Oklahoma Heart Institute

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New Developments in the Noninvasive Diagnosis of Coronary Disease

by Roger D. Des Prez, MD, FACC

ST ELEVATION MI: A New Twist on an Old Theme

by Frank J. Gaffney, MD

Using Insulin in Type 2 Diabetes

by Kelly Flesner-Gurley, MD

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Oklahoma Heart Institute

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Cover photo: Tulsa's historic Mid-Continent Building lights the February night sky. Photo by Rick Stiller

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To Our Readers

DESPITE ALL THE ADVANCES in treating and preventing coronary disease, the prevalence of acute myocardial infarction remains high as the size of the population at risk increases. As the baby boomer generation enters into the age group at risk for cardiac events, newer technologies are being developed to better diagnose, treat, and more importantly, prevent the epidemic of symptomatic coronary artery disease.

In this year's winter issue of the Oklahoma Heart Institute magazine, Dr. Roger Des Prez discusses the utility of multi-slice CT angiography in diagnosing patients at risk of coronary artery disease. This new technology offers great promise for a simple way to better screen large populations at risk. On the other hand, there are still significant limitations associated with multi-slice CT angiography.

Dr. Frank Gaffney discusses current guidelines on anti-platelet and anti-coagulation strategies for patients presenting with ST segment elevation myocardial infarctions. Several large clinical trials have now provided insight into optimal therapies, which include aspirin, Plavix, heparin and low molecular weight heparin anticoagulants, and thrombolytic therapy.

Prevention still remains the best therapy for atherosclerotic vascular disease. Diabetes mellitus continues to be one of the major risk factors for the development of symptomatic vascular disease. Without aggressive therapy, 90% of patients receiving either insulin or oral therapy will be at risk of a vascular event during their lifetime. The use of insulin for Type II diabetics in order to better control their risk is discussed by Dr. Kelly Flesner, one of the endocrinologists with Oklahoma Heart Institute.

As always, the research corner provides information on newer therapies being investigated at Oklahoma Heart Institute. This issue addresses the obesity epidemic.

We hope you enjoy these articles and welcome your comments or suggestions with regard to the magazine content.

Sincerely,
Wayne N. Leimbach, Jr., MD

by Roger D. Des Prez, MD, FACC

New Developments in the Noninvasive Diagnosis of Coronary Disease

Non-invasive tests are essential in the evaluation of patients with possible or known coronary disease. Invasive cardiac catheterization ideally should be done only as a prelude to anticipated revascularization procedures.

CURRENT STANDARD APPROACHES

A recent New England Journal of Medicine article on stable angina summarized the current widely available non-invasive diagnostic alternatives for patients presenting with stable angina[1]. Exercise ECG has significant prognostic but limited diagnostic power. Stress imaging with echo or with nuclear myocardial perfusion imaging substantially improves diagnostic accuracy, with nuclear imaging being more sensitive.

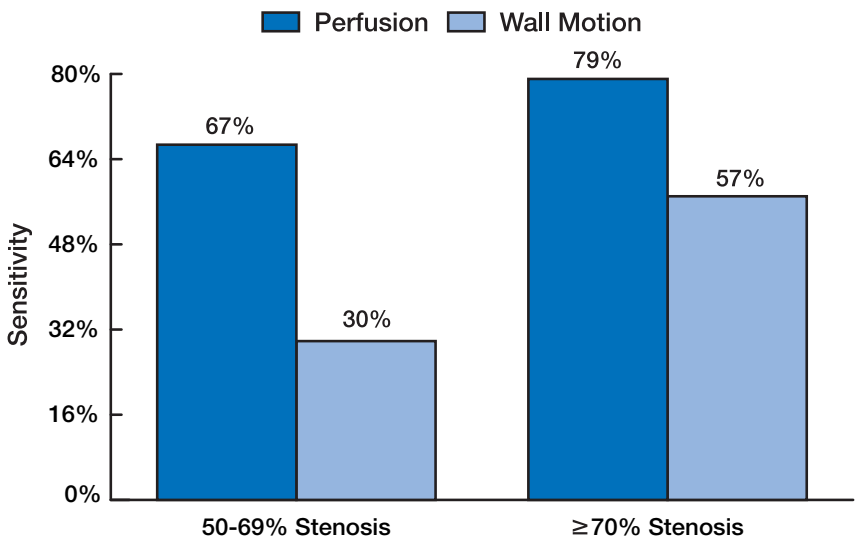
NEW DEVELOPMENTS

Stress Echo

New in stress echo is the use of intravenous echo contrast — microscopic hydrocarbon or albumin derived bubbles — to demonstrate myocardial tissue perfusion. Normal myocardium that is normally perfused enhances quickly with intravenous contrast; whereas ischemic myocardial areas will have relatively delayed and/or diminished contrast enhancement. This is similar to a nuclear perfusion test. Myocardial perfusion abnormalities with contrast echo improve the sensitivity of stress echo, as compared with wall motion abnormalities alone (Figure 1)[2,3]. This promising technique is in research protocols.

Figure 1

Pooled regional sensitivities of wall motion analysis and myocardial contrast echocardiography for the diagnosis of coronary stenoses between 50% and 69% and ≥70%



Elhendy, A. et al. J Am Coll Cardiol 2004;44:2185-2191

Nuclear Stress

SPECT ("Thalliums")

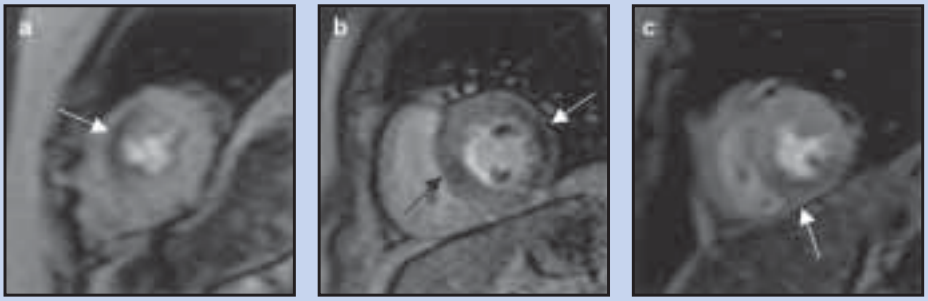
Myocardial Perfusion Imaging (MPI), studies continue to be the standard for the non-invasive diagnosis of coronary disease. These are usually done with SPECT (Single Photon Emission Computed Tomography) cameras. The clinical power of SPECT studies to diagnose coronary disease and to assess its prognosis in an individual patient has been better demonstrated with more studies and with more patients than other techniques[4]. Relatively new in this area is accumulating information on the cost-effectiveness of SPECT[5]. At Oklahoma Heart, these studies are referred to as "Thalliums," because we commonly use the radioisotope thallium for our MPI SPECT studies. These studies can also be done with other radioisotopes, such as the technetium based radioisotopes, sestamibi (Sestamibi) or tetrofosmin (Myoview). A problem with SPECT studies is the relatively low energy of the radioisotopes, which limits spatial resolution and which contributes to attenuation artifacts, in turn limiting the sensitivity and specificity of SPECT imaging.

PET

New in nuclear stress imaging is a resurgence of interest in PET (Positron Emission Tomography), an alternative type of MPI, which uses higher energy radioisotopes – commonly rubidium – and a different nuclear camera, together resulting in reduced artifacts and improved spatial resolution, yielding improved sensitivity and specificity compared with SPECT. An increased interest in and utilization of PET has been fueled by gains in cameras, software, protocols, and computing power. Rubidium PET protocols have been developed that allow the patient to have both rest and stress studies completed in 35 minutes, compared with several hours for SPECT studies, and fasting is less essential, resulting in a more convenient test for patients. The radiation dose to the patient with rubidium PET is lower than with SPECT studies, in spite of rubidium's higher energy, this apparent paradox because of the extremely short half-life of rubidium (75 seconds, compared with approximately 72 hours for thallium and 8 hours for technetium agents). PET perfusion imaging is currently only practical with pharmacologic stress. For pharmacologic stress, PET may become the preferred nuclear stress technique, because of the improved patient convenience, reduced radiation to the patient, and improved diagnostic power[6]. It may be the best stress test for the large patient or for other patients in whom imaging is difficult because of body habitus, because its higher energy results in improved imaging compared with other techniques.

Figure 2

Cardiac Magnetic Resonance Imaging Examples from Three Study Patients with a Variety of Myocardial Perfusion Deficits



Plein, S. et al. J Am Coll Cardiol 2004;44:2173-2181

Figure 2. Cardiac magnetic resonance imaging examples from three study patients with a variety of myocardial perfusion deficits. All examples show only one midventricular slice of the stress images. (a) Inducible anteroseptal subendocardial perfusion defect (white arrow). X-ray angiography showed subtotal occlusion of the proximal left anterior descending coronary artery (LAD). (b) Inducible lateral perfusion defect in a thinned lateral wall (white arrow) and further small transmural septal perfusion defect (black arrow). X-ray angiography showed significant stenosis of the mid-LAD and an occluded left circumflex coronary artery. (c) Inferior transmural perfusion defect (white arrow). X-ray angiography showed a significant stenosis in the mid-right coronary artery.

Table 1

Accuracy of Clinical Prediction Tools

(Grover JAMA 1995; 274:801)

CHD deaths in the Lipid Research Clinic Trial:			
	Sensitivity	Specificity	ROC
NCEP II	45%	70%	0.74
Framingham	70%	82%	0.85
The "Detection Gap". At least 30% of cardiac deaths occurred in a clinically "low risk" population. Absolute number: 650,000			

MRI

Cardiac stress MRI — exclusively done with pharmacologic stress – combines gated wall motion and gadolinium contrast perfusion imaging, with excellent resolution, and without radiation (Figure 2). Early information is that it may be more sensitive and specific than either nuclear or echo techniques[7]. This information will need to be confirmed in more studies, especially with outcomes data.

Cardiac CT

There are two distinct Cardiac CT procedures, calcium scoring and non-invasive coronary angiography with multislice CT (MSCT).

Calcium Scoring

Calcium scoring is based upon the observation that the overall coronary plaque burden (calcified and soft plaque), and hence a patient's risk for coronary events, is directly proportional to the amount of calcified plaque. Coronary artery calcium (CAC) scoring is not new. There are, however substantial new data to demonstrate its prognostic power, especially in assymptomatic patients[8,9,10,11]. The problem with the current risk assessment tools is that they are relatively insensitive. A significant number of patients without suspected coronary disease by traditional criteria—such as Framingham or National Cholesterol Education Program—suffer cardiac deaths (Table 1)[12] a portion of which are sudden. The new data emphasizes that calcium scores' prognostic power is independent of, but also additive to, traditional risk factors. Also new in this area are the recommendations of Berman and others that even assymptomatic patients with high calcium scores (over 400) be considered for nuclear stress perfusion imaging because of the high incidence of ischemic findings in such patients[13,14].

MSCT (Multislice computed tomography)

Multislice CT is a hot topic, even in the lay press. These scanners offer the potential for rapid and accurate non-invasive coronary angiograms that could improve diagnostic accuracy and reduce risk. The scanners are rapidly improving, with the 64 slice scanners only having been introduced a

Table 2

Consensus Table of Stenosis Severity Determined by 64-Slice CT Versus QCA

QCA	64-Slice CT			
	No Stenosis	<50%	51% to 75%	>75%
No Stenosis	638	8	9	2
<50%	14	40	10	2
51% to 75%	4	7	22	7
>75%	2	3	2	28

Leber W, et al; JACC 2005; 46:147-154

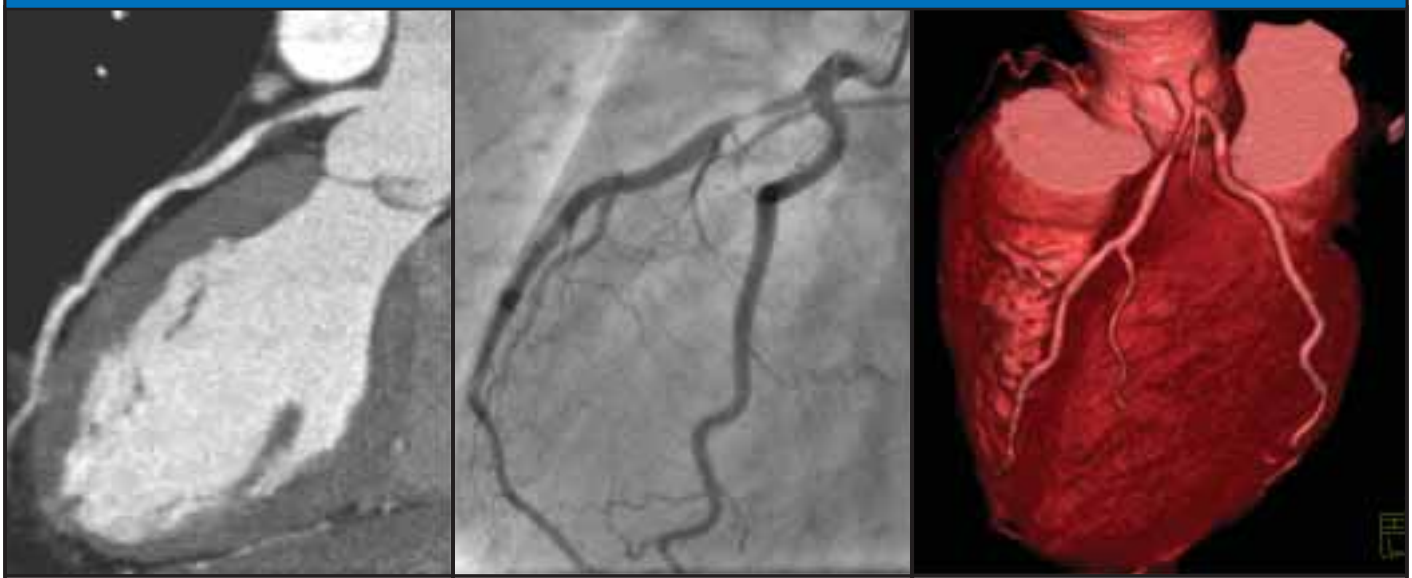
year ago. Images can be impressive. An example of a physician with atypical chest pain is shown, along with the invasive cardiac catheterization correlation (Figure 3).

One of only a few published evaluations to date of 64-slice CT coronary angiography (CTA) is an evaluation of 59 patients who had CTA performed before their cardiac catheterization scheduled to evaluate angina[15]. CTA was compared with qualitative coronary angiography (QCA) on a per coronary segment basis; for instance comparing the distal right by CT with the distal right by QCA. The overall accuracy of CTA was very good (Table 2). CTA was particularly accurate compared with QCA for finding no stenoses (97.0% agreement). Ruling out coronary artery disease blockages was where the CTA was most accurate. CTA also demonstrated high sensitivity for clinically important disease when considered on a per patient basis, where CT had an overall sensitivity of 94% (17 of 18 patients) for detecting patients who required revascularization.

continued on page 27

Figure 3

General Practitioner, 45 years, atypical chest pain



A planar reconstruction of a CTA of the LAD, from a physician.

An invasive cardiac catheterization of the LAD.

A 3-D reconstruction of the left coronaries from the same patient.

Images are used with permission, courtesy of Stephan Achenbach, University of Erlangen, Germany.

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Board certified in Internal Medicine and Endocrinology, Diabetes and Metabolic Diseases

by **Wayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHA**

Obesity Epidemic: Research for Future Therapies

The endocannabinoid system is a recently discovered physiologic system acting both centrally and in the periphery to help regulate body weight and metabolic processes. Research continues to focus on how chemicals that block the endocannabinoid receptors might be effective weight loss medications. In addition, blockade of an overactive endocannabinoid system may provide doctors and patients an effective therapeutic option for the treatment of the metabolic syndrome.

In 1964, 9-tetrahydrocannabinol was isolated as the active ingredient in marijuana that caused hunger even after users had achieved satiety. In 1988, cannabinoid receptors were discovered in the brains of rodents. In 1991, human cannabinoid receptors were cloned. Since then, endogenous cannabinoids have been discovered, endocannabinoid receptor blockers have been developed, and clinical trials assessing their utility have begun.

Cannabinoid receptors are found in the central nervous system and in peripheral tissues including adipose tissue, liver, pancreas, skeletal muscle and the GI tract. These are predominantly CB-1 receptors. CB-2 receptors are found in immune cells, and their role is still unclear.

CB-1 receptors are found in areas of the brain controlling food intake. Knock-out mice that are deficient in CB-1 receptors are characterized by decreased body weight, reduced fat mass, and hypophagia. Based on these and other findings, selective cannabinoid-1 receptor blockers were developed. Initial clinical trials included the assessment of weight loss with CB-1 receptor blockade. Two recently published trials in obese subjects did demonstrate significant weight loss with use of the selective CB-1 receptor blocker rimonabant. In the RIO-Europe study (Lancet, April 16, 2005) and the RIO-Lipid study (New England Journal of Medicine, November 17, 2005) mean weight loss in the range of 15 to 20 pounds occurred in patients randomized to rimonabant 20mg per day for one year. This degree of weight loss was significantly greater than for those patients randomized to diet and placebo therapy.

Studies are also ongoing in regard to using the selective CB-1 receptor blockers in patients with metabolic syndrome. These patients have been shown at increased risk for cardiovascular events, such as heart attacks and strokes. Metabolic syndrome is associated with abdominal obesity, elevated triglycerides, low HDL-cholesterol, elevated fasting blood glucose and elevated blood pressure. The RIO-Lipid study examined the effects of rimonabant, a selective CB-1 receptor blocker, on several of the metabolic risk factors. In addition to weight loss, the 20mg rimonabant treated patients experienced a reduction in waist circumference, an increase in HDL-cholesterol, a reduction in triglycerides, and an increase in plasma adeponectin levels (a hormone produced by adipose tissue that increases insulin sensitivity).

Numerous additional studies are currently underway evaluating the safety and efficacy of blocking the endocannabinoid system. Oklahoma Heart Institute physicians are involved with studies looking at the effects of endocannabinoid blockade on the progression of atherosclerotic artery disease.

Oklahoma Heart Institute

by **Frank J. Gaffney, MD**

ST ELEVATION MI: A New Twist on an Old Theme

The theory of the vulnerable plaque that ruptures or erodes, causing a cascade of platelet activation, adhesion, aggregation and subsequent thrombin generation and formation, is now widely accepted as the overwhelming cause of an acute coronary syndrome. If the infarct-related artery is totally occluded with thrombus and there is no collateral blood supply, then usually an ST elevation myocardial infarction (STEMI) ensues.

STEMI poses a major public health problem in the U.S., with roughly 500,000 new cases a year. The good news is that there has been a steady decline in the mortality rate for STEMI over the last several decades. Many things are thought to contribute to the declining mortality, including: 1) aggressive treatment of the risk factors that contribute to CAD, 2) smoking cessation, 3) education of the general public about the early signs and symptoms of MI and the appropriate course of action, and 4) early recognition and treatment of MI once the patient enters the health care system.

The ACC/AHA has recently updated the guidelines for management and treatment of patients with STEMI, focusing on numerous advances in the diagnoses and management of patients with STEMI. These guidelines again emphasize the importance of reducing door to needle time to less than 30 minutes for patients receiving thrombolytic therapy, and reducing door to balloon inflation time to less than 90 minutes for patients receiving percutaneous coronary intervention (PCI).

It comes as no surprise that one of the main reasons the guidelines needed updating was the rapid advancement of catheter based therapy since the last update in 1999. No less than 22 randomized clinical trials have compared fibinolysis vs PCI in recent years, with overall results suggesting that PCI treated patients experience lower short term mortality rates, less nonfatal reinfarction, and less hemorrhagic stroke (although a higher risk of major bleeding was noted with PCI) (1). As cardiologists, my colleagues and I at Oklahoma Heart Institute have applauded the recent advances in PCI therapy, and, in fact, have been involved in some of the recent clinical trials. Our practice has adopted an aggressive, timely, PCI approach to all STEMI presenting to the hospitals in which we practice, 24 hours a day, seven days a week.

For many of our patients who live in the outlying rural areas, getting to a hospital that offers PCI in a timely fashion can be challenging. For those patients who cannot achieve the 90 minute door to balloon time, thrombolytic therapy at one of our smaller community-based hospitals by an experienced emergency room physician still represents the fastest option to achieve early coronary artery reperfusion.

Since 1999 however, there has been nothing new in the armamentarium of thrombolytic therapy. For fibrin-specific fibrinolytic treated patients, unfractionated heparin in a weight-based algorithm is still the recommended antithrombin therapy, along with aspirin as an antiplatelet agent. All of the recent trials that tried to incorporate the combination of GP IIb/IIIa Inhibitors with fibrinolytic agents resulted in an unacceptable increased risk of bleeding. However, two new studies have added a new twist borrowed from the Non ST Elevation Myocardial Infarction (NSTEMI) guidelines: the use of clopidogrel (Plavix).

The ACC/AHA has recently updated the guidelines for management and treatment of patients with STEMI, focusing on numerous advances in the diagnoses and management of patients with STEMI.

The first trial, the COMMIT (2) trial, was completed in China. 45,852 patients presenting with STEMI or new LBBB were randomized within 24 hours of onset to clopidogrel 75mg once daily or placebo. Those undergoing primary PCI or at high risk of bleeding were excluded. 26% of the patients were over 70 years old, 67% presented within 12 hours of symptom onset, 49% received thrombolysis, 75% were on anticoagulants and 68% on Ace inhibitors. All patients received aspirin 162mg daily. The primary end point was the composite of death, reinfarction, or stroke at hospital discharge, a mean of 16 days later. There was a significant risk reduction of 9% in the clopidogrel group. Mortality was significantly reduced by 7%, as was reinfarction (13%). There was no associated increased risk of major bleed or hemorrhagic stroke.

The next trial was the CLARITY-TIMI 28 (3). This trial enrolled 3491 patients 18 to 75 years of age who presented within 12 hours after onset of STEMI and randomly assigned to receive clopidogrel (300mg loading dose followed by 75mg once a day) or placebo. Patients received aspirin, a fibrinolytic agent and, when appropriate, heparin. They were scheduled to undergo angiography 48 to 192 hours after the start of the study medication. The primary efficacy endpoint was a composite of an occluded infarct related artery on angiography or death or recurrent MI before angiography. The results showed the rates of primary efficacy endpoint were 21.7 % in the placebo group and 15% in the clopidogrel group. At 30 days, clopidogrel therapy reduced the odds of the composite endpoint of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1 to 11.6%, P=.03). The rates for major bleeding and intracranial hemorrhage were similar in both groups.

Both of these trials show convincing evidence of the efficacy and safety of using clopidogrel in the acute STEMI patient. The COMMIT trial shows that even starting clopidogrel without a loading dose can be beneficial and safe to a broad spectrum of patients, including the elderly. Likewise, the CLARITY trial shows that in patients under the age of 75, loading with 300mg of clopidogrel is safe and effective combined with thrombolytic therapy in improvising the rate of patency of the infarct-

related artery and in reducing the rate of ischemic complication. Additionally, it should be noted that only 6% of patients enrolled in the CLARITY trial went on to need CABG during the index hospitalization, which is a relatively small number and should not deter the use of clopidogrel in this population.

To say this is the last word about clopidogrel and STEMI would be short sighted. Currently there is ongoing debate about the proper loading dose of clopidogrel in NSTEMI patients, as well as for patients with stable coronary artery disease. Several small studies have shown benefit and no excess bleeding with a 600mg and even a 900mg loading dose strategy. Further trials will be needed to answer that question but enough evidence exists currently to change our existing practice to include clopidogrel in the treatment strategy of the STEMI patient.

(Frank J. Gaffney, MD is an invasive and noninvasive cardiologist with subspecialty expertise in transesophageal echocardiography.)

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New Developments in the Noninvasive Diagnosis of Coronary Disease

continued from page 8

There are important limitations to CTA. Spatial and temporal resolutions for MSCT are still not optimal, still far from invasive cardiac catheterization. Because of limited temporal resolution, fast or irregular heart rates severely compromise image quality. With suboptimal spatial resolution, a precise evaluation of the degree of stenosis is difficult: mild, moderate, and severe may be the best way to grade stenoses with this technique. Implanted coronary stents, heavily calcified lesions, and small vessels all are difficult to evaluate. Obese patients can be difficult to image. CT involves radiation. Good results from MSCT require careful meticulous attention to detail and processing by both technologist and physician. Even with meticulous attention and with good patient selection, a significant portion of patients' images will be non-diagnostic.

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An important limitation of CT coronary angiography is that it is – currently – exclusively an anatomic study. It can demonstrate stenoses and plaque, but cannot demonstrate the functional significance of these lesions. Studies have shown that demonstrable cardiac ischemia is usually a more important factor than anatomy in determining prognosis, and in determining the likely clinical benefit of revascularization, than the presence of a coronary stenosis. Cardiac CT coronary angiography currently cannot assess ischemia. Hence, functional tests — such as MPI studies (SPECT or PET), stress echo or stress MRI — are likely to continue to be important, at times done instead of, and at times done in addition to CT coronary angiography.

(Roger D. Des Prez is a noninvasive cardiologist with subspecialty expertise in echocardiography, nuclear cardiology and transesophageal echocardiography at Oklahoma Heart Institute.)

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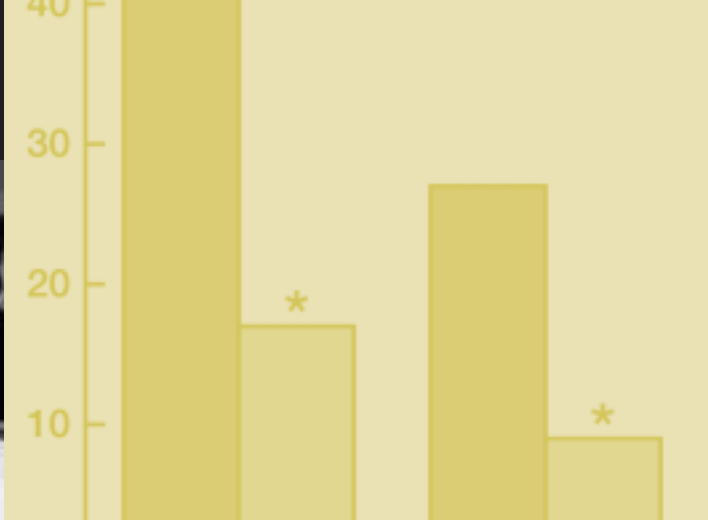
■ *by* **Kelly Flesner-Gurley, MD**

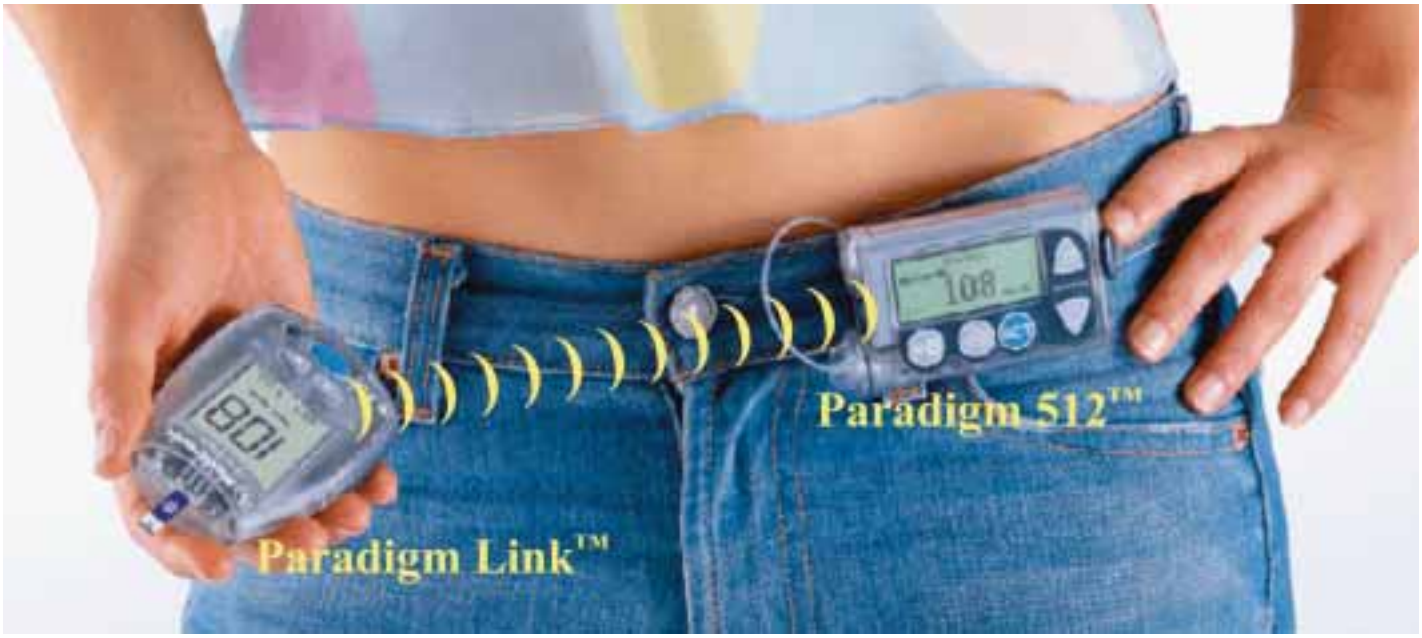


Using Insulin in Type 2 Diabetes

Since the discovery of insulin over 80 years ago we have learned much about the pathogenesis of diabetes and have developed numerous agents to treat the various defects leading to the hyperglycemic state. The treatment for type 1 diabetes is more straightforward, as patients are completely insulin deficient and must be managed with insulin. Type 2 diabetes, however, is due to a combination of insulin resistance and relative insulin deficiency, making the choices for treatment more complex. Therefore, most patients with type 2 diabetes are managed with multiple agents to achieve glycemic goals.

The previous practice model for type 2 diabetes was to initiate one agent and maximize the dose until treatment failure, and then slowly add on other agents. Finally, after many years of uncontrolled sugars and complications, insulin is added late in the stage of the disease progression. The results of the UKPDS, however, have taught us about the natural history of beta cell failure in type 2 diabetes, and that by diagnosis, beta cell function has already decreased by 50%. The implication of this is limited effectiveness of oral agents and increasing need for exogenous insulin in most patients with type 2 diabetes over time.

So, when is insulin indicated in type 2 diabetes? Any patient who is not reaching target blood sugars goals on current agents is a candidate for insulin therapy – in fact, insulin remains the most powerful



agent we have for blood sugar control. Despite large randomized trials supporting tight control of blood sugars, and newer guideline for lowering glycemic thresholds for the diagnosis of prediabetes and treatment goals, only 37% of adults with diabetes in the United States are achieving target A1c of less than 7%, as reported in the third National Health and Nutrition Examination Survey (NHANES III). One of the major reasons cited for not reaching glycemic targets in our diabetic patients is the reluctance to use insulin therapy.

What are some of the barriers to using insulin?

- Patient resistance – multiple factors include fear of injections, pain, complexity of insulin regimens, and psychological resistance. Many patients mistakenly fear that insulin therapy causes the complications of diabetes, having known someone on insulin with complications. One study that looked at attitudes of patients when starting insulin showed that the majority of patients in the study are extremely troubled by the idea of more than one injection versus fear of the actual needle. It seems the thought of having to be inconvenienced by learning about and using insulin is a huge hurdle for patients to overcome. Many patients procrastinate starting insulin for years because they feel they can do better on lifestyle, and they see insulin therapy as a failure on their part versus a natural progression of the disease process.
- Physician resistance – initiating and supervising patients on insulin is more labor intensive, and lack of time and resources delay initiation of insulin. Previously, there was a debate that insulin treatment could increase cardiovascular risk: however multiple studies, including the UKPDS and DIGAMI trials, show that exogenous insulin does not increase cardiovascular risk. On the contrary, cardiovascular benefit has been seen.

- Medical limitation – hypoglycemia and weight gain are the main medical limitations of using insulin. To overcome insulin resistance, many patients with type 2 diabetes require large amounts of exogenous insulin to control the blood sugars. Weight gain can occur by retention of calories previously lost in the urine, and hypoglycemia, or the perception of it, when the blood sugars are starting to normalize may encourage defensive eating, resulting in greater caloric intake.

How can we overcome these barriers?

Communication and education remain the cornerstone for using insulin to get patients to glycemic goals. Physicians should not use insulin as a punishment or threat to try to motivate patients. Early discussion about insulin's role as an important tool to reach glycemic targets should be emphasized. Numerous studies have shown the benefits of diabetes education in achieving glycemic goals. Group programs have been shown to be equally or more effective than individual counseling. Programs that can train patients to use insulin and self manage their disease become invaluable time savers for the physicians. All patients with diabetes should have glucometers and learn self-monitoring of blood glucose.

The results of the UKPDS have taught us about the natural history of beta cell failure in type 2 diabetes, and that by diagnosis beta cell function has already decreased by 50%.

New agents and devices are helping to overcome some of the barriers mentioned above. In order to overcome the limiting physiologic features of standard insulins, which frequently lead to increased hypoglycemia, insulin analogs were developed in the 1990s to produce safer insulin formulations that more closely mimic natural basal and prandial components of endogenous insulin secretion. The analogs are based on the structure of insulin, but undergo selected amino acid substitutions or

additions to either enhance or protract the subcutaneous absorption without altering the biologic properties. Examples are listed below:

Insulin Analogues
Typical Times of Action

Insulin Preparations	Onset of Action	Peak	Duration of Action
Aspart-Novolog Glulisine-Apidra Lispro-Humalog	~15 minutes	1-2 hours	4-6 hours
Glargine-Lantus	2-4 hours	Flat	~24 hours

Amylin is a beta-cell hormone co-secreted with insulin, which acts to reduce postprandial glucose excursions by delaying gastric emptying and suppressing glucagon secretion. Patients with type 2 diabetes taking insulin have clearly reduced amylin responses to meals. Pramlintide (Symlin) which is a synthetic analog of amylin is now available by injection before meals for patients taking insulin, and has been shown to modestly reduce A1c levels while promoting weight loss.

Insulin pens have made education and acceptance of insulin initiation much less threatening. Needles are much improved, and most patients find that injections are less painful than the fingersticks they have already been doing. Insulin pumps, which use an external programmable pump connected to an indwelling subcutaneous catheter to deliver rapid acting insulin, have been shown to reduce hypoglycemia and improve ease of administering insulin for patients on multiple dose insulin. New insulins in clinical development include other insulin analogs, inhaled insulin and buccally absorbed agents.

(Kelly Flesner-Gurley is an endocrinologist with Oklahoma Heart Institute, who specializes in diabetes, lipids, hypertention and thyroid diseases.)

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What is a simplified approach to initiating insulin therapy in type 2 diabetes?

(See http://www.texasdiabetescouncil.org)

Oral agent failure or A_1c above target

Start basal insulin with once daily Glargine (Lantus) or nighttime NPH
- — continue oral agents at the same dose
- — beginning dosage 10 units or 0.1-0.25 units/kg

Use weekly titration-
If fasting SMBG

mg/dl	units
>180	add 6
141-180	add 4
121-140	add 2
100-120	add 1
<80	subtract 2

If A_1c remains >6.5% over 3 months – consider discontinuing oral secretagogue and initiating multi-dose insulin or intensive insulin therapy or consult an Endocrinologist.

One major limiting factor in this algorithm has been the referral time to see an endocrinologist. At Oklahoma Heart Institute, we now have 4 full time adult endocrinologists and look forward to providing timely consults to help empower patients to achieve therapeutic success.

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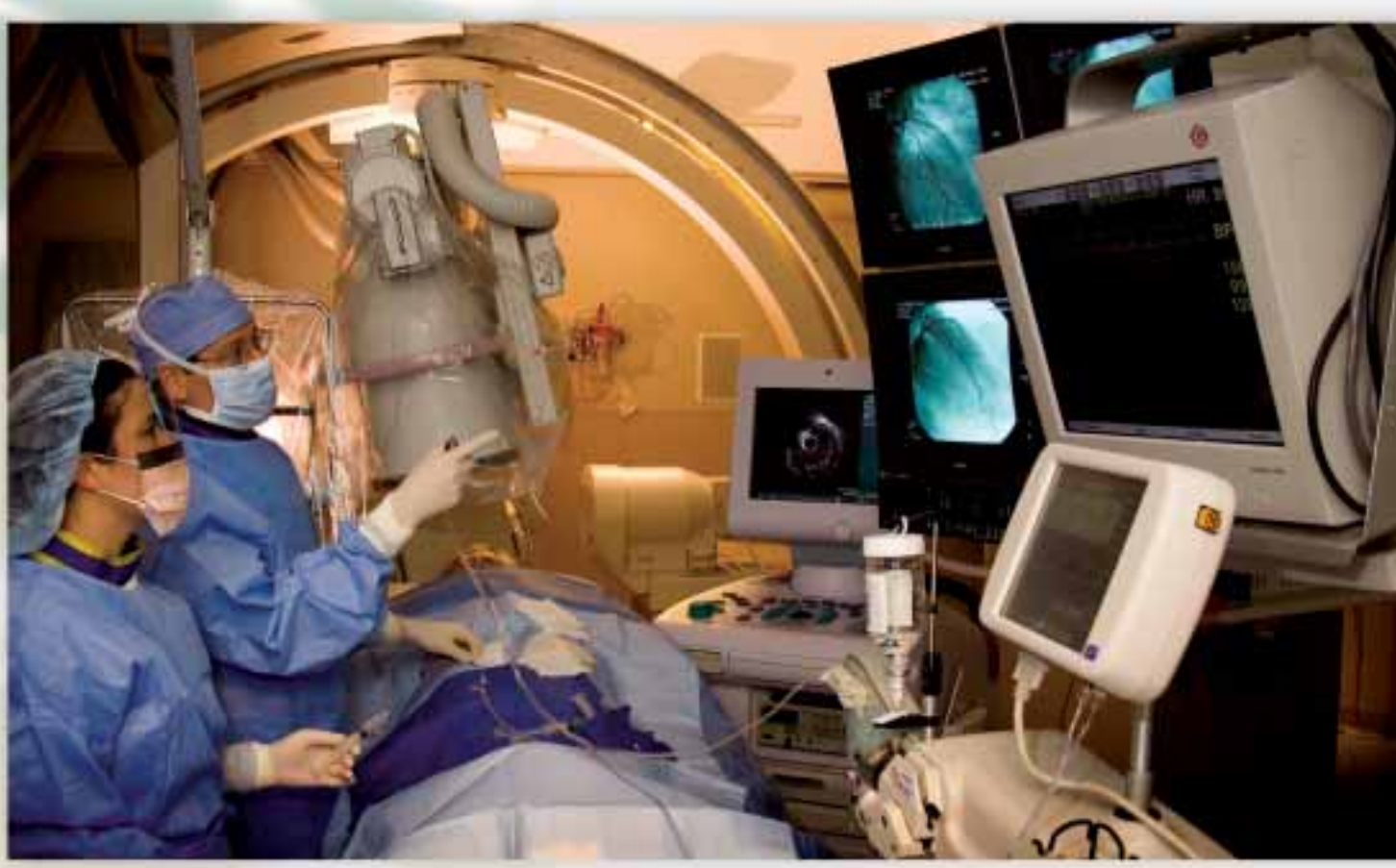

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