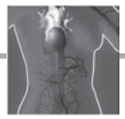
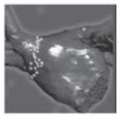


Plaque characterization to identify patients at high risk of acute complications during PCI

Periprocedural myocardial infarction and angiographic no-reflow represent acute complications that may occur during percutaneous coronary intervention, and have been associated with both short- and long-term mortality. Intravascular ultrasound (IVUS), optical coherence tomography and near-infrared spectroscopy are all capable of identifying target lesions that are at heightened risk of inducing these acute percutaneous coronary intervention-related complications. The morphologic characteristics of target lesions that are most associated with these complications include attenuated plaque by IVUS, necrotic core by virtual histology-IVUS, thin-capped fibroatheroma by optical coherence tomography and lipid core plaque by near-infrared spectroscopy. Future studies are needed to determine whether routine use of IVUS, optical coherence tomography or near-infrared spectroscopy prior to percutaneous coronary intervention can improve procedural safety.

KEYWORDS: intravascular ultrasound ■ lipid core plaque ■ near-infrared spectroscopy ■ no-reflow ■ optical coherence tomography ■ periprocedural myocardial infarction ■ plaque characterization ■ vulnerable plaque

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Acute coronary complications during percutaneous coronary intervention

Despite advancements in the equipment and technique used to perform percutaneous coronary intervention (PCI), acute coronary complications during PCI continue to occur with considerable frequency [1–3]. These acute complications often occur unexpectedly during balloon inflation or stent deployment and include abrupt vessel closure, intimal dissection, vessel perforation, angiographic no-reflow and periprocedural myocardial infarction.

Often defined as reduced coronary flow (less than thrombolysis in myocardial infarction grade 3) in the absence of a mechanical obstruction in the epicardial coronary artery, angiographic no-reflow indicates reduced myocardial tissue perfusion and is caused by microvascular obstruction [3–6]. Depending on the clinical setting in which angiographic no-reflow occurs, the underlying microvascular obstruction may be attributable to multiple pathophysiologic mechanisms, including reperfusion injury, vasospasm, and embolization of thrombus and plaque components [3–6]. Supporting the concept that embolization of plaque components may precipitate no-reflow, plaque debris, such as necrotic core, inflammatory cells and cholesterol, have been retrieved from distal portions of infarct-related arteries after primary PCI [7,8]. Similar to angiographic no-reflow, periprocedural myocardial infarction may, in some cases, arise directly from embolization of debris from the target plaque during PCI [3–6,9]. Although the definition continues to evolve [10,11], periprocedural myocardial infarction remains commonplace, complicating 3–15% of PCI procedures [5,12]. Importantly, both periprocedural myocardial infarction and angiographic no-reflow have been associated with both short- and long-term mortality [6,13–15].

With embolization of plaque components probably playing a role in many cases of no-reflow and periprocedural myocardial infarction, the susceptibility of patients to suffer from these acute complications during PCI may directly relate to morphologic characteristics of the target plaque. Accordingly, both no-reflow and periprocedural myocardial infarction have been shown to occur with greater frequency when PCI is performed on target lesions having certain morphologic features detectable by advanced imaging. As a result, pre-PCI imaging using advance techniques may play a role in identifying target lesions prone to triggering acute PCI-related complications. The focus of this review is to highlight the ability of advanced imaging techniques, including coronary computed tomographic angiography (CTA), intravascular ultrasound (IVUS), optical coherence tomography (OCT) and near-infrared spectroscopy (NIRS), to assess the risk of acute procedural complications prior to performing PCI.

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Coronary CTA predictors of angiographic no-reflow

Coronary CTA is a noninvasive imaging technique, capable of accurately detecting atherosclerosis, that provides considerable information regarding coronary stenosis severity and plaque morphology [16–18]. Given the advent of coronary CTA as a diagnostic tool to evaluate patients with acute chest pain [19,20], interventionalists may increasingly encounter patients in the catheterization laboratory who have undergone coronary CTA prior to PCI.

Preprocedural coronary CTA imaging may be useful to assess the risk of acute PCI-related complications [21–23]. Accordingly, Kodama *et al.* identified both low-attenuation plaque and circumferential plaque calcification detected by preprocedural CTA to be independently associated with the occurrence of angiographic no-reflow during PCI [21]. Low-attenuation plaque is defined by attenuation <30 HU and plaque calcification is defined by a rim of calcification extending >180° around the periphery of a plaque. Whereas plaque calcification has been hypothesized to increase the risk of plaque rupture and distal embolization by creating a buttress against which angioplasty leads to excessive intraplaque pressure [21], low-attenuation plaque by CTA is thought to increase the risk of PCI-related complications owing to its presumably lipid-rich nature [18,21,24]. Two additional reports have similarly demonstrated low-attenuation plaque by CTA to be associated with angiographic no-reflow during PCI [22,23].

IVUS predictors of angiographic no-reflow & periprocedural myocardial infarction

Current clinical practice guidelines support the use of IVUS to assess lesions of intermediate stenosis severity, to guide coronary stent implantation and to determine the mechanism of stent restenosis or thrombosis [25]. Although not formally addressed by these guidelines, IVUS may be used to image target lesions prior to PCI in order to assess the risk of acute PCI-related complications. Several studies have found that when certain morphologic characteristics of the target lesion are identified by IVUS prior to PCI, there is an increased risk of angiographic no-reflow and periprocedural myocardial infarction during PCI. These morphologic characteristics include attenuated plaque, larger plaque burden, positive remodeling, a lipid pool-like image and intracoronary thrombus.

■ Attenuated plaque by IVUS

Defined by the presence of attenuation of the ultrasound signal in the absence of overlying calcification (Figure 1), attenuated plaque by IVUS has been associated with an increased risk of both angiographic no-reflow and periprocedural myocardial infarction during PCI [26–28]. In acute coronary syndromes (ACS), attenuated plaque at the target lesion is associated with worse thrombolysis in myocardial infarction flow after first balloon inflation [27]. In some cases, this deterioration in thrombolysis in myocardial infarction flow may not improve during the procedure as final coronary flow remains less favorable after PCI is performed on attenuated plaques compared with nonattenuated lesions [27]. In addition to impairing coronary blood flow, attenuated plaques may adversely impact myocardial perfusion and have been associated with worse myocardial blush grades after PCI compared with nonattenuated lesions [27].

In further support of attenuated plaques being associated with an increased risk of PCI-related complications, Kimura *et al.* found attenuated plaque at the target lesion to be the strongest independent predictor of no-reflow [27]; furthermore, Lee *et al.* found attenuated plaque at the target site to be the only independent IVUS predictor of periprocedural myocardial infarction [28]. Although more commonly found in ACS, attenuated plaque has also been described at nonculprit locations in stable patients and at target lesions in stable angina [27–29]. Among patients with stable angina, attenuated plaque at the target lesion has been similarly associated with an increased risk of acute PCI-related complications [27,28].

The connection between attenuated plaque and the occurrence of no-reflow and periprocedural myocardial infarction may be attributable to embolic release of plaque material during PCI. Histologic analysis of atherectomy specimens shows that attenuated plaques are composed of greater amounts of lipid-rich atheromatous tissue and cholesterol clefts compared with nonattenuated plaques [27]. Similarly, attenuated plaques contain more fibrofatty content and necrotic core than nonattenuated plaque as demonstrated by post-mortem analysis of cadaveric hearts [30]. As further evidence of the lipid-rich nature of attenuated plaques, a recent comparison of IVUS and OCT findings demonstrated that nearly 90% of attenuated plaques by IVUS met OCT criteria for being lipid-rich [28].

Whereas the mere presence of attenuated plaque may be associated with acute PCI-related complications, the extent of attenuated plaque,

including the circumferential degree and length of attenuation, may likewise be a marker of PCI-related risk. In patients with ST-segment elevation myocardial infarction, the mean attenuation score, which reflects the circumferential degree of attenuation, was the only IVUS characteristic associated with angiographic no-reflow in an analysis of patients in the HORIZONS-AMI trial [26]. This study showed that an attenuation angle >90° predicted the occurrence of angiographic no-reflow with a sensitivity and specificity that exceeded 80% [26]. Similarly, Shiono *et al.* recently demonstrated that attenuated plaque having an attenuation angle >180° and a length of >5 mm was an independent predictor of microvascular obstruction after primary PCI for ST-segment elevation myocardial infarction, whereas the mere presence of attenuation without consideration for its extent was not associated with PCI-related complications [31].

■ Other grayscale IVUS characteristics

Additional plaque characteristics by IVUS associated with angiographic no-reflow during PCI include larger plaque burden, positive remodeling, intracoronary thrombus and a lipid pool-like image [8,32,33]. A lipid pool-like image is characterized as a localized hypoechoic plaque surrounded by hyperechoic material [8,32,33]. In patients with acute myocardial infarction, Tanaka *et al.* demonstrated that a lipid pool-like image at the culprit site was the strongest independent predictor of no-reflow [8]. However, the study by Tanaka *et al.* did not evaluate for attenuated plaque by IVUS. More recent studies that have assessed lesions for both a lipid pool-like image and attenuated plaque by IVUS have not shown a lipid pool-like image to be a significant independent predictor of periprocedural infarction or angiographic no-reflow by multivariate analysis [26–28].

■ Virtual histology-IVUS predictors of acute PCI-related complications

By using radiofrequency analysis of backscattered IVUS signals, virtual histology (VH)-IVUS provides information regarding plaque composition. VH-IVUS classifies intracoronary plaque using a color-code scheme, wherein fibrotic plaque is displayed as green, fibrofatty plaque as light green, densely calcified plaque as white and necrotic core plaque as red [34].

The impact of the various VH-IVUS plaque types on periprocedural complications during PCI has been extensively studied [35–44]. Although two singular studies have reported no-reflow to occur more frequently in the setting of fibrofatty plaque [35,36], the majority of studies have implicated VH-IVUS necrotic core plaque in PCI-related complications, including angiographic no-reflow [37,38], periprocedural myocardial infarction [39,40] and distal embolization [41]. Importantly, VH-IVUS necrotic core has been linked to these complications in both ACS and in the setting of elective PCI for stable angina [42]. The association between necrotic core plaque by VH-IVUS and PCI-related complications has been further highlighted by a recent systematic review [43] and meta-analysis [44].

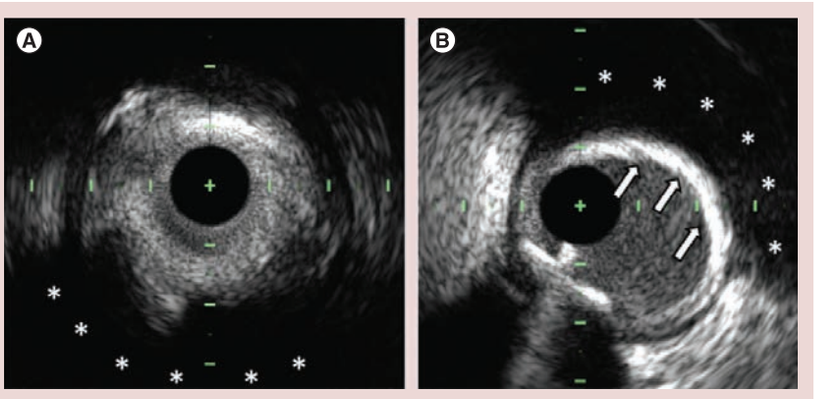

Figure 1. Attenuated plaque by intravascular ultrasound. (A) Attenuated plaque by intravascular ultrasound is shown and is defined by the presence of attenuation of the ultrasound signal (asterisks) in the absence of overlying calcification. **(B)** Attenuation of the ultrasound signal (asterisks) secondary to calcification (arrows) is shown. Attenuated plaque should not be confused with attenuation secondary to calcification.

OCT predictors of periprocedural myocardial infarction & angiographic no-reflow

OCT works on the principle of back reflection of infrared light and produces high-quality images having an axial resolution of 10–20 µm [45–47]. Owing to this superb spatial resolution, OCT provides visualization of structures currently beyond the capabilities of traditional IVUS imaging. Hence, OCT remains the only intracoronary imaging technique with sufficient spatial resolution to visualize the fibrous cap of coronary atheroma. This unique aspect of OCT imaging may be beneficial in evaluating the risk of acute coronary complications during PCI, since OCT-derived thin-capped fibroatheroma (TCFA) requires visualization of the fibrous cap and has been associated with adverse outcomes during stent placement [9,48].

■ OCT-derived TCFA

An OCT-derived TCFA is typically defined as a plaque that is both lipid-rich and has

an overlying thin-fibrous cap (Figure 2). For a plaque to be considered 'lipid-rich' by OCT, most studies have required the presence of a lipid arc involving at least two quadrants in a cross-sectional image, or covering an angle >90° [9,48,49]. These same studies have defined a thin-fibrous cap as one having a thickness of <65 or 70 µm [9,48].

Using time-domain OCT technology, which requires vessel occlusion for image acquisition, Lee *et al.* imaged target lesions prior to PCI to delineate plaque characteristics associated with periprocedural myocardial infarction [48]. Multivariable analysis showed that the presence of OCT-derived TCFA at the target lesion was the strongest independent predictor of periprocedural myocardial infarction [48]. Using frequency-domain OCT technology, which does not require vessel occlusion for imaging and is currently available for clinical use in the USA, Porto *et al.* similarly studied plaque characteristics associated with periprocedural myocardial infarction [9]. Consistent with the findings of Lee *et al.* [48], Porto *et al.* found OCT-derived TCFA to be the only morphologic feature significantly associated with periprocedural myocardial infarction [9]. Taken together, these two studies demonstrate that, when identified at the target lesion prior to PCI, OCT-derived TCFA is associated with periprocedural myocardial infarction in 50–76% of cases [9,48]. Furthermore, these studies provide evidence that OCT-derived TCFA may be associated with an increased risk of periprocedural myocardial infarction in the setting of both ACS and stable angina [9,48].

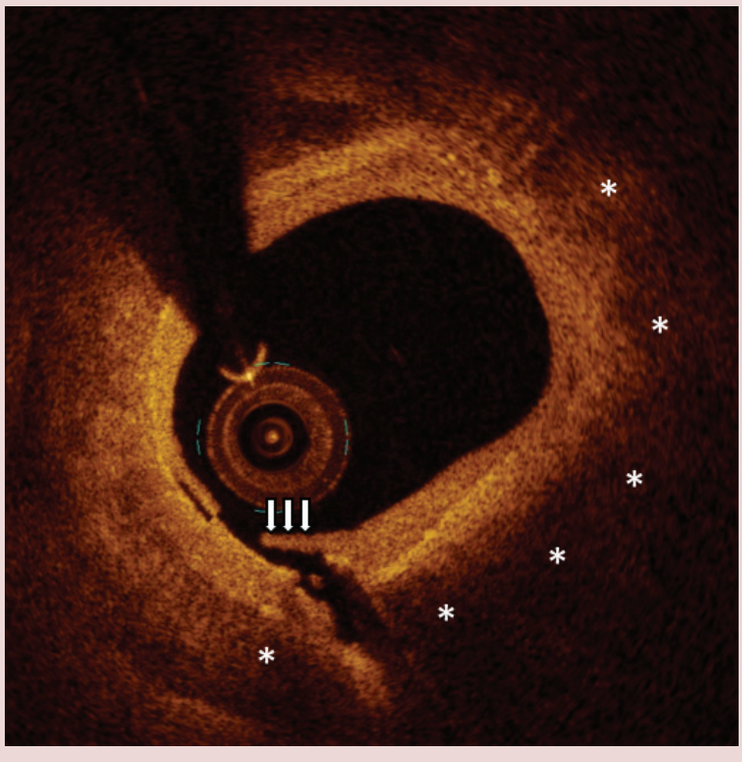

Figure 2. Thin-capped fibroatheroma as defined by optical coherence tomography. An optical coherence tomography-derived thin-capped fibroatheroma is shown and is defined as having lipid (asterisks) with an angle >90° and an overlying thin fibrous cap measuring <65 µm (arrows). In this case, the fibrous cap has ruptured (arrows).

■ Lipid-rich plaque by OCT

Although the presence of a lipid-rich plaque as a standalone variable was not found to be associated with periprocedural infarction in the above studies [9,48], it may be that the quantity of lipid, rather than its mere presence, is a marker of acute complications during PCI. In a study by Tanaka *et al.*, target lesions characterized by OCT as having a lipid arc of 1–90, 91–180 and >180° were associated with angiographic no-reflow in 4.7, 35.0 and 75.0% of cases, respectively [49]. Interestingly, angiographic no-reflow did not occur in any patient in the absence of lipid-rich plaque [49]. By multivariable analysis, the degree of lipid arc was determined to be the only significant predictor of angiographic no-reflow after PCI [49]. Yonetsu *et al.* further highlighted the importance of the lipid arc in a study where increasing arc was associated with a greater frequency of periprocedural myocardial infarction [50]. These observations are congruent with those of IVUS studies that have demonstrated the circumferential extent of attenuated plaque, a potential surrogate marker of the extent of lipid core, to be similarly associated with acute complications during PCI [26,31].

NIRS predictors of periprocedural myocardial infarction

Intracoronary NIRS has been validated to detect the presence of lipid core plaque within the coronary arteries [51,52]. NIRS is performed in a manner analogous to IVUS, in which the NIRS catheter is positioned distal to a region of interest within an artery and an automated pullback is performed, thereby generating a NIRS chemogram (Figure 3) [53]. The NIRS technique is relatively simple to perform and NIRS chemograms are easy to interpret; a yellow color indicates the presence of lipid and red indicates the absence of lipid at any given location [53].

■ Lipid core burden index

Not only can NIRS detect the presence of lipid within the arterial wall but, unlike IVUS and OCT, it is also capable of providing a rapid automated assessment of lipid quantity, reported as the lipid core burden index (LCBI). The LCBI is a metric defined as the fraction of pixels within a region of interest indicating lipid multiplied by 1000 [53–56]. The maximum LCBI in a 4-mm subsegment of the artery (maxLCBI$_{4\,mm}$) has been used to characterize the lipid burden of individual lesions [55,56]. An example of a large lipid core plaque detected by NIRS and its associated LCBI and maxLCBI$_{4\,mm}$ is provided in Figure 3.

Using data from a large multicenter registry, Goldstein *et al.* studied patients with ACS and stable angina undergoing NIRS imaging of the target lesion prior to PCI and found the quantity of lipid within the target lesion to be associated with periprocedural myocardial infarction risk [55]. Consequently, the median maxLCBI$_{4\,mm}$ of target lesions in those suffering from a periprocedural infarction was 592 compared with a median maxLCBI$_{4\,mm}$ of only 219 in those without a periprocedural infarct. In further support of the concept that larger lipid cores are associated with a greater risk of periprocedural infarction, 50% of patients with a maxLCBI$_{4\,mm}$ ≥500 suffered a periprocedural myocardial infarction compared with only 4% of those with a maxLCBI$_{4\,mm}$ <500 [55].

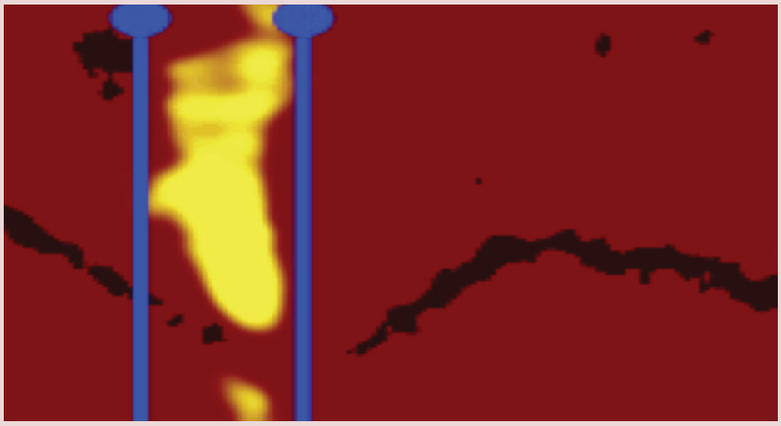

Figure 3. Large lipid core plaque by near-infrared spectroscopy.
A near-infrared spectroscopy chemogram demonstrating a large lipid core plaque (yellow). The x-axis of the chemogram represents the longitudinal position along the length of the artery and the y-axis represents circumferential position around the artery from 0–360°. Whereas red indicates the absence of lipid at that site, yellow (located between the two vertical lines) indicates the presence of lipid. The lipid core plaque between the blue lines has a lipid core burden index of 503 and a maximum lipid core burden index in a 4-mm subsegment of the artery of 784.
Please see color figure at www.futuremedicine.com/doi/pdf/10.2217/ica.13.76

■ Combined NIRS–IVUS imaging

The only intracoronary NIRS imaging technology currently available for clinical use is a combined NIRS and IVUS imaging system [57,58]. Using a single catheter and requiring only one pullback within the artery, this combined system provides coregistered NIRS images with traditional grayscale IVUS images [57,58]. Although NIRS alone is capable of identifying lesions at risk of periprocedural myocardial infarction [55], the combined NIRS–IVUS system, by providing information on lipid quantity and the presence of attenuated plaque, may be particularly well-suited to assess the risk of acute coronary complications during PCI. However, future studies are needed to determine the utility of combined NIRS–IVUS in this regard.

Limitations of pre-PCI plaque characterization

There are several potential limitations to consider with respect to performing intracoronary imaging prior to PCI. First, although the risk of serious complications, such as coronary dissection or inducing plaque rupture with the imaging catheter, is low, coronary spasm has been reported to occur in as many as 1–2% of IVUS cases [59,60]. Owing to this risk of catheter-induced coronary spasm, it is commonplace to administer intracoronary nitroglycerin prior to intracoronary imaging. Second, in the case of OCT, additional intravenous contrast is required for imaging. As a result, OCT carries a risk of contrast-induced acute kidney injury in those with underlying kidney disease; OCT should be used judiciously in such patients. Third, the use of intravascular imaging with OCT, NIRS or IVUS requires the operator to conceptually place the intracoronary imaging findings in the appropriate location within the artery. This process can theoretically lead to geographic miss and may be overcome in the future by the development of imaging systems that automatically coregister the angiographic and intravascular images [61].

Finally, although considerable evidence that intracoronary imaging can identify target lesions at increased risk of inducing no-reflow and periprocedural myocardial infarction, it is unclear whether identification of such 'high-risk' lesions prior to PCI should alter clinical management. The absence of studies demonstrating a clinical benefit to morphologic characterization of the target lesion prior to PCI represents a barrier to widespread adoption of pre-PCI intracoronary imaging. Whereas routine use of distal embolic protection devices in PCI without consideration of underlying plaque morphology is not beneficial [62], a study evaluating the selective use of an

Table 1. Morphologic characteristics of target lesions associated with an increased risk of acute complications during percutaneous coronary intervention.

Modality	Plaque characteristic	Definition	Threshold associated with adverse events	Associated outcomes	Ref.
Coronary CTA	Low-attenuation plaque	<30 HU	Unknown	No-reflow	[21–23]
	Circumferential plaque calcification	Rim of calcium extending >180° around the plaque	Unknown	No-reflow	[21]
IVUS	Attenuated plaque	Attenuation of the ultrasound signal in the absence of overlying calcification	Attenuation angle >180° and length >5 mm	No-reflow and PPMI	[26–28,31]
	Lipid pool-like image	Localized hypoechoic plaque surrounded by hyperechoic material	Unknown	No-reflow	[8,32,33]
VH-IVUS	Necrotic core	Plaque that is displayed as red by VH–IVUS	Unknown	No-reflow and PPMI	[35–44]
OCT	TCFA	Lipid present over an angle >90° and fibrous cap <65 µm	Unknown	PPMI	[9,48]
	Lipid-rich plaque	Lipid present over an angle >90°	Circumferential extent of lipid arc is associated with adverse events	No-reflow and PPMI	[49]
NIRS	$MaxLCBI_{4\ mm}$	Maximum LCBI in a 4-mm coronary segment	$MaxLCBI_{4\ mm} \geq 500$	PPMI	[55]

CTA: Computed tomographic angiography; IVUS: Intravascular ultrasound; LCBI: Lipid core burden index; $MaxLCBI_{4\ mm}$: Maximum LCBI in a 4-mm coronary segment; NIRS: Near-infrared spectroscopy; OCT: Optical coherence tomography; PPMI: Periprocedural myocardial infarction; TCFA: Thin-capped fibroatheroma; VH: Virtual histology.

embolic protection device based upon plaque morphology is underway. The CANARY study, which requires performance of NIRS to evaluate the target lesion prior to PCI, is randomizing patients with large lipid cores by NIRS to a strategy of distal embolic protection or routine care during PCI [101]. Although it is not yet known whether such an approach will reduce the incidence of periprocedural myocardial infarction, similarly designed studies using IVUS and OCT are needed.

Conclusion & future perspective

In summary, IVUS, OCT and NIRS are all capable of identifying target lesions at heightened risk of inducing acute PCI-related complications. The morphologic characteristics most associated with these complications include attenuated plaque by IVUS, necrotic core by VH-IVUS, TCFA by OCT and lipid core plaque by NIRS (Table 1), all of which seemingly indicate the presence of lipid within the target lesion. As underscored by studies with each imaging modality, it is not the mere presence of lipid *per se*, but rather the extent of lipid within the target lesion that may be best associated with the risk of acute PCI-related complications. Interestingly, these same imaging markers have all been identified at culprit sites in ACS [54,56,63–71], which may, in a broader sense, identify plaques that are likely to rupture, whether induced by PCI or occurring spontaneously and thereby triggering acute coronary events or plaque progression [72–76]. The value of advanced coronary imaging to characterize vulnerable plaques with the goal of predicting future acute coronary events has been recently published [77].

Although advanced intracoronary imaging with IVUS, OCT and NIRS are capable of predicting acute PCI-related complications, periprocedural myocardial infarction and angiographic no-reflow continue to occur with considerable frequency in clinical practice. Techniques to prevent these complications at the present time are lacking. Clearly, additional studies are needed to determine whether routine plaque characterization using IVUS, OCT or NIRS prior to PCI can improve the safety of PCI performance. This will probably be achieved through prospective clinical trials in which patients are randomized to protective therapies based on the presence of high-risk intracoronary imaging findings.

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Executive summary

Acute coronary complications during percutaneous coronary intervention

- Acute percutaneous coronary intervention (PCI)-related complications, including angiographic no-reflow and periprocedural myocardial infarction, are often due to embolization of plaque components and are associated with increased short- and long-term mortality.
- The susceptibility of patients to suffer no-reflow and periprocedural myocardial infarction relates to the morphologic characteristics of the target plaque that are detectable by advanced coronary imaging.

Coronary computed tomographic angiography predictors of angiographic no-reflow

- Low-attenuation plaque and circumferential plaque calcification detected by coronary computed tomographic angiography are independently associated with angiographic no-reflow during PCI.

Intravascular ultrasound predictors of angiographic no-reflow & periprocedural myocardial infarction

- Attenuated plaque by intravascular ultrasound (IVUS), which is probably a marker of lipid-rich plaques, is independently associated with an increased risk of both angiographic no-reflow and periprocedural myocardial infarction during PCI.
- Additional IVUS characteristics associated with angiographic no-reflow include a large plaque burden, positive remodeling, intracoronary thrombus and a lipid pool-like image.
- Necrotic core plaque by virtual histology-IVUS is independently associated with angiographic no-reflow and periprocedural myocardial infarction.

Optical coherence tomography predictors of periprocedural myocardial infarction & angiographic no-reflow

- Optical coherence tomography-derived thin-capped fibroatheroma is independently associated with the occurrence of periprocedural myocardial infarction.
- It is not the mere presence of lipid-rich plaque *per se*, but rather the degree of the lipid arc by optical coherence tomography that is associated with periprocedural myocardial infarction.

Near-infrared spectroscopy predictors of periprocedural myocardial infarction

- Unlike IVUS and optical coherence tomography, near-infrared spectroscopy is capable of providing a rapid automated assessment of lipid quantity reported as the lipid core burden index, which is defined as the fraction of pixels within a region of interest indicating lipid multiplied by 1000.
- A maximum lipid core burden index in a 4-mm subsegment of the artery ≥500 is associated with a 50% rate of periprocedural myocardial infarction during PCI.
- Although near-infrared spectroscopy alone is capable of identifying lesions at risk of periprocedural myocardial infarction, the combined near-infrared spectroscopy–IVUS system, by providing information on lipid quantity and the presence of attenuated plaque, may be particularly well-suited to assess the risk of acute coronary complications during PCI.

Limitations of pre-PCI plaque characterization

- The risk of serious complications imposed by pre-PCI intracoronary imaging is low.
- Although intracoronary imaging can identify target lesions at increased risk of inducing no-reflow and periprocedural myocardial infarction, it is currently unclear how identifying high-risk plaque morphology prior to PCI could alter clinical management.

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