and even adverse cardiac events.[84]

The spatial resolution of coronary angiography is approximately 300 μm and is inadequate to visualize the coronary microcirculation that comprises smaller arteries, arterioles, and capillaries.[85] The contribution of microvascular dysfunction to the pathophysiology of INOCA has been revealed with the advancement of diagnostic tools for coronary microcirculation.[86-88] Vasomotor dysfunction, which manifests as vasospastic angina, can also be a cause of INOCA, and it is more prevalent among Asians than in Caucasians.[89-91] Moreover, microvascular dysfunction and vasospastic angina often coexist in patients with INOCA,[92] and INOCA is now recognized as a heterogeneous entity comprising coronary microvascular angina, vasospastic angina, or both (Table 4). In the CorMicA (Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina) trial[92] of 134 patients with INOCA who had abnormal coronary function, 109 (81%) had microvascular angina, one-third of which were complicated with vasospastic angina.

Given the nonbenign prognosis of INOCA, its pathophysiology has been intensively investigated, and diagnostic procedures are being standardized.[93,94] A European expert panel organized by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) has advocated a systematic diagnostic approach for INOCA, which was endorsed by the COVADIS (Coronary Vasomotor Disorders International Study) Group[93] and includes 3 steps of

FIGURE 5 Diagnosis and Management of INOCA



INOCA can be suspected when a coronary angiogram shows no obstructive epicardial arteries and FFR or NHPR is negative in patients with chest pain. Coronary flow is determined by CFR and microvascular resistance, such as IMR. If either the CFR or IMR is abnormal, MVA is diagnosed. VSA is diagnosed based on the response to acetylcholine provocation. INOCA includes patients with MVA, VSA, or both.
ACEi = angiotensin-converting enzyme inhibitor; CFR = coronary flow reserve; ECG = electrocardiogram; FFR = fractional flow reserve; INOCA = ischemia with no obstructive coronary artery; IMR = index of microvascular resistance; MVA = microvascular angina; NHPR = nonhyperemic pressure ratio; VSA = vasospastic angina.

invasive assessment: invasive coronary angiography, physiologic assessment, and vasoreactivity test with acetylcholine provocation (Figure 5). In the systematic approach to the comprehensive assessment of INOCA, wire-based invasive physiologic assessment plays a pivotal role in 2 aspects. One is to confirm the absence of a significant pressure gradient in the epicardial coronary arteries, and the other is to assess microvascular function, which can be defined as low CFR (<2.0), high IMR (≥25 U), or high hyperemic microvascular resistance (>2.5 mm Hg/cm/s). The consensus document proposed a sequence of invasive functional coronary angiography with the following 3 steps: angiography, FFR or NHPR measurement, and acetylcholine test for vasomotor function.[93] This sequence has remained controversial because of the potential impact of nitrates on the assessment of vasospasm caused by acetylcholine provocation.[95] Precedent injection of nitrates may attenuate abnormal vasoconstriction of coronary arteries during acetylcholine provocation. Therefore, the use of glyceryl trinitrate is recommended rather than other compounds, such as isosorbide mononitrate or isosorbide dinitrate, because of its shorter half-life. Another practical approach is performing an acetylcholine challenge test first without any pretreatment and then proceeding with the intracoronary physiologic assessment with nitroglycerine and hyperemic agents.

Microvascular spasm, which has not been described in the consensus document by the COVADIS group,[93] has been advocated by the Japanese study group.[96] Microvascular spasm can be diagnosed by measuring lactate concentration in blood samples from the coronary sinus and aorta during acetylcholine provocation[97] or by the presence of typical symptoms with corresponding ischemic electrocardiographic changes in the absence of epicardial vasospasm with acetylcholine.[92] The consensus document proposed a stratified therapeutic strategy based on the INOCA phenotype (Figure 5). For patients with microvascular angina, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, ranolazine, and trimetazidine are recommended.[93] The CorMicA trial investigated the clinical impact of targeted therapy for patients with INOCA based on their INOCA subtypes and found that such a strategy was associated with improved symptoms and better quality of life.[98] Nevertheless, the optimal medical treatment for patients with INOCA

TABLE 5 Sex Differences in Clinical Application of Invasive Physiologic Indexes

	FFR	NHPR	CFR
	• Relatively high FFR compared with men • More favorable outcomes in cases with deferral of PCI by FFR compared with men • Favorable outcomes compared to angiography-guided PCI strategy	• Similar rate of lesion significance compared with FFR • Similar event rate compared with FFR-guided PCI strategy	• Lower CFR compared with men • Higher resting flow compared with men • Low CFR is dissociated with poor outcome
	• Relatively low FFR compared with women • Favorable outcomes compared with angiography-guided PCI strategy	• Lower rate of lesion significance compared with FFR • Similar event rate compared with FFR-guided PCI	• Higher CFR compared with women • Lower resting flow compared with women • Low CFR is associated with poor outcome

CFR = coronary flow reserve; FFR = fractional flow reserve; NHPR = nonhyperemic pressure ratio; PCI = percutaneous coronary intervention.

has not been fully elucidated, and further studies are warranted.

SEX ISSUES IN CORONARY PHYSIOLOGY

Women have different phenotypes of coronary artery disease in terms of development, clinical presentation, and prognosis compared with men.[99,100] The influence of sex hormones and unique biological attributes, such as small myocardial mass, small vessel size, and higher resting coronary blood flow, lead to unique coronary physiologic status in women. The lack of enough clinical data and sex-specific clinical guidelines has resulted in clinical practice for women being based primarily on findings in men. Sex differences should be considered in the application of physiologic assessment and interpretation in the cardiac catheterization laboratory.

Several studies reported that FFR is higher in women than men for comparable severity of anatomic stenosis.[101,102] This can be explained by various factors such as fewer high-risk plaques, smaller myocardial mass, smaller coronary vessels, and less plaque burden in female patients.[103-105] In daily practice, such a tendency of overestimating stenosis severity by angiography alone in women could lead to an overtreatment without FFR measurement.[106] A FAME substudy on sex differences demonstrated that FFR-guided PCI strategy is equally beneficial in women and men despite the different FFR values between sexes.[101] When the outcomes after the deferral of PCI according to FFR were compared, women appeared to have more favorable outcomes compared with men.[107,108]

It is interesting to note that NHPR, such as iFR, showed no difference between the sexes, unlike FFR for similar angiographic stenosis. A DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) substudy, which evaluated sex differences in procedural characteristics and clinical outcomes of iFR- and FFR-guided PCI, demonstrated that both FFR- and iFR-guided strategies brought comparable clinical outcomes regardless of sex, although FFR guidance was associated with a higher rate of PCI in men than iFR-guidance.[109,110]

Another important issue is the sex difference in microvascular function as ischemic symptoms with no obstructive coronary disease are more frequent in women than in men.[111] It was initially thought that this difference could be explained by the difference in microvascular functions between sexes. In the Women's Ischemia Syndrome Evaluation study, 47% of women with no obstructive coronary disease had a CFR of <2.5,[112] and the CFR value of women was lower than that of men.[113] However, a series of recent studies suggested that the low CFR in women is predominantly caused by a higher resting flow rather than insufficient hyperemic flow.[107,114] Furthermore, low CFR in women was not associated with worse clinical outcome [107] Therefore, the role of CFR may be limited in evaluating microvascular dysfunction and predicting prognosis in women with no obstructive coronary disease. More microvascular-specific parameters, such as IMR, can better discriminate the influence of microvascular dysfunction.

In summary, understanding sex differences in coronary physiology remain challenging. Despite this, it is clear that physiologic assessment by FFR or NHPR is equally beneficial in both sexes (Table 5).

COMPLEMENTARY ROLE OF IMAGING AND PHYSIOLOGY

High-risk plaque features derived from various coronary-imaging modalities refer to plaque

TABLE 6 Prognostic Value of High-Risk Plaque Features in Deferred Lesions With FFR >0.80

First Author (Ref. #) (Year)	Study Size (Lesions)	Imaging Modality	High-Risk Plaque Features	Prevalence	Main Findings
Lee et al[122] (2019)	772	CCTA	MLA ≤4.0 mm^2, plaque burden ≥70%, low-attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign	7.1%	≥3 vs <3 high-risk plaque features (HR: 4.0, 95% CI: 1.5-10.8, $P = 0.007$)
Cho et al[123] (2020)	552	IVUS	MLA ≤4.0 mm^2, plaque burden ≥70%, and positive remodeling	5.6%	All presence of 3 features vs. not (HR: 2.9, 95% CI: 1.3-6.4, $P = 0.010$)
Kedhi et al[124] (2021)	390	OCT	TCFA	25.1%	TCFA vs non-TCFA (HR: 4.7, 95% CI: 2.0-10.9, $P < 0.001$)

CCTA = coronary computed tomography angiography; IVUS = intravascular ultrasound; MLA = minimum lumen area; OCT = optical coherence tomography; TCFA = thin-cap fibroatheroma. Other abbreviations as in Table 5.

characteristics that are associated with an increased risk of plaque rupture and future acute coronary events. Intravascular ultrasound-derived criteria including minimum lumen area (MLA) ≤4 mm^2, plaque burden ≥70%, and thin-cap fibroatheroma (TCFA) phenotype have been found to be associated with adverse coronary events.[115] Near-infrared spectroscopy can identify lipid-rich plaque at high risk for future events with a cutoff of the maximum 4 mm lipid core burden index ≥400.[116] Optical coherence tomography provides the detailed superficial structure of lumen and vessel walls with a high resolution. Optical coherence tomography-derived macrophage infiltration, fibrous-cap thickness <75 μm, or lipid arc circumferential extension >180° are predictive of cardiac death or target-vessel myocardial infarction.[117] Despite a lower spatial resolution than that of invasive imaging, coronary CT angiography-derived low-attenuation plaque, positive vessel remodeling, and quantified lipid-rich plaque features are independent predictors of acute coronary events.[118,119] There have been 2 randomized trials that compared the clinical outcomes of imaging- vs physiology-guided strategies. In a single-center randomized trial with 350 patients with intermediate stenosis, the optical coherence tomography-guided strategy was associated with a lower rate of major adverse cardiac events or significant angina at 13 months than the FFR-guided strategy.[120] In a large multicenter randomized trial of 1,682 patients, the FFR-guided strategy demonstrated noninferior clinical outcomes at 24 months compared with the intravascular ultrasound-guided strategy, with no difference in quality of life between the 2 strategies.[121] In both studies, the imaging-guided strategy was associated with more frequent PCI than the FFR-guided strategy. Therefore, the physiology-guided strategy is still the standard approach for patients with intermediate stenosis.

In addition to the individual value of coronary imaging and physiology, several studies have investigated whether they might have an additive role in the prediction of clinical outcomes and guidance for revascularization decision making. When the impact of high-risk plaque features on clinical outcomes in nonischemic coronary lesions was evaluated, the presence of high-risk plaque features consistently showed the prognostic implications in medically treated lesions with FFR >0.80, regardless of the imaging modality used (**Table 6**).[122-124] In addition, a recent coronary CT angiography study expanded this relationship between various physiologic indexes and imaging-derived criteria as the presence of 3 or more of plaque burden ≥70%, minimum lumen area <4 mm^2, low-attenuation plaque, and positive remodeling was associated with a higher probability of cardiovascular events in lesions with normal resting and hyperemic pressure, flow, or microvascular resistance.[125] With respect to the treatment strategies for high-risk plaque, intensive lipid-lowering treatment using statins or proprotein convertase subtilisin-kexin type-9 inhibitors can increase the fibrous-cap thickness and reduce lipid-rich plaque.[126,127] Local treatment might also have preventive effects for future events, even in nonischemic lesions, but accompanying high-risk plaque characteristics. Based on the potential benefit of bioresorbable vascular scaffold implantation to stabilize thin-cap fibroatheroma by neointimal tissue development,[128] a pilot randomized trial assigned 182 patients who had FFR- or NHPR-negative lesions with plaque burden ≥65% to 1:1 bioresorbable vascular scaffold treatment and medical treatment arms. As a result, the bioresorbable vascular scaffold treatment arm had higher minimum lumen area and fewer lesion-related events than the medical treatment arm at 25 months.[129] Ongoing clinical studies, such as the PREVENT (Preventive PCI or Medical Therapy Alone for Vulnerable Atherosclerotic Coronary Plaque; NCT02316886) study or the DEBuT-LRP (Intravascular Identification and Drug-Eluting Balloon Treatment of Vulnerable Lipid-Rich Plaques; NCT04765956), are

expected to provide further insights into the efficacy of PCI on these lesion subsets.

In summary, the integrative use of coronary imaging and physiologic assessment can provide complementary insight into the identification of high-risk lesions that cannot be fully detected by coronary physiology alone and in the selection of optimal treatment strategies in nonischemic coronary lesions.

OPTIMAL MEDICAL THERAPY AFTER PHYSIOLOGIC ASSESSMENT

GUIDELINE-DIRECTED MEDICAL THERAPY. Regardless of whether or no revascularization is performed after physiologic assessment, guideline-directed medical therapy adherence has been associated with better clinical outcomes in patients with coronary artery disease.[130,131] After FFR-guided deferral of revascularization, the optimal guideline-directed medical therapy group (antiplatelet drug, angiotensin blockade, beta blocker, and statin) showed significantly lower incidence of major adverse cardiac events (MACE) compared with the suboptimal guideline-directed medical therapy group (≤3 types of medications),[130] which was more prominent in patients with high thrombotic risk features. In patients deferred following negative FFR, a high thrombotic risk phenotype was also associated with an increased risk of target-vessel failure and any myocardial infarction.[132] In addition, antiplatelet therapy and statin use decreased the rate of adverse clinical events significantly. In patients with AMI, preprocedural assessment of ex vivo thrombogenicity (eg, platelet-fibrin clot strength measured by thromboelastography) was significantly associated with the risk of coronary microvascular dysfunction (defined as index of microcirculatory resistance >40 U using the invasive physiologic test).[133] In addition, a combined risk stratification with these measures increased the prognostic power to predict the long-term clinical outcomes. Optimal control of thrombogenicity by adjunctive antithrombotic therapy may reduce the risk of coronary microvascular dysfunction and improve long-term clinical prognosis.

OPTIMAL ANTIPLATELET THERAPY. Current "standard-of-care" dual antiplatelet therapy (DAPT) for patients with ACS undergoing PCI comprises aspirin with a potent $P2Y_{12}$ inhibitor (ticagrelor or prasugrel) for 12 months.[131] In patients presented with stable angina, DAPT with aspirin and clopidogrel is recommend for 6 months following PCI. Increased awareness regarding the prognostic implication of bleeding episodes has prompted the investigation of strategies to de-escalate DAPT. Furthermore, the East Asian population shows the tendency toward lower ischemic events, higher bleeding risk, and different responses to antithrombotic agents (eg, $P2Y_{12}$ inhibitor and non-vitamin K antagonist oral anticoagulant).[134] The Western guideline-based DAPT regimen may have less benefit in reducing ischemic events and a higher risk in this population ("East Asian Paradox"). In the setting of ACS, ischemic risk clusters within the first month, whereas bleeding risk remains stable and may exceed ischemic risk beyond the first few months. During the stabilized period, DAPT de-escalation strategy must be considered in East Asian patients.

The timing and strategy regarding DAPT de-escalation should be determined based on the patients' combined thrombotic and bleeding risks. The Academic Research Consortium (ARC) recently developed a consensus definition of patients at high bleeding risk[135] (Supplemental Table 2). Patients at high bleeding risk (approximately 40% of post-PCI subjects) were decided if at least 1 major or 2 minor criteria were present.[136] However, this criteria system is at risk of underestimating bleeding risk as several risk factors for bleeding were not included in the criteria (eg, low body weight, frailty, heart failure, and peripheral artery disease).[137] Clinical risk factors associated with atherothrombotic events include the disease acuity (eg, ACS) and traditional cardiovascular risk factors.[138] Lesion complexity or PCI can also increase the risk of atherothrombotic events. In addition, a low FFR value, either deferred or after PCI, is associated with the long-term risk of target-vessel failure.[139,140]

Patients with high bleeding risk features may not benefit from 12-month DAPT with potent $P2Y_{12}$ inhibitor and long-term DAPT maintenance.[141] A recent analysis reporting on the long-term outcomes of patients with acute myocardial infarction demonstrated that a single ischemic risk factor was insufficient to recommend prolonged DAPT, and ≥2 risk factors could define a patient with truly high ischemic risk.[142]

DAPT DE-ESCALATION STRATEGY. Type, potency, and duration of the DAPT regimen are related to the risk of serious bleeding. The bleeding risk relating to the different oral $P2Y_{12}$ inhibitors largely reflects the extent of platelet $P2Y_{12}$ inhibition. Currently approved doses of prasugrel (10 mg a day) and ticagrelor (90 mg twice a day) achieve a higher level of platelet inhibition than clopidogrel, which are associated with higher rates of serious bleeding and early discontinuation of DAPT in East Asian patients.[143,144]

De-escalation strategies in East Asian patients can be instituted at different time points according to the clinical evidence. De-escalation of intensity

(switching or downgrading from the potent $P2Y_{12}$ inhibitors at conventional doses to either clopidogrel or reduced-dose of potent $P2Y_{12}$ inhibitors) may be instituted at 1 month if unguided.[145,146] Abbreviation of DAPT duration may be considered after 1 to 3 months of DAPT if switching to monotherapy with ticagrelor or clopidogrel[147-149] or after 3 to 6 months of DAPT if switching to aspirin monotherapy.[150] If patients with ACS have high bleeding-risk phenotype, de-escalation of DAPT intensity may be a default strategy to maximize the net benefit of efficacy and safety.

CONCLUSIONS

The Asia-Pacific Expert Consensus Document was developed by experts in the Asia-Pacific region and international board members to provide a practical guide and future direction based on the fundamental principles of coronary physiology and latest data on coronary physiologic assessment. This field has recently undergone rapid development with a significant number of new data. In particular, indexes and treatment guides based on novel concepts, such as image-based physiologic assessment, are starting to be applied in daily clinical practice. Through this consensus document, it is hoped that the use of physiologic assessment will be expanded, and physicians will be better equipped to understand the pathophysiology of coronary artery disease in each patient and select appropriate treatment strategies based on this understanding. This is expected to lead to improved prognoses for patients with coronary artery disease, thereby laying the foundation for better cardiovascular prevention and treatment of disease in the Asia-Pacific region.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.