Intravascular ultrasound (IVUS) has played a critical role in understanding the pathophysiology of coronary atherosclerosis and has facilitated the refinement of diagnostic and therapeutic strategies. In vitro and in vivo observations have highlighted discrepancies between contrast angiography (a two-dimensional silhouette) and IVUS (cross-sectional tomographic perspective and direct visualization of the vessel wall) and have led to a reappraisal of the relative strengths and weaknesses of contrast “luminology” (1). Specifically, insights into the mechanisms of percutaneous coronary intervention (PCI), as well as identification of the complications of the various approaches to percutaneous revascularization, including acute and subacute vessel closure and restenosis, have facilitated the refinement of these treatment strategies. However, the role of IVUS guidance of PCI in the contemporary era of routine coronary stent implantation remains controversial and is subject to continuing debate. This review outlines the evidence in support of routine IVUS guidance of coronary implantation and places it in the context of contemporary clinical practice.

IVUS AND CONTEMPORARY STENT TECHNIQUES

Early in vivo applications of IVUS. Cross-sectional IVUS imaging before and after balloon angioplasty has demonstrated the anatomic boundaries of the intima, media, and adventitia and has characterized the morphology of atherosomatic plaque (2,3). Furthermore, qualitative characteristics of injury from balloon dilation, atherectomy, and stent implantation, including plaque disruption, dissection, and intimal flaps, have been defined and correlated with angiographic, procedural, and clinical outcomes (4–8).

Refinement of coronary stent technique and periprocedural drug treatment. After presentation and publication of the BElgium NEtherlands Stent (BENESTENT) and STent REStenosis Study (STRESS) trials, routine coronary stent implantation became increasingly popular (9,10). However, the incidence of subacute closure (stent thrombosis) and major bleeding, due to the intensive anticoagulation regimen, was unacceptable and limited the initial clinical applicability of IVUS. High-pressure stent deployment with IVUS guidance, as well as treatment with dual antiplatelet therapy (aspirin and ticlopidine), in preference to systemic anticoagulation, established the safety and efficacy of this alternative treatment strategy and expanded the role of routine elective coronary stent implantation in clinical practice (11). Subsequently, similar results with this strategy (high-pressure stent deployment and dual antiplatelet therapy) were also achieved without IVUS guidance (12,13).

In-stent restenosis. Intravascular ultrasound has also played an important role in establishing the mechanisms of in-stent restenosis. Restenosis after balloon angioplasty is largely driven by concentric geometric remodeling, with neointimal hyperplasia playing a lesser role; however, in-stent restenosis is almost exclusively the consequence of exuberant neointimal proliferation (14). In a serial ultrasound study of the patterns and mechanisms of in-stent restenosis, late lumen loss within stents correlated strongly with tissue growth (neointimal tissue accumulation, r = 0.975, p < 0.001), but only weakly with stent recoil (r = 0.2, p < 0.001) (15). These in vivo IVUS observations were instrumental in the development of strategies to treat in-stent restenosis, including intracoronary brachytherapy,
but most importantly they led to the development of drug-eluting stents (DES), which appear to have dramatically reduced neointimal proliferation and the incidence of in-stent restenosis and may also replace intracoronary brachytherapy as the preferred treatment for in-stent restenosis (16).

**OPTIMIZING THE RESULTS OF BALLOON ANGIOPLASTY: THE SIPS STUDY AND THE BEST TRIAL**

The IVUS-guided optimization of balloon angioplasty results (with provisional stenting) has also been investigated as an alternative to routine stenting. The Strategy for Intracoronary ultrasound-guided PTCA and Stenting (SIPS) trial randomized 269 patients to IVUS-guided or angiography-guided balloon angioplasty with provisional stent implantation (17). Approximately 50% of patients in each group received a stent at the time of the index procedure. Acute gain was greater in the IVUS-guided group than in the angiography-guided group, but angiographic six-month follow-up revealed no difference in the primary end point of minimum lumen diameter (MLD) or the secondary end points of binary restenosis rate and short-term or two-year major adverse cardiac events (death, myocardial infarction [MI], or target vessel revascularization [TVR]). However, clinical follow-up (602 ± 307 days) showed a significant decrease in clinically driven TVR in the IVUS group compared with the angiography group (17% vs. 29%, p = 0.02).

The Balloon Equivalent to STent (BEST) study randomized 254 patients to either “aggressive” IVUS-guided balloon angioplasty (with provisional stenting) or routine angiography-guided stent implantation (18). Approximately 44% of patients in the balloon angioplasty group required adjunctive stent implantation. At six months, 20 of 119 patients in the aggressive balloon angioplasty group and 21 of 116 patients in the routine stent implantation group had restenosis, fulfilling the prespecified criteria for noninferiority. Similarly, there were no statistically significant differences in the MLD or lumen cross-sectional area at six months or one-year clinical event rates.

The results of these two studies suggest that IVUS-guided balloon angioplasty may be an acceptable alternative to routine stenting (feasible, safe, and noninferior), but this approach is certainly more time-consuming and requires meticulous attention to detail and expertise in IVUS image acquisition and interpretation. Furthermore, it is apparent from both these studies that the crossover rate is high, with ~50% of patients requiring adjunctive stent implantation, negating much of the anticipated cost-savings, particularly in the contemporary era of falling prices of bare-metal stents. The realities of clinical practice have therefore resulted in widespread adoption of a strategy of routine stent implantation in preference to balloon angioplasty with provisional stent implantation (19).

**ROUTINE IVUS-GUIDED CORONARY STENT IMPLANTATION: THE EVIDENCE**

Several studies have demonstrated that IVUS is better than contrast angiography at defining post-deployment stent dimensions, confirming complete stent apposition, and excluding edge dissections—all important procedural variables that may predispose to both early and late complications, including in-stent restenosis (Table 1). Specifically, several small, single-center studies have identified IVUS measurement of minimum stent area as the most powerful predictor of long-term patency and clinical outcomes (20,21). However, it has been more difficult to prove this putative clinical benefit utilizing more rigorous research methodology.

**Observational and case-control studies: MUSIC, CRUISE, and others.** The Multicenter Ultrasound Stenting In Coronaries (MUSIC) study established the safety and feasibility of IVUS-guided stent implantation (22). A total of 161 patients were prospectively enrolled, 155 of whom underwent an IVUS examination. During the follow-up period (198 ± 38 days), one patient (0.6%) suffered a Q-wave MI, one patient (0.6%) underwent bypass surgery, and seven patients (4.5%) had repeat target lesion revascularization. Repeat angiography at six months was performed in 144 patients (92%), and angiographic restenosis (percent diameter stenosis ≥50%) was documented in 12 patients (8.3%), 2 of whom required repeat PCI for stent thrombosis, so the cumulative angiographic restenosis rate was 9.7%. This compared favorably with historical controls and was regarded as proof of both the safety and feasibility of this interventional strategy.

Similarly, Fitzgerald et al. (23) enrolled 525 patients as a subset of the larger Stent Antithrombotic Regimen Study (STARS)—the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. The use of IVUS was assigned on a center-by-center basis; 16 of 45 STARS study centers were chosen for their experience with IVUS. In the seven centers that performed only angiography-guided percutaneous intervention, a blinded documentary IVUS study was performed on completion of the procedure. No optimal IVUS-determined stent criteria were prespecified. The IVUS group achieved a larger MLD by quantitative coronary angiography and a larger minimum stent area by quantitative coronary ultrasound, and these differences were
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Characteristics and Study Design</th>
<th>Primary End Point(s)</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRUISE, Fitzgerald et al., 2000 (23)</strong></td>
<td>Case-control study, 525 patients, IVUS-guided vs. angiography-guided stent implantation</td>
<td>Postprocedural MLD by QCA (diameter) and IVUS (area, diameter)</td>
<td>MLD: 2.9 ± 0.4 mm (IVUS) vs. 2.7 ± 0.5 mm (angiography), p &lt; 0.001; stent area: 7.78 ± 1.72 mm² (IVUS) vs. 7.06 ± 2.13 mm² (angiography), p &lt; 0.001</td>
<td>TVR: 8.5% (IVUS) vs. 15.3% (angiography), p &lt; 0.05; death: 0% (IVUS) vs. 1% (angiography), p = NS; MI: 7% (IVUS) vs. 6% (angiography), p = NS; death/MI/TVR: 12.6% (IVUS) vs. 21.4% (angiography), p = 0.09</td>
</tr>
<tr>
<td><strong>Albiero et al., 1997 (24)</strong></td>
<td>Case-control study, 346 patients, IVUS-guided (Milan) vs. angiography-guided (Hamburg) stent implantation</td>
<td>Dichotomous angiographic restenosis (≥50% DS)</td>
<td>Restenosis, early phase: 9.2% (IVUS) vs. 22.3% (angiography), p = 0.04; restenosis, late phase: 22.7% (IVUS) vs. 23.7% (angiography), p = 1.0</td>
<td>TLR: 7% (IVUS) vs. 11.7% (angiography), p = 0.17; high complication rate in early (aggressive dilation) phase</td>
</tr>
<tr>
<td><strong>RESIST, Schiele et al., 1998 (26)</strong></td>
<td>RCT, 155 after stenting patients randomized to group A (no further dilation) and group B (further dilation to achieve IVUS criteria)</td>
<td>Six-month angiographic restenosis (&gt;50% DS)</td>
<td>Angiographic restenosis: 28.8% (group A) vs. 22.5% (group B), p = 0.25</td>
<td>18-month death/MI/TLR: 37% (group A) vs. 25% (group B); OR 1.7, 95% CI 0.82–3.63</td>
</tr>
<tr>
<td><strong>AVID, Russo et al., 1999 (28)</strong></td>
<td>RCT, 759 patients, IVUS-guided vs. angiography-guided stent implantation</td>
<td>“Clinical outcomes”</td>
<td>Death: 0.3% (IVUS) vs. 0.6% (angiography), p = 0.39; MI: 8.9% (IVUS) vs. 5.2% (angiography), p = 0.07; CABG: 3.1% (IVUS) vs. 3.2% (angiography), p = 0.92</td>
<td>TLR, small vessels (≤3.25 mm): 7.9% (IVUS) vs. 14.6% (angiography), p = 0.04; TLR, SVG PCI: 5.7% (IVUS) vs. 20.4% (angiography), p = 0.05</td>
</tr>
<tr>
<td><strong>OPTICUS, Mudra et al., 2001 (29)</strong></td>
<td>RCT, 550 patients, IVUS-guided vs. angiography-guided stent implantation</td>
<td>Six-month angiographic restenosis (&gt;50% DS), MLD, and %DS</td>
<td>Restenosis: 24.5% vs. 22.8%, p = 0.68; MLD: 1.95 ± 0.72 mm vs. 1.91 ± 0.68 mm, p = 0.52; %DS: 34.8 ± 20.6% vs. 36.8 ± 19.6%, p = 0.29</td>
<td>MACE: RR 1.07, 95% CI 0.75–1.52, p = 0.71; repeat PCI: RR 1.04, 95% CI 0.64–1.67, p = 0.87</td>
</tr>
<tr>
<td><strong>TULIP, Oemrawsingh, et al., 2003 (30)</strong></td>
<td>RCT, 144 patients, stenosis &gt;20 mm, stent diameter ≥3.0 mm; IVUS-guided vs. angiography-guided stent implantation</td>
<td>Six-month MLD and MACE (death/MI/TLR)</td>
<td>MLD: 1.82 ± 0.53 mm (IVUS) vs. 1.51 ± 0.71 mm (angiography), p = 0.042; MACE: 23% (IVUS) vs. 27% (angiography), p = 0.026</td>
<td>Benefit in this specific patient population (long stenoses in large vessels)</td>
</tr>
</tbody>
</table>

AVID = Angiography Versus Intravascular ultrasound Direct stent implantation; CABG = coronary artery bypass grafting; CI = confidence interval; CRUISE = Can Routine Ultrasound Influence Stent Expansion; DS = diameter stenosis; IVUS = intravascular ultrasound; MACE = major adverse cardiac events; MI = myocardial infarction; MLD = minimum lumen diameter; OPTICUS = Optimization with ICUS to reduce stent restenosis; OR = odds ratio; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RCT = randomized, controlled trial; RESIST = Restenosis after IVUS guided Stenting; RR = relative risk; SVG = saphenous vein graft; TLR = target lesion revascularization; TULIP = Thrombocyte activity evaluation and effects of Ultrasound guidance in Long Intracoronary stent Placement; TVR = target vessel revascularization.
associated with a 44% reduction in the rate of target vessel revascularization (TVR) at nine months, but there was no difference in mortality or MI nor the secondary end point—a composite of death, MI, and TVR (Table 1).

Although part of a large, randomized, controlled trial (STARS), this analysis is an observational study with a control group drawn from the same study population (STARS) and is therefore subject to all of the limitations of this study design. Most importantly, there were statistically significant differences in the prevalence of single- and multi-vessel disease, and, despite statistical adjustment for these and other differences between the two groups, residual confounding cannot be excluded. The results of this study should be regarded as provocative (hypothesis-generating), but certainly not definitive.

A similar case-control methodology was employed by Albiero et al. (24), who matched 173 patients who were treated with IVUS-guided Palmaz-Schatz stent implantation at a single center (Milan, Italy) with 173 patients treated by angiography-guided Palmaz-Schatz stent implantation at a different center (Hamburg, Germany). Immediate and six-month angiographic results were retrospectively compared, thus distinguishing an “early phase” from a “late phase”; this distinction was based on the more aggressive dilation strategy with larger balloons and more demanding IVUS criteria for optimal stent expansion used in Milan (IVUS center) in the early phase. In both phases, a larger MLD immediately after stent implantation, as well as after six months, was achieved in the IVUS group compared with the angiography group. In the early phase, the dichotomous restenosis rate was lower in the IVUS group than in the angiography group. However, a high procedural complication rate and a high incidence of intracoronary vessel rupture were observed, possibly related to the use of oversized balloons (25). In the late phase, there was no difference in the dichotomous restenosis rate between the groups, and the incidence of repeat revascularization was not significantly different between the two groups. The results of this analysis were similarly provocative, suggesting a lower angiographic restenosis rate, but must be interpreted within the context of the limitations of this study design.

Randomized, controlled clinical trials: RESIST, AVID, OPTICUS, and TULIP. The RESStenosis after IVUS-guided STenting (RESIST) trial randomized 155 patients to IVUS- or angiography-guided coronary stent implantation (26). At six months, there was a significant difference in minimum cross-sectional lumen diameter, favoring the IVUS group, but no difference in MLD or angiographic restenosis (Table 1). A second cost-effectiveness analysis reported 18-month clinical outcomes: death, MI, or target lesion revascularization occurred more frequently in the angiography group than in the IVUS group (37% vs. 25%, odds ratio 1.7, 95% confidence interval 0.82 to 3.63), but this did not reach statistical significance (27).

Similarly, the Angiography Versus Intravascular ultrasound Direct stent placement (AVID) trial randomized 759 patients who had undergone coronary stent implantation with an optimal angiographic result with IVUS-guided direct coronary stent implantation or angiography-guided direct coronary stent implantation (28). A blinded documentary IVUS study was performed on completion of the angiography-guided procedure. The IVUS criteria for optimal stent deployment was percent area stenosis <10%, absence of dissection, and complete stent apposition. At 12 months, there was no significant difference in the cumulative rate of death, MI, or coronary artery bypass graft surgery (Table 1). The results of a number of retrospective subgroup analyses have been presented, documenting lower TLR rates in patients with vessels \( \geq \)3.25 mm and saphenous vein graft interventions, but these data are subject to all of the limitations of such retrospective analyses and should be interpreted with caution.

The OPTimization with ICUS to reduce stent restenosis (OPTICUS) trial randomized 550 patients to IVUS-guided or angiography-guided coronary stent implantation (29). At six months, repeat angiography revealed no significant differences between the groups with respect to the dichotomous restenosis rate, MLD, or percent diameter stenosis (Table 1). At 12 months, neither the incidence of major adverse cardiac events nor repeat PCI was reduced in the IVUS group.

Finally, the Thrombocyte activity evaluation and effects of Ultrasound guidance in Long Intracoronary stent Placement (TULIP) trial randomized 144 patients with long coronary lesions (>20 mm) and a reference vessel diameter \( \geq \)3.0 mm to IVUS- or angiography-guided coronary stent implantation (30). This trial documented significant reductions in the incidence of both TLR alone and the combined end point of death, MI, and TLR (Table 1).

As documented, there is heterogeneity with respect to the patient populations, study methodologies, and results of the aforementioned studies and trials of IVUS- versus angiography-guided PCI. Although there is a trend toward a benefit with respect to TLR favoring IVUS-guided coronary stent implantation, it is likely that this effect is driven by improved outcomes in small vessels, long coronary stenoses, and possibly saphenous vein graft interventions, as suggested by the retrospective subgroup analyses of the AVID trial and the results of the TULIP trial. No consistent trend in the incidence of death or MI is apparent. Routine IVUS guidance of all elective procedures is not supported by the results of the RESIST, AVID, and OPTICUS trials, although each is underpowered to detect small differences in the prespecified study end points. Furthermore, interpretation of both the RESIST and AVID trials is limited by incomplete reporting of the study design and methodology (AVID); patient, angiographic, and procedural characteristics (AVID); and procedural and clinical outcomes (AVID and RESIST).

Efficacy versus effectiveness. The aforementioned clinical trials provide us with evidence that addresses the efficacy (likelihood of beneficial outcome of a particular intervention
under optimal or ideal experimental conditions) of IVUS-guided stent implantation, but they do not address the issue of effectiveness (likelihood of beneficial outcome of a particular intervention under usual and routine conditions). The widespread clinical application and expected effectiveness of IVUS-guided coronary stent implantation is likely to be limited by a number of factors, including the cost of the ultrasound catheter, the additional time to perform serial IVUS examinations, and the availability of appropriately trained personnel capable of accurately acquiring and interpreting the images. It may also prove difficult to advance the ultrasound catheter through a deployed stent, and there are isolated reports of stent damage attributable to the ultrasound catheter (31). Finally, although generally regarded as a safe procedure, IVUS is associated with clinically relevant complications, including coronary spasm (2.9%) and dissection, thrombosis, and acute occlusion (0.4%) (32). The complication rate appears to be highest in patients with unstable angina or acute MI (2.9%), as compared with patients with stable angina pectoris and asymptomatic patients (0.8 and 0.4%, respectively; p < 0.01). In an era of significant improvements in procedural safety (33), this limitation may assume greater significance in future analysis of the relative merits of IVUS-guided stent implantation.

ANATOMIC VERSUS PHYSIOLOGIC PARAMETERS TO DETERMINE OPTIMAL STENT IMPLANTATION

An alternative to contrast angiography and IVUS for the determination of optimal stent deployment is measurement of fractional flow reserve (FFR). This is defined as the maximum blood flow to the myocardium achieved in the presence of a narrowing, compared with the theoretical maximum blood flow possible in the absence of a narrowing. It is a physiologic parameter that is an easily obtainable, accurate, and lesion-specific index of the functional severity of coronary stenosis, and it has been correlated with a variety of conventional noninvasive tests of myocardial ischemia in patients with intermediate coronary lesions (34–37). Conversely, it has been proposed that after optimal stent deployment, no hyperemic gradient should persist across the treated segment.

The FFR index has been compared with IVUS as a measure of optimal stent deployment (38). An FFR $\geq 0.94$ was retrospectively defined by receiver-operating characteristics curve analysis as the physiologic measure of optimal stent deployment; this corresponds exactly to the lower limit of the normal range, as found in earlier studies. Concordance between both techniques was present in 91% of all observations, and the investigators concluded that the usefulness of coronary pressure measurement to guide stent implantation was comparable to IVUS. However, a second study that compared FFR after stent implantation with standard IVUS criteria for optimal stent deployment concluded that an FFR $<0.96$, measured after stent deployment, predicts suboptimal results, based on these aforementioned, validated IVUS criteria, but that an FFR $\geq 0.96$ does not reliably predict optimal stent results (39). However, interpretation of these results is confounded by a number of limitations, including the use of intracoronary (vs. intravenous) adenosine and the absence of a slow pullback across the diseased segment to exclude significant (but angiographically undetected) stenoses occurring outside the stented segment. Furthermore, the results of both studies should be interpreted in the context of concerns regarding the sensitivity of FFR to detect subtle differences in distal coronary pressure that fall within the normal range, as is the case after stent deployment.

Coronary pressure measurement and the FFR index have also been correlated with the incidence of adverse events after both balloon angioplasty and stent implantation. Bech et al. (40) evaluated pressure-derived myocardial FFR in 60 patients after conventional balloon angioplasty and concluded that in patients with a residual percent diameter stenosis $\leq 35\%$ and FFR $\geq 0.90$, the clinical outcome up to two years is excellent and significantly better than in those patients in whom the angiographic or functional result, or both, were suboptimal (88 ± 6% vs. 59 ± 9%, p = 0.014). Similarly, in a multicenter registry, Pijls et al. (41) investigated the relationship between optimal stent implantation (FFR) and outcome at six months. A post-stent FFR $>0.90$ was associated with a low rate of the composite end point of death, MI, or TVR at six months (28 [5.5%] of 507 patients), compared with an incidence of 10.2% for the total study population (final FFR range 0.75 to 1.00). The lowest event rate (4.9%) was seen in patients in whom the FFR became normalized (FFR $= 0.96$) after stent implantation. These findings are at least comparable with published estimates of major adverse cardiac events after IVUS-guided coronary stent implantation. For example, the OPTICUS investigators reported a six-month incidence of the composite end point of death, MI, or TVR of 14.3% in the IVUS arm of this randomized, controlled trial (29).

There are obvious problems with making the aforementioned comparisons between the results of randomized, controlled trials and a multicenter registry, and these findings should be regarded as provocative and hypothesis-generating, but not definitive proof of the relative merits of either treatment strategy. First, there is no definitive evidence (randomized, controlled trial) that adjunctive measurement of post-stent FFR results in improved clinical outcomes compared with standard angiography-guided PCI. Second, it might be argued that IVUS-guided stent implantation is the “gold standard,” and that a direct comparison of this strategy with an FFR-guided strategy is necessary. Finally, it should be remembered that coronary pressure measurement, in contrast to IVUS, does not elucidate the cause of suboptimal stent deployment. It is reasonable to conclude that, in some cases, these two diagnostic modalities are complementary and not mutually exclusive.
DRUG-ELUTING STENTS:
LIMITING IN-STENT RESTENOSIS

The reported differences in IVUS- versus angiography-guided coronary stent implantation in the CRUISE study and the TULIP trial were driven by differences in the incidence of TVR (23,30). The results of the SIRIUS (A Multicenter, Randomized, Double-Blind Study of the Sirolimus-Coated BX Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions) and TAXUS (A Randomized, Double-blind Trial to Assess TAXUS Paclitaxel-Eluting Coronary Stents, Slow-Release Formulation in the Treatment of High Risk De Novo Coronary Lesions) trials have demonstrated dramatic reductions in the incidence of in-stent restenosis after implantation of rapamycin- and paclitaxel-coated stents, respectively, and this now further undermines the clinical applicability of the reduction in the incidence of TVR seen when IVUS guidance of bare-metal stent procedures is performed (42).

However, IVUS continues to provide important insights into the effects of DES on neointimal proliferation and vascular healing. For example, it has been suggested that the inhibition of neointimal proliferation after implantation of a DES, perhaps exacerbated by post-procedural positive remodeling, may result in late stent malapposition that exceeds the background incidence of this finding after bare-metal stent implantation (43). This was noted in the IVUS substudy of the RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial (44), which identified a 21% incidence of late stent malapposition in the sirolimus group, but was not associated with stent thrombosis or other adverse clinical sequelae in this trial. More recently, further concerns regarding the incidence of subacute closure after DES implantation have been raised, prompting the U.S. Food and Drug Administration to issue a public health web notification (45). However, an increase in the incidence of subacute thrombosis has not been a consistent finding in either the treatment arms of the various randomized, controlled trials of sirolimus or paclitaxel DES or published data from observational registries (46–48). Nevertheless, this controversy has prompted many to urge particular attention to optimizing the procedural technique with DES implantation; for this, IVUS is exceedingly valuable (49).

Similarly, IVUS has provided insight into the morphologic patterns and possible causes of restenosis after sirolimus-eluting stent implantation. Lemos et al. (50) analyzed the angiograms (and IVUS studies, if available) of 19 patients (20 lesions) who had angiographic evidence of restenosis after implantation of a sirolimus-eluting stent (percent diameter stenosis >50%). Edge restenosis was frequently associated with local trauma outside the stent, and in-stent restenosis was commonly focal and occurred in association with an area of discontinuity with the DES. The authors concluded that TVR in patients after implantation of a sirolimus-eluting stent was most likely to be the result of local factors and not related to intrinsic drug resistance, information which is likely to influence future developments in stent design, polymer and drug pharmacokinetics, and stent implantation techniques.

“NICHE” INTERVENTIONAL APPLICATIONS OF IVUS

“Niche” IVUS applications have been described. Left main coronary stenoses are notoriously difficult to characterize, and IVUS may be useful in accurately defining the cross-sectional area. There is no consensus regarding the cross-sectional area at which the left main obstruction is considered critical, but a stenosis area >50% or an absolute area <9 mm² has been proposed (51). Similarly, FFR has been used as an adjunct to contrast angiography in this complex group of patients (52).

Transplant coronary artery disease may be particularly difficult to characterize using contrast angiography alone, because it is a diffuse process, and there is no true “normal” reference segment. Therefore, IVUS is useful for the identification of intimal thickening (>0.5 mm)—the hallmark of transplant vasculopathy—and serial ultrasound surveillance studies have demonstrated an association between the severity of transplant vasculopathy and clinical outcomes (53).

Intravascular ultrasound has also been widely utilized to characterize eccentric plaque and to plan debulking procedures. Studies have clearly demonstrated that contrast angiography does not accurately identify the distribution of plaque, and that IVUS is more accurate at guiding selective plaque removal (atherectomy) (54). Similarly, differentiating between superficial (intimal) and deep calcium deposits may be important when planning debulking procedures: rotational atherectomy is most appropriate when calcification is superficial, thus facilitating differential cutting (55). Directional atherectomy may be impossible in this group of patients (superficial calcification) but is most appropriate for eccentric lesions, with or without deep calcification (56,57).

Future challenges in the field of interventional cardiology include characterization of vulnerable plaque. A number of IVUS studies have attempted to characterize the appearance of lipid-laden plaque—the atherosclerotic lesion thought to be at greatest risk of rupture, thus exposing the highly thrombogenic components of the subendothelium and lipid core and initiating coronary thrombosis. Studies have compared the ultrasound appearance of plaques to histologic studies of freshly explanted human arteries (58). Lipid-laden lesions appear hypoechoic; fibromuscular lesions generate low-intensity echoes; and fibrous or calcified tissues are relatively echogenic. However, although IVUS is certainly accurate in determining the thickness and echogenicity of vessel wall structures, these findings do not consistently correlate with tissue histology, and alternative diagnostic modalities may prove to be superior to even
contemporary high-resolution IVUS for the detection of vulnerable plaque (59).

CONCLUSIONS

Intravascular ultrasound has played an integral role in the evolution of interventional cardiology. Specifically, IVUS has demonstrated the effects of balloon angioplasty and helped to elucidate the mechanisms of both vessel injury and healing. Similarly, the problem of stent thrombosis was largely solved by clinical evaluation of IVUS-guided, high-pressure stent deployment and dual, oral antiplatelet therapy, and the mechanisms of in-stent restenosis were demonstrated by serial IVUS examinations—insights that have contributed to the development of intracoronary brachytherapy and DES. There is every reason to believe that IVUS will continue to play a critical role in the development of interventional techniques and provide further insights into the pathophysiology of coronary artery disease; IVUS guidance of DES implantation may be of particular importance. However, routine IVUS guidance of coronary stent implantation is not supported by this critical reappraisal of the available evidence, and the safety, efficacy, and effectiveness of this imaging technology should be taken into account when considering the goals, risks, benefits, and alternatives to such a treatment strategy.

Reprint requests and correspondence: Dr. David R. Holmes, Cardiovascular Diseases and Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: dholmes@mayo.edu.

REFERENCES


