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The Role of Imaging in Disease Detection and Treatment

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There is no doubt that intravascular ultrasound (IVUS) provides information that a luminogram obtained through angiography just simply cannot provide. Not only can the artery wall be visualized, but changes in plaque volume can be accurately measured with IVUS. There are many examples of cases where angiography would have misled the clinician because there is value in looking at the arterial wall over and above looking at the changes in the lumen. In fact, the change over time in plaque burden correlates much more closely with the remodeling over time than with the lumen. Negative remodeling (reduction in total vessel volume resulting from plaque volume decreases) can lead to the underestimation of change in plaque burden, if you are just looking at the lumen either on IVUS or on the angiogram. In fact, we also show that this negative remodeling process is much more marked in patients that have positive remodeling to start with. Due to IVUS imaging, we now understand that adaptive remodeling can accommodate plaque burden until approximately 40% of the total vessel size is occupied by plaque. Vascular remodeling is a bidirectional phenomenon and those individuals that get more negative remodeling are those that initially had more positive remodeling.

Quantitative coronary angiography (QCA) but not IVUS has been used by FDA, Health Canada, EMEA and other agencies to approve drugs or gain new indications. This is probably true for a couple of reasons. First of all, QCA has been around for a longer period of time. Correlations between "on treatment" LDL levels and angiographically demonstrated rate of change have been demonstrated. What we also have with QCA that we don't quite have yet with IVUS is a study to show that the rates of changes correlate with future cardiovascular events. With QCA progression or non-progression as determined by QCA was correlated with future cardiovascular events. I think that when the predictive ability of IVUS is demonstrated more people will be convinced of the potential value of IVUS.

Currently we have a fair amount of compelling data which demonstrates the utility of IVUS. Von Birgelen and colleagues published data a couple of years ago where they showed that patients experiencing cardiovascular events had much higher rates of change in plaque burden over time as measured by IVUS. This study also showed the relationship between left main coronary plaque progression and cardiovascular risk

factors such as high LDL and low HDL. So we do have some data, but we need more of that kind of data to convince us of the prognostic value and the link between known biomarkers and IVUS as a biomarker. As far as data linking rate of change on IVUS with clinical outcomes, I think we have indirect evidence. One piece of evidence we have comes from the REVERSAL study. REVERSAL compared atorvastatin 80mg to pravastatin 40 mg. and showed persistent progression of atherosclerosis with pravastatin 40 as compared with a halting of progression with atorvastatin 80. These are the same two statins at the same two dosages that were used in the PROVE-IT trial which demonstrated that intensive lipid lowering was associated with better outcomes. Again, these are not the same patients and not the same study, but I think this does provide further evidence of a link between IVUS and clinical outcomes.

Another point I want to make is about endpoint selection with IVUS. Many people believe that percent atheroma volume (PAV) is the best endpoint. My view is that PAV is one good endpoint but I do not think that this should be a religion. There are basically three ways of looking at change of plaque using IVUS. One is very simple, and I think adds a lot of value. If you want to see if a given drug has an effect on plaque, you can simply look at plaque burden at the beginning and at the end of the experiment, which is absolute change in plaque burden. The other way measuring effect is by dividing absolute change by plaque burden at the baseline, which is percent change in atheroma volume. The third way to measure effect is by evaluating PAV, which is basically dividing atheroma burden or volume by total vessel size. So if you think about it, PAV could theoretically change without any change in plaque burden if you have positive remodeling. PAV could be dependent on how much adaptive remodeling has occurred. It is not a paradox. You just need to understand what we are computing. When deciding which IVUS endpoint to use in a clinical trial, you should probably think in terms of what is known about the pre-clinical effect of the drug on both plaque burden and vascular remodeling.

IVUS is a useful tool to apply in Phase 2 studies. One example of the use of IVUS in Phase 2 is in the development of the acylCoA:cholesterol acyltransferase (ACAT) inhibitor, avasimibe. A-PLUS, the IVUS study designed to evaluate avasimibe using IVUS, included three different dosages of that drug to try to determine the dose response relationship. In A-PLUS, all patients received statin therapy with the addition of placebo or avasimibe. The results of this trial informed us that the addition of avasimibe did not cause a favorable effect on plaque burden, probably due in part to interactions between statins and avasimibe. This demonstrated an effective use of IVUS in a Phase 2 study to better understand the drug and determine whether or not to proceed with development. The CART study was also a good example of successful application of IVUS in Phase 2 where the treatment effect with AGI-1067 was evaluated, followed by further development consisting of a large endpoint trial, the ARISE study. With the completion of ARISE, along with results obtained with the cholesterol ester transport protein (CETP) inhibitor torcetrapib, both programs in which there are outcome and imaging trials, it will be extremely important to understand the results and potential correlations between biomarkers and outcomes.

Finally, I would like to suggest that IVUS has utility in validating other biomarkers including non-invasive imaging technologies such as multi-detector computed tomography (MDCT) as well as soluble biomarkers. Based on preliminary results from ongoing studies at the Montreal Heart Institute, we have reason to believe that the relationship between these biomarkers will soon be more fully understood and that some of these newer technologies will prove to have important clinical application. We need to continue to look to the future. The future is the epidemics of metabolic syndrome, diabetes and the aging of the population. Even with powerful statins, we are still faced with a large percentage of the population experiencing cardiovascular events. We need to reach beyond LDL reduction to find new therapeutic options. The advancement and application of imaging technology can be expected to contribute significantly to our ability to find such treatment options.