SJHG Heartbeat

Number 114 **March 2007**

Reducing CV Risk of MetS & T2DM—Part 2

The last *Heartbeat* discussed the risk of MetS and T2DM and outlined a plan for the diagnosis and aggressive treatment of a cluster of risk factors known as MetS (a pre-diabetic condition), with the goal of preventing the development of T2DM and its' associated CVD risk (Part 1). This month, *Heartbeat* will cover the medications available to treat hyperglycemia, the central metabolic abnormality of T2DM. Maintaining glycemic levels as close to the non-diabetic range as possible has been shown to greatly decrease complications.

Treatment of T2DM (FBS > 126mg/dL)

Medical management of T2DM, diagnosed by having two FBSs > 126mg/dL or a 2 hour postprandial blood glucose (PPBG) > 200mg/dL, is a challenging endeavor. The literature on the subject is expansive, and new data is emerging rapidly. However, there is minimal high-quality evidence in the form of head-to-head trials that directly compare different diabetic treatment regimens, and this makes recommending one class of drugs over another difficult.

Further complicating the situation is the individual patient. As the number of comorbidities rise and the list of medications lengthen, our task of managing the diabetic patient becomes more difficult. Medication side effects, interactions, and efficacy must be closely scrutinized for each individual. This *Heartbeat* will review some of the general goals of diabetic management, along with the various agents currently available. The goal of glycemic control, in diabetes, is to achieve HbA1cs as close to normal (< 6%) as possible. According to the American Diabetes Association (ADA) and the American Heart Association the current general goal for HbA1c is < 7% and < 6% in individuals without causing significant hypoglycemia[1] (these recommendations are based on a 15% to 18% increase in relative CVD risk for each 1% increase on HbA1c). The American Association of Clinical Endocrinologists (AACE) recommends HbA1c ≤ 6.5%. Prospective randomized trials (UKPDS) have shown that improved control is associated with decreased rates of microvascular damage (nephropathy, retinopathy, and neuropathy).[2] Epidemiologic studies and a recent meta-analysis have shown decreased macrovascular complications (CVD) with tight glycemic control. This benefit has not been supported by a randomized clinical trial, but most physicians strive for this goal.

Medications: After initiating TLC, the process of choosing a diabetic medicine should take several factors into consideration. First, the expected decrease in HbA1c must be established. Secondly, as with any medication, you must know the possible and most common side effects of each drug (Table 1 appendix). Thirdly, the patient's current level of hyperglycemia needs to be considered. When glucose is high (HbA1c > 8.5%), more potent and more rapidly acting agents, often in combination, should be the initial therapy. When hyperglycemia is closer to goal (< 7.5%), less potent and/or slower acting agents may be the initial choice. In any case, T2DM is a

progressive disease, and most, if not all, patients will eventually require combination therapy[7].

Metformin is the drug of first choice for the treatment of T2DM, according to the ADA and the European Association for the Study of Diabetes (EASD).[3] Metformin is the only biguanide available in the US and most of the world. It exerts its primary effect by decreasing hepatic glucose output and increasing insulin sensitivity, resulting in the lowering of fasting glucose levels. Typically, HbA1c is lowered by ~1.5% with this drug. It is generally well tolerated, with the most common complaints being gastrointestinal upset. A rare occurrence is lactic acidosis. To minimize the chance of the latter, metformin should not be given to patients with chronic renal insufficiency, (creatinine > 1.5 in males or > 1.4 in females), liver disease, CHF, or history of alcohol abuse. Also it should be held 48 hours after any surgical procedure or administration of IV contrast. Benefits include low risk of hypoglycemia, weight loss, low cost, as well as beneficial effect on CVD outcomes.[6]

Sulfonylureas improve glucose levels by enhancing insulin secretion (secretagogues). Treatment effect is similar to metformin, lowering HbA1c by ~1.5%. Most common side effects include weight gain and hypoglycemia. Severe hypoglycemia, characterized by coma or seizure, is infrequent but seen more often in the elderly. Newer sulfonylureas [Amaryl (glimepiride), Glucotrol (glipizide), and Micronase/Diabeta (glyburide)] have less risk of hypoglycemia than the first generation drugs [Orinase (tolbutamide), Tolinase (tolazamide), Diabinese (chlorpropamide)]. The University Group Diabetes Program demonstrated an increase in CVD mortality with sulfonylureas.[4] This was not supported by UKPDS or the ADOPT studies, which will be discussed later.

Glinides, another class of secretagogues, are of short duration of action but are costly and require 3x daily dosing. The drugs act by binding to a different site within the sulfonylurea receptor on the beta cell. There are two glinides available in the US, repaglinide (Prandin) and nateglinide (Starlix). Prandin is somewhat more effective, decreasing HbA1c levels by ~1.5%. The half-life is shorter than the sulfonylureas, but the possible side effects are similar: weight gain and hypoglycemia. Both sulfonylureas and glinides are approved for use alone or combined with metformin.

Alpha glucosidase inhibitors are a less tolerated weight-neutral class of drugs. Acarbose, the primary medication in this class, requires 3 x daily dosing and is also expensive. Inhibiting the rate of digestion of polysaccharides in the proximal small intestine lowers postprandial glucose levels without causing hypoglycemia. Acarbose is less effective than metformin, sulfonylureas, or glinides for lowering glucose. This class typically lowers HbA1c levels by 0.5-0.8 percentage points. Side effects are the major barrier to consistent use of this relatively safe medication, with up to 45% of patients in clinical trials discontinuing it secondary to GI upset and increased gas production.[5] A prevention trial published in 2003 demonstrated a reduction in severe CVD outcomes with Acarbose.[6] However further study is needed.

Thiazolidinediones (TZDs or glitazones) are primarily insulin sensitizers. These medications affect insulin sensitivity through modulation of the peroxisome proliferator-activated receptor gamma (PPAR gamma). They lower HbA1c levels 0.5-1.4 percentage points when used alone. They are expensive, and major side effects include weight gain and fluid retention. The latter has been implicated in new cases of CHF and worsening existing heart failure. TZDs appear to have a beneficial effect on lipids by alteration of the small dense LDL-C particle seen in T2DM to a lighter, fluffy (larger) less atherogenic particle. Pioglitazone (Actos) is believed to have more beneficial lipid effects compared to rosiglitazone (Avandia).[7] A recent prospective study (PROactive) showed no significant effect on primary CVD outcome with pioglitazone, although, after 3 years of follow

up, a marginally statistically significant reduction in death, MI and CVA was observed as a secondary endpoint.[8]

The ADOPT study, published in *NEJM* December 2006, also did not show a decrease in macrovascular events with TZDs.[9] This double blind randomized trial compared rosiglitazone, metformin, and glyburide as initial treatment in newly diagnosed T2DM. The authors concluded that several factors need consideration for each patient and did not designate any agent as the absolute first line of therapy. In contrast to the University Group Diabetes Program, the sulfonylurea glyburide was associated with fewer cardiac events in the ADOPT study.

Insulin is the oldest and most widely available diabetic medication—and the most effective for lowering blood glucose. There is no maximum dose and no level of HbA1c that cannot be treated to therapeutic goal. T2DM patients may require large doses of insulin (>1u/Kg) secondary to insulin resistance. Favorable effects on HDL and triglyceride levels have been observed with insulin.[10] Side effects include weight gain and hypoglycemia, although newer, non-peaking preparations (i.e. Lantus) and very short acting insulin decrease these risks.

Glucagon-like peptide 1 (GLP-1) agonists are one of the newer classes of drugs on the market and are called *incretin mimetics*. Exenatide (Byetta) simulates a naturally occurring peptide produced by the small intestine and binds to the GLP-1 receptor on the pancreatic beta cell, stimulating glucose-mediated insulin secretion.[7] Glucose is also lowered through suppression of glucagon secretion and slowing of peristalsis. It is an injection drug that lowers HbA1c 0.5-1.0 %. Major side effects have been primarily GI, with up to 45% of patients experiencing nausea, vomiting, or diarrhea.[11] Exenatide causes weight loss (*nice side effect*) but has the disadvantages of injections, little clinical experience and high cost. Byetta is currently approved for combination therapy with metformin or sulfonylureas.

Pramlintide (Symlin), approved by the FDA in March 2005, is a synthetic form of the hormone amylin which is normally secreted with insulin from the pancreatic beta cell. This hormone is absent in T1DM patients and is deficient in T2DM. Given before meals as an injectable, it lowers post-prandial glucose by inhibiting glucagon production, delaying gastric emptying, and centrally modulating appetite. HbA1c is decreased by 0.5-0.7 percentage points. The majority of reported side effects are GI in nature, and mild weight loss has been observed. Symlin is currently approved only as adjunctive therapy with insulin.

Sitagliptin (Januvia), the newest oral hypoglycemic agent, is a dipeptidyl peptidase-4 (DPP-4) inhibitor. By inhibiting DPP-4, sitagliptin maintains the endogenous incretin effect thereby increasing the release of insulin and decreasing the release of glucagon, particularly in the fed state. This mechanism is glucose dependent and decreases the possibility of hypoglycemia. HbA1c levels are decreased up to 1.4%. Side effects include sinus congestion, URI, HA, and sore throat. Januvia is currently approved for the treatment of T2DM as monotherapy or in combination with metformin and TZDs.

Treatment

The recently published consensus statement of the ADA and the EASD recommends a stepwise approach to treating the newly diagnosed T2DM patient (Figure 1. appendix).[7] ***The first recommended intervention is to begin metformin and TLC concurrently*.** Metformin should be titrated to its maximally effective dose (2000 mg in divided doses) over 1-2 months. It was chosen because of its effectiveness, safety profile, tolerability and low cost.

The next step is to add other medications within 2-3 months if metformin and TLC fail to achieve glycemic goals. At this point the algorithm diverges into three possibilities. One would choose insulin, TZDs, or sulfonylureas, based on

the needs of each individual patient. If hyperglycemia is severe (HbA1c > 8.5%), then insulin is probably the best choice. Trying to avoid hypoglycemia favors the use of a TZD. A sulfonylurea would be the best choice if cost is a concern but hypoglycemia is not. *Most physicians are inclined to maximize the effects of reducing insulin resistance by combining metformin with a TZD before giving a sulfonylurea*. Newer agents and Acarbose were not included in the algorithm because of their decreased effectiveness, increased cost, and lack of sufficient clinical data, but they may be the appropriate choice in certain patients.

When TLC, metformin, and a second medication fail to meet HbA1c goals, the third step in the algorithm recommends intensifying or adding insulin therapy. While adding a third oral agent is a possibility, this approach may be more costly and less effective when HbA1c is close to goal.[12] If a third agent is chosen, it is important to use drugs that are synergistic, generally anti-hyperglycemic drugs with different mechanisms of action. Intensifying insulin regimens involves lowering postprandial glucose levels. This is achieved primarily through the injection of short acting insulin prior to meals. The ADA recommends the tapering and discontinuation of sulfonylureas and glinides when rapid acting insulin is added to the patients' treatment regimen, due to the lack of synergy between insulin and secretagogues.

Although not included in the current guidelines a new area of interest is emerging regarding postprandial hyperglycemia. Epidemiological studies have shown postprandial hyperglycemia to be a direct and independent risk factor for CVD[13]. There is emerging evidence that the postprandial state with 'hyperglycemic spikes' may contribute to late complications of diabetes and the development of atherosclerosis.

In conclusion, the treatment goal in T2DM is achieving glucose or HbA1c as close to normal as possible. TLC and metformin are the first weapons, followed by the addition of insulin, TZDs, or sulfonylureas, depending on the individual patient. The third line of treatment is insulin. At this point an insulin regimen can be added to the oral program or intensified to reach the desired HbA1c goal. Currently, the role of newer agents is not well defined, but they do have a role in selected patients. The guideline algorithm needs more clarity and should include more options as more experience and outcomes data is obtained with newer medications. Ultimately, the decision lies with the physician to tailor each medical regimen on an individual basis. The key is to get to appropriate HbA1c goals.

Although management of hyperglycemia, the hallmark metabolic abnormality associated with T2DM, is the central theme of this Heartbeat, it cannot be over emphasized that in order to substantially reduce CV morbidity and mortality and renal complications, the associated HBP, dyslipidemia and hypercoagualability also have to be aggressively treated as outlined in Part 1. All diabetics should be on AII blockade, statins and aspirin if not contraindicated.

Summary

The incidence and prevalence of MetS and T2DM DM are rapidly increasing. CHD in diabetic individuals represents a major worldwide public health problem. MetS and T2DM form a continuous spectrum of risk of CVD. Glucose intolerance and the associated traditional risk factors for CVD, such as dyslipidemia and hypertension, might be present for many years before the diagnosis of T2DM. In patients with CHD and MetS (prediabetic state), primary prevention of T2DM is now feasible and effective. In particular, TLC measures are recommended, and emerging evidence supports the role for therapeutic prevention of T2DM (metformin or a glitazone and maybe AII blockade).

The most effective strategy to slow the rapidly increasing morbidity and mortality from CVD in diabetic patients is to prevent prediabetic states

and T2DM. Screening for at-risk subjects can be a cost-effective intervention. Reduction of the increased risk of CVD in patients with CHD and MetS or T2DM requires a multifactorial approach. The data currently available suggest that this can be achieved by intensive glycemic control (HbA1c < 6.5 %), which should include aggressive treatment of postprandial hyperglycemia to prevent spikes, and aggressive treatment of other CV risk factors, such as dyslipidemia, hypertension, and smoking. Compliance, particularly with TLC and prescription of evidence-based therapies as outlined in part 1 & 2 are the goal.

Special Guest Editor: Louis Haenel DO
Clinical Assistant Professor of Medicine UMDNJSOM

Thomas Kopinski DO
PGY III UMDNJSOM

Mario L Maiese DO, FACC, FACOI
Clinical Associate Professor of Medicine, UMDNJSOM Email: maiese1@comcast.net
Heartbeats online: www.sjhg.org

***Heartbeat* is a South Jersey Heart Group publication.**

Figure 1. Algorithm forTreatment of T2DM.

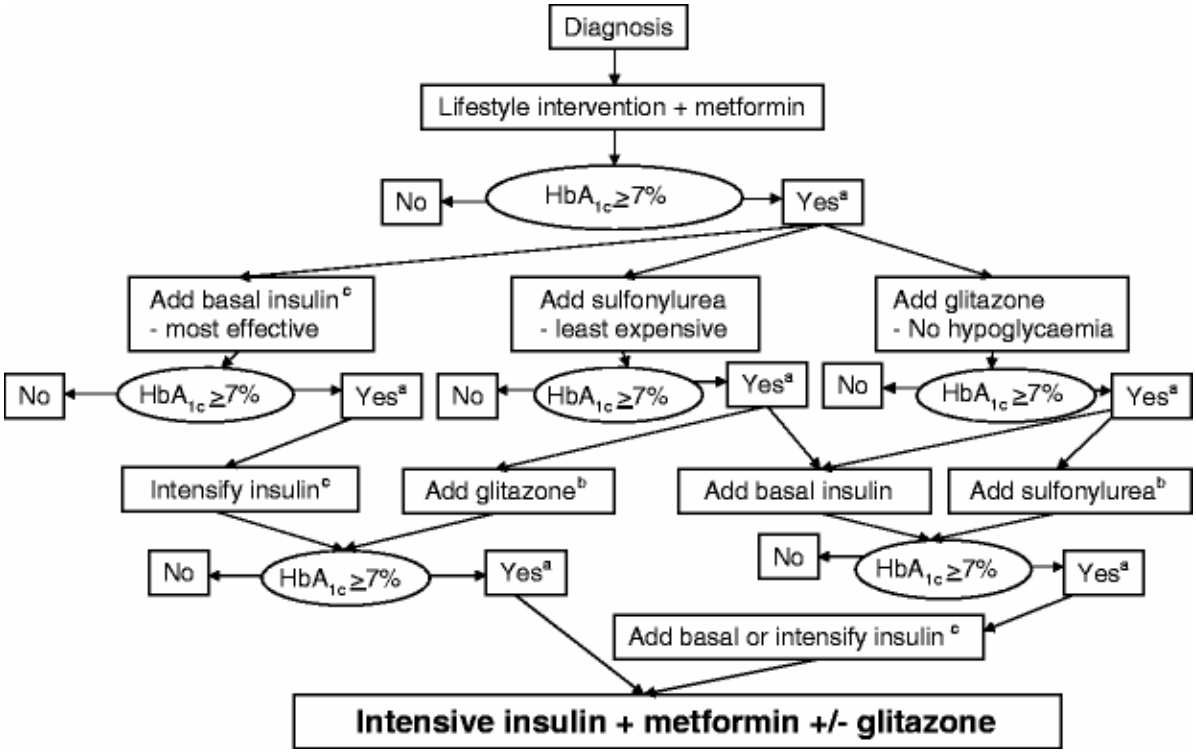

Table 1 Summary of antidiabetic interventions as monotherapy

Interventions	Expected decrease in HbA_{1c} (%)	Advantages	Disadvantages
Step 1: initial			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in first year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: additional therapy			
Insulin	1.5–2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycaemia, weight gain
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycaemia[a]
TZDs	0.5–1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Other drugs			
α-Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5[b]	Short duration	Three times/day dosing, expensive
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience

[a]Severe hypoglycaemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (e.g. chlorpropamide, glyburide [glibenclamide], and sustained-release glipizide) are more likely to cause hypoglycaemia than glipizide, glimepiride and gliclazide. [b]Repaglinide is more effective at lowering HbA_{1c} than nateglinide. *GI* Gastrointestinal

[1] Primary prevention of CVD in people with Diabetes Mellitus. A Scientific statement from the AMA and ADA. *Circulation* January 2/9 2007; 115: 114-126.

[2] UKPDS United Kingdom Prospective Diabetes Study Group : Relative efficacy of randomly allocated diet, sulphonylureas, insulin, or metformin in patients with newly diagnosed Type 2 DM followed for three years. *BMJ* 1995; 310:83. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complication in patients with Type 2 DM. *Lancet* 1998; 352:837-853; Effect of intensive blood glucose control with metformin on complication in overweight patients with type 2 DM. *Lancet* 1998; 352:*854-865.*

[3]Nathan DM, et al. Management of hyperglycemia in Type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. (A consensus statement from the ADA and EASD) *Diabetologia 2006*; 49:1711-1721.

[4] Klimt CR, et al. The University Group Diabeetes program: a study of the effect of hypoglycemic agents on vascular complications in patients with adult onset diabetes. *Diabetes* 1970; 19(Suppl 2):747-830.

[5] Van de Laar FA. Alpha-glucosidase inhibitors for Type 2 DM. *Cochrane Database Syst Rev* 2005; CD003639.

[6] Chiasson JL, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM Trial. *JAMA* 2003; 290; 486-494.

[7] Goldberg RB, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 DM and dyslipidemia. *Diabetes Care* 2005; 28:1547-1554.

[8] Dormandy JA, et al. Secondary prevention of macrovascular events in patients with type 2 DM (PROactive). *Lancet* 2005; 366:1279-1289.

[9] Kahn SE, et al. (ADOPT) A Diabetes Outcome Progression Trial: Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. *NEJM* December 2006; 355:2427-43.

[10] Nathan DM, et al. Glyburide or insulin foe metabolic control in NIDDM: a randomized double blind study. *Ann Internal Med* 1988; 108:334-340.

[11] Kendall Dm, et al. Effects of exenatide on glycemic control and weight over 30 weeks in patients with type 2 DM treated with metformin and a sulfonylurea. *Diabetes Care* 2005; 28: 1083-1089.

[12] Schwartz S, et al. Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 DM after failure of two oral drugs. *Diabetes Care* 2003; 26:2238-2243.

[13] Ceriello, Antonio. Postprandial Hyperglycemia and Diabetes Complications: Is It Time to Treat? *Diabetes* 2005; 54(1):1-7.