Combined Therapy: Insulin and Oral Hypoglycemic Agents in Type 2 Diabetes Mellitus

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INTRODUCTION

Diabetes mellitus is a serious longstanding disease, which will cause chronic complications in several target organs throughout the body if left untreated. Subsequently, death might ensue. Prevention againts the occurrence of such a grave outcome should be done in the first priority at all levels of health authority. Several large-scale epidemiological studies (Diabetes Complication Control Trial = DCCT in Type 1 DM and United Kingdom Prospective Diabetes Survey = UKPDS in Type 2 DM) have given proof that chronic complications of diabetes could be prevented through an effort to keep blood glucose within desirable optimal levels. In UKPDS, the incidence of retinopathy, neuropathy and nephropathy were significantly lower in the intensively treated group (HbA1c 7.1%) as compared to the conventionally treated group (HbA1c 7.9%).

The lower the HbA1c, the lower the incidence of chronic complications of diabetes mellitus. However, data from several centers showed that a larger proportion (55%) of the diabetics were not well controlled or were poorly controlled.

Nowadays, glycosilated hemoglobin is used as a gold standard for monitoring long-term blood glucose control. HbA1c < 7% is considered to be the cut off level to determine the degree of optimal blood glucose control. In clinical practice, the measurement of HbA1c is not always feasible. Fasting blood glucose of < 120 mg/dL and postprandial blood glucose < 160 mg/dL are used as the surrogate for HbA1c < 7%.

In the natural history of DM, the basic abnormality of Type 2 Diabetes Mellitus (T2DM) is insulin resistance. Thereafter, compensatory hyperinsulinemia occurs. In the long run, pancreatic β cells become exhausted and insulin production will no longer be sufficient to cope with underlying abnormalities. Glucose intolerance and then Diabetes Mellitus ensue. With time, the β cell's capacity to produce insulin becomes less and less. Available insulin is no longer sufficient to supply muscles and other peripheral cells, causing postprandial hyperglycemia. When insulin production decline further, available insulin is not enough to prevent hepatic glucose production, and fasting hyperglycemia ensues. Both fasting and postprandial hyperglycemia become more severe as less insulin becomes available. Diabetics would thus need additional exogenous insulin to help the body to cope with hyperglycemia.

In clinical practice, we can therefore divide the hyperglycemic condition in T2DM into several stages according to the β cell's capacity to produce insulin.

1. IGT
2. Postprandial Hyperglycemia, with normal fasting blood glucose
3. T2DM phase 1, during which we face both fasting and postprandial hyperglycemia, but β cell reserve capacity still respons to external stimulation (insulin secretagogue). Blood glucose can be normalized using insulin secretagogues
4. T2DM phase 2, during which β cell capacity is very low and hyperglycemia can only be normalized with a combination of oral hypoglycemic agents
5. T2DM phase 3, during which insulin production is very low, both the fasting and postprandial blood glucose are very high, and can only be controlled with additional exogenous insulin.

To achieve the targeted glycemic control, it is important to remember that the basic mechanisms causing

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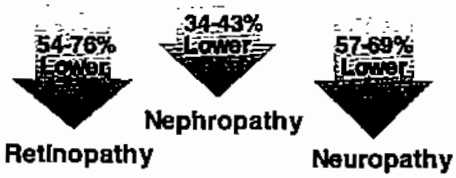
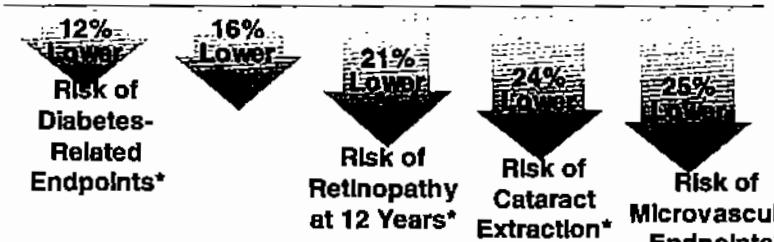
Key Studies Support the Need for Tighter Control to Reduce Risk Factors

Percentage of Risk

Intensive Glucose Control in DCCT Results in:



Intensive Glucose Control in UKPDS Results in:



*** The reduction were statistically significant**

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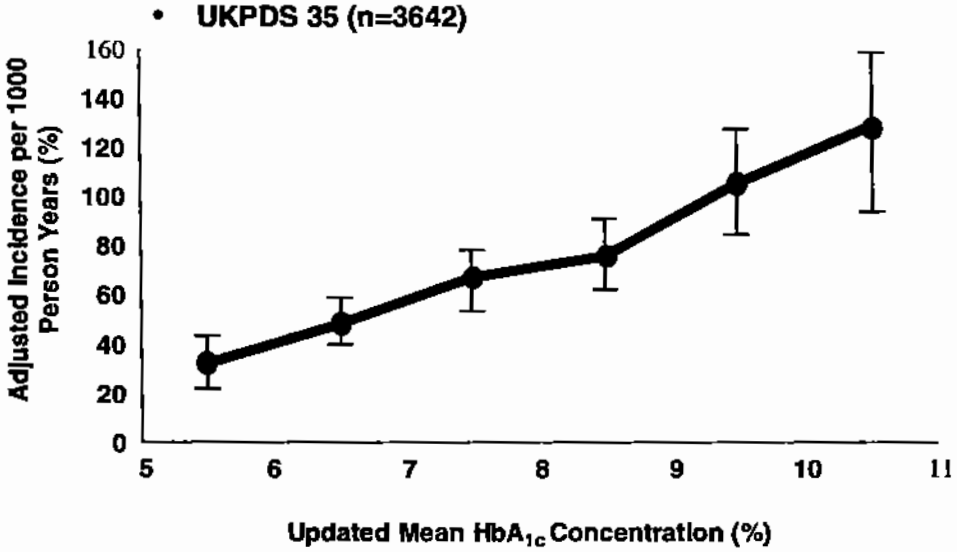
The Lower the Glycemia, the Lower the Risk of Complications



(From Stratton et al. BMJ. 2000;321:405-12.)

ADA Treatment Goals for Glycemic Control

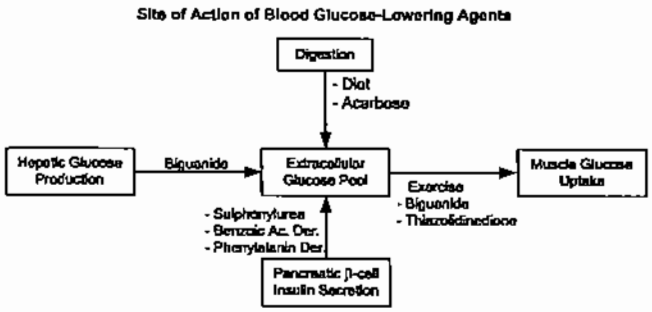
Glycemia	Normal	Goal	Further Action Required
Average Preprandial Fasting Glucose (mg/dL)	< 110	80 to 120	< 80 > 140
Average Postprandial Glucose (mg/dL)	< 140	< 160	> 180
HbA_{1c} (%)	< 6	< 7	> 8

high blood glucose levels in diabetics are:

1. Insulin resistance in peripheral tissue, especially in muscles tissue,
2. Impaired insulin secretion,
3. Increased hepatic glucose production, and of course
4. Glucose absorption from the gastrointestinal tract.

In addressing these pathogenic mechanisms, there are several different drugs with different mechanisms of action that can be used as monotherapy or in combination to achieve the recommended glycemic control. Good glycemic control is very important to be achieved to prevent the emergence of chronic complications of diabetes mellitus as proven by UKDPS. In T2 DM, clinically, patients can be grouped into obese and non-obese groups, with differing choice of initial treatment. For patients with predominant insulin resistance (typically obese), The use of medication(s) with dominant action on insulin resistance, is recommended. While for patients with predominantly impaired insulin secretion (typically lean, non obese), the recommended initial drug is insulin secretagoque, and exogenous insulin is recommended when insulin secretion becomes very low. Insulin is indicated in T2DM, where the use of oral hypoglycemic agent is contraindicated, in severe insulin production insufficiency, and also to prevent the glucose toxicity.

To achieve good glycemic control/near normalization of glucose control, we have to approach patients individually, while we also have to consider the main/ dominant underlying mechanism causing hyperglycemia,



and address these abnormal mechanisms using drug(s) with different mechanisms of action, and last but not least, targeted postprandial blood glucose control to be able to prevent chronic complications of Diabetes Mellitus.

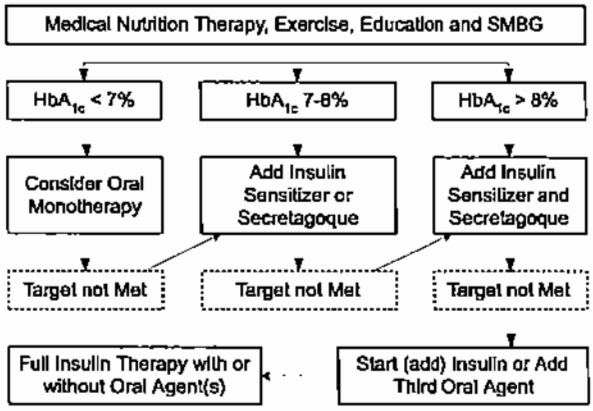
The staging of the severity of the decline in β cell capacity has an impact on clinical practice, changing the choice of therapy given to the diabetics to address the progression of diabetes, as follows:

I. Life style changes
II. Oral Hypoglycemic agents, monotherapy
III. Oral Hypoglycemic agents, combination therapy
IV. Insulin with or without OHA

In clinical practice, ADA proposed HBA1c as a guideline to determine when to determine different stages of β cell capacity. (See ADA algorithm).

Theoretically, (and possibly for implementation in clinical practice), up to 4 combination of oral hypoglycemic agents may be used in order to achieve good glycemic control, and insulin may also be added to achieve

Proposed New Treatment Paradigm for Type 2 Diabetes



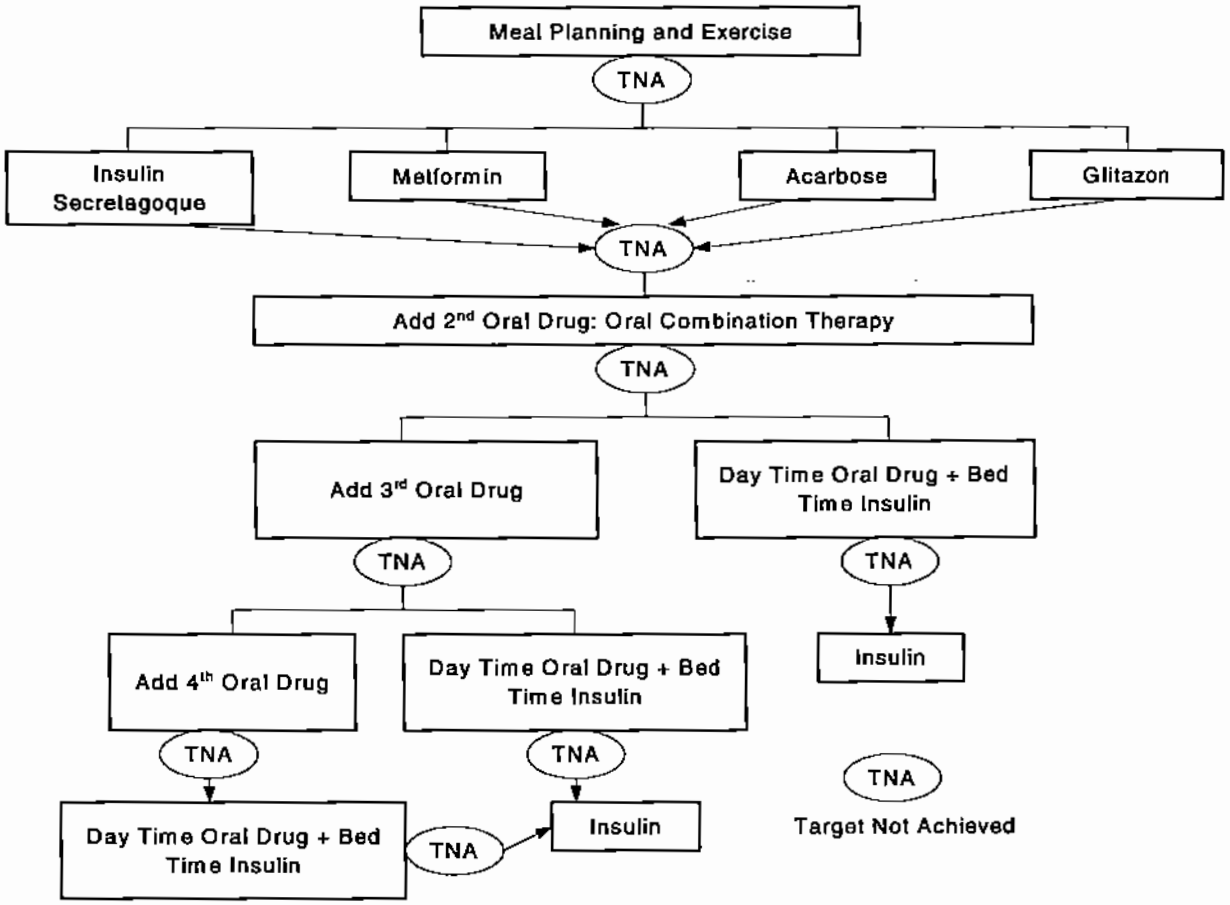
the recommended blood glucose target in our attempt to avoid the emergence of chronic diabetes complications. The recommended algorithm for combining hypoglycemic agents can be seen below.

COMBINATION THERAPY: INSULIN AND ORAL HYPOGLYCEMIC AGENT(S)

Combination therapy of insulin and oral hypoglycemic agent (OHA) has the following benefits compared to Insulin treatment alone:

- Improved glycemic control
- Treats multiple pathologic abnormalities
- Less insulin is needed to achieve good glycemic control

Algorithm for Combination Therapy in T2DM



- Reduced potential weight gain
- For the patients, combination of insulin and OHA is more practical
- Improved psychological acceptance, because the patient can continue their previous OHA regimen
- Less/minimal education is needed
- Treatment can be started in an outpatient setting
- Better compliance and also lower cost

There are several possible combinations of Insulin and OHA, with their own benefit(s):

- Insulin plus Sulphonylurea-BIDS
  Some insulin is endogenous, with natural secretory pattern
- Biguanide Plus Insulin
  Reduces hepatic resistance
  May achieve better control with less insulin
  Can reduce weight gain
- Alpha Glycosides Inhibitor plus Insulin
  Reduces postprandial glucose level
- Thiazolidinedione Plus Insulin
  Reduces peripheral insulin resistance
  Reduces insulin requirement
  Must balance TZD and insulin carefully to minimize weight gain

Recently Jarvinen HK published the result of a metaanalysis on studies concerning the Combination Therapy of Insulin and OHA in T2DM. Some important findings are shown below.

GLYCEMIC CONTROL

In Insulin Naïve Patients, there were all-together 15 comparisons, comparing treatment with insulin alone with treatment combination of insulin and OHA. Most (11 out of 15 studies) showed that the glycemic control achieved were similar between the two methods of treatments, while four other studies showed better glycemic control on combination therapy insulin and OHA.

In previously insulin-treated patients, there were 25 comparisons. Most (19 out of 25) studies showed that a combination of insulin and OHA can achieve better control than insulin alone.

INSULIN NEEDS

As a whole, patients receiving combination of OHA plus Insulin need less insulin compared to those receiving insulin alone. In Insulin naïve patients, combination of Insulin and OHA showed that less insulin was needed. The insulin sparing effect of metformin was 32%, sulphonylurea 42% and thiazolidinedione 53% respectively, while the insulin sparing effect of a combination of metformin and sulphonylurea was 62%.

In previously insulin treated groups, available studies showed a mean insulin sparing effect of metformin was 19% and sulphonylurea was 21%.

WEIGHT GAIN

In the management of T2DM, holistic approach is very important. Several other risk factors parameters have to be considered and addressed together. Weight gain is very important to be addressed in the management of T2DM. Concerning weight gain, the metaanalysis done by Jarvinen HK showed that weight gain was significantly less in Insulin combination with Metformin. In combination Insulin and sulphonylurea however, there was no difference in weight gain as compared to the insulin alone group, while in Insulin combined with Thiazolidinedione, more weight gain was found.

HYPOGLYCEMIA

In the metaanalysis done by Jarvinen HK, the occurrence of hypoglycemic episodes were less in insulin combined with Metformin as compared to insulin alone, but no difference was found in the amount of hypoglycemic episodes between Insulin combined with Sulphonylurea as well as Insulin with Acarbose, as compared to insulin alone. In Insulin combined with Thiazolidinedione however, more hypoglycemic episodes were found.

As for the choice of Insulin Regimen, when we used Intermediate acting insulin at 21.^{00} p.m. (bedtime), the maximal blood glucose reduction occured between 4.^{00}–8.^{00} a.m. and there was no more effect by 3.^{00} p.m. (18 hours).

In a study comparing long acting insulin analog Gargline vs NPH in combination therapy with OHA, among 423 insulin naïve T2DM patients, for 1 year, Insulin Gargline showed an overall rate of hypoglycemia of less than 35%, nocturnal hypoglycemia of less than 56% and the dinner-time glucose levels were lower compared to combination with NPH.

Studies comparing the use of Short acting insulin vs NPH in insulin combination with OHA found no difference in glycemic control, but found greater weight gain in multiple injection with short acting insulin.

Intermediate insulin combination may be given in the morning as well as at bedtime. There are three studies evaluating such regiment. In 2 studies, bedtime insulin injection yielded less hypoglycemia and less weight gain. In another study, they found no difference in the episode of hypoglycemia as well as weight gain.

Recently, we looked into registered patients attending Dr. Cipto Mangunkusumo General Central National Hospital in 1999 and 2000, evaluating their clinic attendance during the last three months (August, September and October 2001). We found that the percentage of good and sustainable compliance were very low, only 8.8% and 13.1% respectively for registered patients in 1999 and 2000.

Patients attending the diabetic clinic for the First Time in 1999

The Total number of newly registered patients in 1999 = 1119

The Total number of attendees (3 months) = 98

The Total number of visit (3 months) = 172

GOOD AND SUSTAINABLE COMPLIANCE8.8%

Patients attending the diabetic clinic First Time in 2000
The Total number of newly registered patients in 2000 = 1050
The Total number of attendees (3 months) = 138
The Total number of visit (3 months) = 172
GOOD AND SUSTAINABLE COMPLIANCE 13.1%

We also found a low percentage of good controlled diabetics of, only 33% (71/212) as measured by fasting blood glucose criteria (Table 1), and 21% (46/147) as measured by 2 hours blood glucose Post Prandial criteria (Table 2) respectively. The use of multiple OHA combinations as well as combination of Insulin and OHA were not much implemented, even though the blood glucose was still uncontrolled as seen in Table 1 and Table 2. Many factors might have caused this attitude. Beside the system and the attitude of the health provider, patient factors also play a very important role in the effort to achieve good blood glucose control. The limited variety of oral hypoglycemic agents available (only

Tabel 1. Degree of Glucose Control (Mean Fasting Blood Glucose Last 3 Visits), Registered Cases, Dr. Cipto Mangunkusumo General Central National Hospital on November 2001

Methods of R/	Mean Fasting Blood Glucose in the Last 3 Visits		
	< 120 mg/dL	> 120 mg/dL	Total
Diet Only	22	7	29
Sulphonylurea	18	44	62
Biguanide	17	30	47
Acarbose	-	-	-
Comb. 2 OHA	9	44	53
Comb. 3 OHA	0	1	1
Comb. OHA + Ins.	1	4	5
Insulin	4	11	15
	71	141	212

Degree of Glucose Control and Methods of R/ (Dr. Cipto Mangunkusumo General Central National Hospital, Registered Cases 1999 and 2000)

Tabel 2. Degree of Glucose Control (Mean 2 Hours Post Prandial Last 3 Visits), Registered Cases, Dr. Cipto Mangunkusumo General Central National Hospital on November 2001

Methods of R/	Mean 2 Hours Post Prandial Blood Glucose in the Last 3 Visits		
	< 160 mg/dL	> 160 mg/dL	Total
Diet Only	**13**	**4**	**17**
Sulphonylurea	**15**	**33**	**48**
Biguanide	**10**	**24**	**34**
Acarbose	**-**	**-**	**-**
Comb. 2 OHA	**5**	**29**	**34**
Comb. 3 OHA	**0**	**1**	**1**
Comb. OHA + Ins.	**1**	**3**	**4**
Insulin	**2**	**7**	**9**
	46	**101**	**147**

Degree of Glucose Control and Methods of R/ (Dr. Cipto Mangunkusumo General Central National Hospital, Registered Cases 1999 and 2000)

sulphonylurea and biguanide) might have caused the limited choice of oral hypoglycemic agents' combination.

In the treatment of T2DM patients, the choice of initial oral hypoglycemic should be tailored according to the basic pathophysiologic abnormalities. Sulphonylurea is recommended as the initial treatment for non obese T2DM patients, who have impaired insulin secretion capacity, while Biguanide is recommended as the initial treatment for obese T2DM patients who have predominant insulin resistance as the basic pathophysiologic abnormality. The implementation of this recommended practice could also be seen in our clinic. Sulphonylurea is patients used more frequently, while for Non-Obese T2DM (BMI < 27 Kg/M^2 and Biguanide is more commonly prescribed to more obese patients (BMI > 27 Kg/M^2). (Table 3)

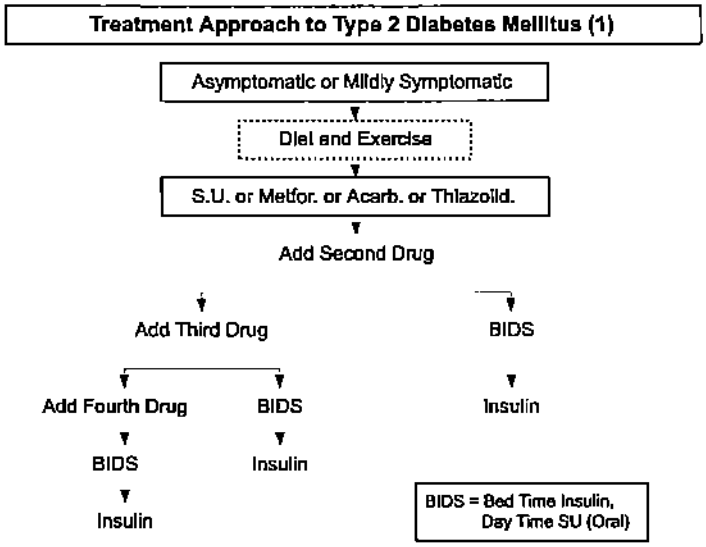
From the health providers point of view, there are many possibilities in combining the available measures

Tabel 3. Type of Diabetes Mellitus Treatment in Different Nutritional Status, Dr. Cipto Mangunkusumo General Central National Hospital, Registered Cases 1999 and 2000

Methods of R/	Body Mass Index		
	< 27 kg/M^2	> 27 kg/M^2	Total
Diet Only	28	5	33
Sulphonylurea	65	6	71
Biguanide	30	20	50
Acarbose	-	-	-
Comb. 2 OHA	52	8	60
Comb. 3 OHA	1	0	1
Comb. OHA + Ins.	5	1	6
Insulin	15	0	15
	196	40	236

Body Mass Index and Methods of R/ (Registered Cases 1999 and 2000, Last 3 Months 2001)

to achieve good blood glucose control (See Algorithms A, B and C). Each physician has their own judgement in making his choice of treatment to be prescribed to diabetics, based on sound knowledge on the basic pathophysiology of diabetes and the recent and updated methods of treatment for the diabetics. Treating T2Dm to achieve optimal blood glucose control is obviously the real medicine. The art of treatment is of paramount importance.



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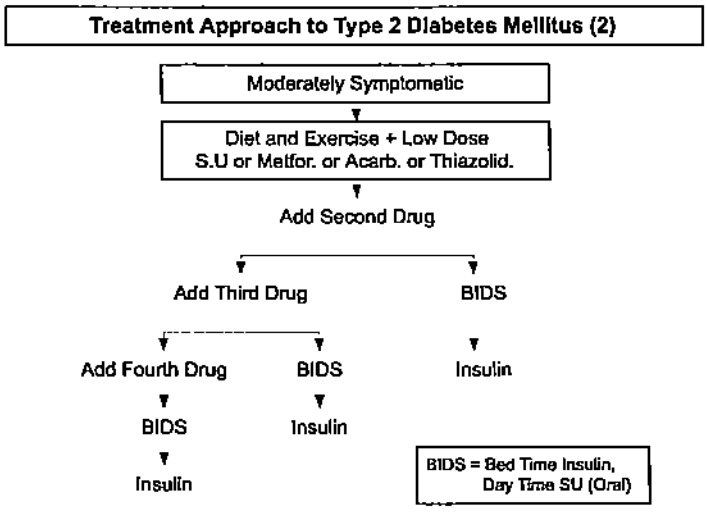

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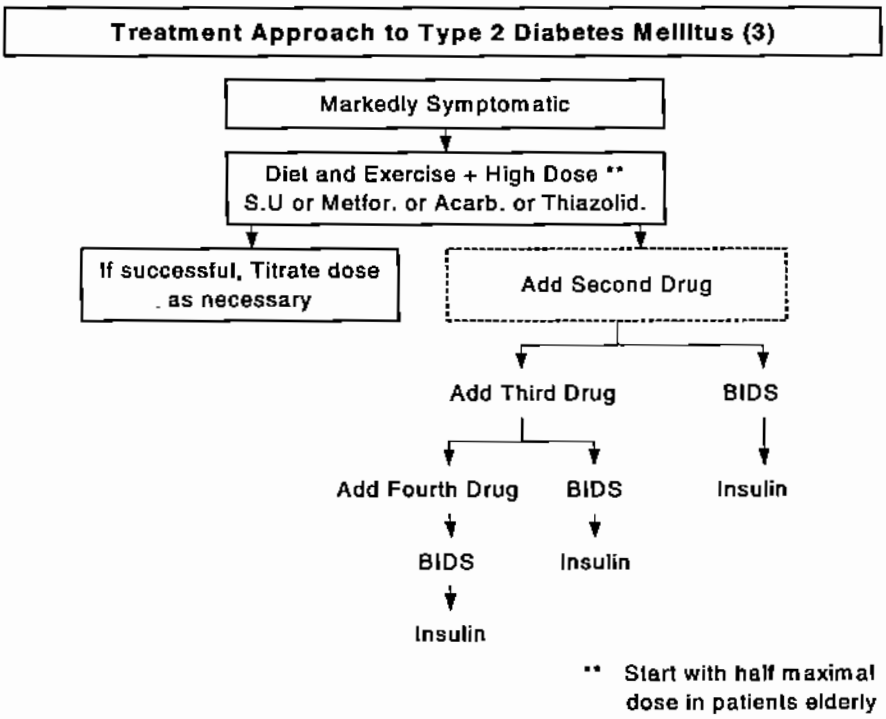

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