Review Article and Clinical Experience:
INSULIN GLARGINE COMBINED WITH ORAL AGENT IN T2DM (CLINICAL USES OF FORMULAS: 1/3, 5-5, 2-2, 1-1, AND 1-2)

Askandar Tjokroprawiro

ABSTRACT

A map of oral agents for diabetes (OADS), either at present or in the future should be well recognized. Four of such OADS (glimepiride, glinides, gliclazide, metformin) have claimed showing atheroprotective properties beyond its hypoglycemic or anti- hypoglycemic effects. On the basis of clinical experiences and molecular mechanisms, glimepiride (GLIM) can be summarized having 3B - 3A - 9D properties: 3-fold higher rate of Binding to receptor (3B), 3-fold lower Affinity to receptor (3A), and 9-fold faster rate of Dissociation from receptor (9D). These effects (3B-3A-9D) may result in potential therapeutical benefits, including: rapid onset (due to 3-fold higher rate of Binding = 3B) and less hypoglycemic events due to lower Affinity (3A) and faster Dissociation (9D). By using therapeutic concentration (in contrast to glibenclamide), GLIM (via PI3-Kinase Pathway) increases insulin - stimulated glycogen synthesis (GS) in human muscle cells (GS effect). In addition, GLIM inhibits platelet aggregation which may in turn have a preventive effect on the development of diabetic vascular complications (more pronounced effect than gliclazide). The ideal basal insulin should ideally have the following six characteristics: 1. mimics normal pancreatic basal insulin secretion, 2. long-lasting 24-hour effect, 3. smooth, peakless profile, 4. reproducible and predictable effects, 5. reduces risk of nocturnal hypoglycemia, and 6. once-daily administration. Insulin Glargine (GLAR) is a novel peakless long-acting insulin analogue that is available for clinical use and it has a smooth profile and long, 24-hour duration of action. Thus, GLAR is an improved basal component for combination regimens (Method A, B, and C) with OADS in the treatment of type 2 diabetes mellitus (T2DM). The most frequent indication of CTOI is, patients with T2DM who failed to be treated with a maximal dose of OHA, although medical nutrition therapy (MNT) and programmed regular exercise have been perfectly adhered to. Based on clinical experiences another 6 (six) indications of CTOI are listed in this manuscript. For the clinical practice point of view, Formulas: 1/3, 5-5, 2-2, 1-1 and Formula 1-2 are provided for the CTOI in the management of patients with T2DM. GLIM can be combined with insulin therapy (f.e. with GLAR) in the treatment of T2DM. Based on the clinical experiences, such a combination can be performed by 3 Methods such as Method- A : both GLIM-GLAR administered in the Morning, Method- B : GLAR-Morning and GLIM-Evening, and Method- C : GLIM-Morning and GLAR-Evening. Conclusions: GLIM is 3 gen. sulphonylurea which shows quintuple pleiotropic cardioprotective properties beyond its hypoglycemic effect. GLAR is a human peakless insulin analogue that exhibits a 24-hours action profile (as a basal insulin) with fewer episodes of nocturnal hypoglycemia. Thus, the CTOI: GLIM and GLAR combination, may provide for cardioprotective properties. On the basis of clinical experiences, Method-A (by using a prebreakfast injection of insulin GLAR coincides with GLIM) has been proven to be most effective and well tolerated.

Abbreviations: OADS = oral agents for diabetes; GLIM = glimepiride; GLAR = insulin glargine; B = binding; A = affinity; D = dissociation; GS = glycogen synthesis; CTOI = combined therapy OAD with insulin; T2DM = type 2 diabetes mellitus; T1DM = type 1 diabetes mellitus; MNT = medical nutrition therapy; GP = general practitioner.

***Keywords**: sulphonylurea, insulin glargine, glimepiride, oral agents T2DM, atheroprotective effects*

INTRODUCTION

Sulphonylureas have been used since the 1950S as the first-line therapy for the treatment of type 2 diabetes mellitus (T2DM) patients whose blood glucose levels were not effectively controlled by MNT and programmed physical exercise. In clinical practice, hypoglycemic and anti-hyperglycemic agents can be categorized into three groups (Tjokroprawiro 2002A, 2002B)

1. Insulin Secretagogues
   A. Sulphonylureas
   B. Non-Sulphonylureas: meglitinides (repaglinide, nateglinide), GLP-1 analogue: extendin-4)

Diabetes and Nutrition Center
Dr. Soetomo Teaching Hospital
Airlangga University School of Medicine, Surabaya
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Sulphonylureas:
Gen-I: tolbutamid,chlorpropamide, etc.
Gen-II: glibenclamide, glipizide IR, glipizide-GITS, gliclazide-MR, gliquidone
Gen-III: glimepiride:
a. No Effects at CV KATP Channels, 3B-3A-9D Properties
b. Insulin Sparing, Glycogenic, Anti Platelet Effect

2. Insulin Sensitizer and Antihyperglycemic Agents
A. Thiazolidinediones
1. Ciglitazone
2. Englitazone
3. Trioglitazone (R/ Resulin)
4. Rosiglitazone (R/ Avandia): FDA May 1999
5. Pioglitazone (R/ Actos): FDA July 1999
6. Darglitazone

B. Biguanides:
1. Metformin: glucophage, glukotika, diabex, glumin, etc.
2. 3-Guanidinopropionic-Acid

3. Intestinal Enzyme Inhibitors
A. a-Glucosidase Inhibitors: acarbose, voglibose (AD-128), miglitol, MDL-73945, castanospermine
B. a-Amylase Inhibitor: tendamistase

4. Other Specific Types
A. Insulin mimetic drugs (glimepiride, chromium, a-lipoic acid, vanadium)
B. B-Cell replacers (GLP-1 analogues, e.g: extendin 4, etc)
C. Inhibitors of dipeptidyl peptidase (DPP-IV): metformin, etc
D. Suppressors of glucagon secretion: amylin analogues, e.g pramlintide, etc

Glimepiride (GLIM) has plenty of pleiotropic effects and benefits. Such specific properties of GLIM will be shortly described in this paper and on presentation. To date, insulin analogues (recombinant human insulin, since 1980S) can be synthesised by means of the rDNA technique, and clinically can be differentiated into 2 groups (Bolli et al 1999).

I. Short-Acting Insulin Analogues
1. Insulin Lispro: on the market in the year 1996 (Lys B28, Pro B29-Human Insulin)
2. Insulin Aspart (by replacing Proline at posisition B28 by Aspartic Acids = Asp B28)
3. Insulin Asp B9
4. Insulin Asp B10
5. Insulin GLU B21
6. Insulin GLU B27

II. Long-Acting Insulin Analogues
1. Insulin Glargine: on the market in year 2000 (21 A-Gly-30Ba-L-Arg-30Bb-L-Arg-Human Insulin)
2. NovoSol Basal
3. NN-304
4. W99-S32
5. C-16-HI

Insulin Glargine (GLAR) is a long-acting peakless insulin analogue which may mimic normal pancreatic basal insulin secretion. On the basis of clinical experiences, 3 methods for combined therapy of GLIM and GLAR will be introduced (Methods A, B, and C). The aim of this paper and presentation is to introduce (in short) the pleiotropic effects of GLIM, Insulin GLAR, Combined Therapy and its clinical benefits with the GPs, Residents, Internists, and also with the associated Specialists.

GLIMEPIRIDE: A NOVEL INSULIN SECRETAGOGUE

There are novel antidiabetic agents (hypoglycemic or antihyperglycemic agents) in development that lower blood sugar levels such as by delaying intestinal glucose absorption, increasing insulin concentration or mimicking insulin action, or by metabolic effects that enhance glucose uptake or reduce hepatic glucose production. Some agents are capable of lowering glucose levels into the hypoglycemia range, whereas others improve hypoglycemia but carry little risk of causing hypoglycemia. Glimepiride (GLIM) is the 3rd generation of sulphonylurea, a novel insulin secretagogue which has pleiotropic properties beyond glucose lowering, such as (Muller et al 1994, 2000, Tjokroprawiro 2002A, 2002B):

1. Cardioprotective Effect
2. Insulin Sparing Effect
3. Specific Properties: 3B-3A-9D Effects
4. Glycogenic Effect
5. Anti platelet agregation

Hence, GLIM can be regarded as the 3rd generation of sulphonylurea with quintuple-effects as mentioned above: I, II, III, IV,V. Glimepiride acts at KATP channels on pancreatic ß-cell to promote insulin release. It binds to 65 kD protein on ß-cell, which appears to be a part of the same sulphonylurea receptor that binds glibenclamide (140 kD). GLIM increases expression of glucokinase in RNA and the glucose transporter GLUT 2 in pancreatic cells in vitro. The effects of GLIM (compared to placebo) on blood glucose and insulin levels in patients with T2DM appear during the first 4 hours after the dose. Over this 4-hour period, greater

reduction in blood glucose occurred on the 4th day of treatment with GLIM 2 mg/day than glibenclamide 10 mg/day (Dills et al 1996).

Glimepiride was also associated with greater reduction in insulinemia than glibenclamide during exercise, despite similar reductions in blood glucose (Muller et al 1994). The drug appears to act within peripheral cells at a point after insulin receptor interaction, increasing glucose transport and glucose transporter expressions (GLUT 1 and GLUT 4) lipogenesis, and glycogenesis. GLIM also appears to reduce insulin resistance and increase hepatic glucose disposal in animal models, but not in patients with T1DM. In a 1-year US comparative study, hypoglycemia occurred in 10% of 289 GLIM recipients and 16.3% of 288 patients receiving glibenclamide.

I. GLIMEPIRIDE:
CARDIOPROTECTIVE EFFECT

The major site of activity of GLIM is thought to be membrane receptors on pancreatic ß-cell, where it acts via the closure of KATP chanels. The closure of the channels may result in reduced coronary blood flow. However, unlike glimepiride, GLIM is though to have no effects at cardiovascular KATP channels in humans (Bijlstra et al 1996). Furthermore, the ability of norepinephrine, serotonin, potasium chloride and PGF2a, to induce contractions in rat aorta in vitro was inhibited by GLIM. In contrast, glibenclamide attenuated response to PGF2a but not to norepineprhrine, serotonin, or potassium chloride. In vitro and in vivo studies in rats revealed that compared with glibenclamide, GLIM showed milder and fewer modest effects on KATP channels, blood vessels, or the heart. In Open-Chest anaesthetized dogs, GLIM had milder-effects than glibenclamide or gliclazide in inducing ST-segment elevation, increasing coronary resistance, myocardial oxygen extraction and serum potassium levels, and reducing coronary blood flow and the mechanical activity of the heart (Giesen et al 1996). Conclusion: GLIM, the 3rd generation sulphonylurea shows cardioprotective effects beyond glucose lowering.

II. GLIMEPIRIDE:
INSULIN SPARING EFFECTS

As reported by Muller (2000), the molecular mechanism of decreases in blood glucose levels provoked by GLIM occurred to early on ß-cell on SURX, and associated with the KATP channels and different from SURX for glibenclamide, in muscle and adipocytes. Such molecular mechanisms are:

1. increased production of DAG and activation of PKC
2. enhanced expression of GLUT
3. insulin receptor-independent activation of the IRS/P13-Kinase Pathway.

Mechanism no. 3 involved a Non-RTK (receptor tyrosine kinase) = Non-RTK and several components, such as caveolin and GPI (glycosyl phosphatidyl inositol) structures, which are assembled in caveolae/DIG (ditergent-insoluble-glycolipid)-enriched rafts of this target cell plasma membrane; hence, that pathway is different from IRTK activity. Conclusion: This insulin-mimetic / sensitizing activation of GLIM can be called insulin sparing effects.

III. GLIMEPIRIDE:
SPECIFIC EFFECTS 3B - 3A - 9D

Based on the results of many studies, compared with glibenclamide, GLIM has a 3-fold higher rate of Binding to Receptor (3B), a 3-fold lower Affinity to Receptor (3A), and a 9-fold faster rate of Dissociation (9D).
Hence, GLIM has 3B - 3A - 9D properties which may result in (Tjokroprawiro 2002A, 2002B):

1. rapid action (due to 3B-effect)
2. less hypoglycemic events (due to 3A and 9D)
3. minimal glucose levels fluctuations or spikes (3A and 9D)
4. not tightly closure of KATP channels; thus, reduced coronary blood flow can be minimized.

Conclusion: Specific properties (3B, 3A, 9D) of GLIM may be of great benefits and therapeutically relevant

IV. GLIMEPIRIDE:
GLYCOGENIC EFFECTS

It was recently reported that incubation of human skeletal muscle cells cultures derived from glucose tolerant subjects with GLIM causing a dose-dependent might increase insulin stimulated glycogen synthesis by using therapeutic GLIM concentration (Haupt et al 2001); this effect seems to be mediated via the PI3 Kinase Pathway. In contrast with GLIM, glibenclamide had no significant effect on either basal or insulin-stimulated glycogenesis. Conclusion: In humans, GLIM has an extra pancreatic action as glycogenesis stimulator.

V. ANTI PLATELET EFFECT

GLIM affects key steps in thrombin-induced activation and aggregation. GLIM inhibits thrombin stimulated increase of intracellular Ca++. GLIM inhibits selectively the cyclooxygenase enzyme, wheres

glibenclamide inhibits both cyclooxygenase an 12-lipooxygenase enzyme. Gliclazide has no effect on either cyclooxygenase or 12-lipooxygenase, GLIM inhibits platelet aggregation which may in turn have a preventive effect on the development of diabetic vascular complications in patients. GLIM has a more pronounced effect than gliclazide and a more specific effect than glibenclamide.

INSULIN ANALOGUES: SHORT AND LONG ACTION (FOCUS ON INSULIN GLARGINE)

A. Structure and Physicochemical Characteristics

Analogues of insulin can be synthesized by means of rDNA technique and can be differentiated into short and long-acting insulin analogues (Bolli et al 1999). The description of insulin analogues will be focused on insulin glargine (GLAR). This insulin analogue (21A-Gly-30Ba-L-Arg-30 Bb-L-Arg-human insulin = HOE 901) produced by rDNA technology, is a human insulin analogue with prolonged action.

GLAR results from two modifications of human insulin. First, two positive charges (two arginine molecules) are added at the C-terminus of the B-chain. This result in a shift of the IEP (iso electric point) from a pH of 5.4 to 6.7 ± 0.2 making the molecule more soluble at slightly acidic pH and less soluble at the physiological pH of subcutanous tissue. Because the derivative is formulated at an acidic pH, a second modification is needed to avoid deamidation and dimerisation by the acid-sensitive asparagine residue at position 21 in the A-chain. The replacement of A-21 asparagine by glycine is neutrally-charged and associated with good stability of the resulting human insulin analogue.

Injected as a clear solution of pH 4.0, GLAR forms a microprecipitate at the physiologic, neutral pH of the s.c space. The stabilization of insulin hexamer and higher aggregates can influence the nature of he precipitate and the rate of its dissolution and absorption from the site of infection. Consequently, GLAR has a delayed and prolonged absorption from the injection site after s.c injection. Because GLAR is formulated as a clear, acidic solution, it cannot be mixed with insulin formulated at a neutral pH such as regular insulin.

B. Example of Clinical Study

Several studies were done in T1DM treated for 4 weeks to evaluate the effectiveness and tolerability of GLAR compared with NPH (Pieber et al 1998, Rosenstock et al 1998), with FPG as the parameter. GLAR given once daily at bedtime reduced FPG statistically more significantly than NPH given once or twice daily. The improvement in glycemic control seen with GLAR compared with NPH in the 4-week studies were achieved with lower (Picker et al 1998) or similar (Rosenstock et al 1998) incidence of nocturnal hypoglycemia. These results have been confirmed in a 28-week randomized trial in 534 patients with T1DM on multiple daily insulin injection regimen allocated to bedtime GLAR or bedtime NPH or NPH b.i.d. Fasting Plasma Glucose (FPG) was approximately 32.5 mg/dl lower and frequency of hypoglycemia was more than 50 % lower with GLAR (Ratner et al 1999). Similar Results have been observed in a 28 week randomized trial in 158 patients with T2DM (Rosenstock et al 1999). Taken together, these data suggest that the majority of patients with T1DM and perhaps also T2DM might benefit from GLAR. This is in line with the Clinical Experiences of the author (2003A, 2003B) CTOI in patients with T2DM who are treated with combined therapy of GLIM and GLAR.

CTOI: INDICATIONS AND CLINICAL EXPERIENCES

As described in PERKENI - Consensus 2002, CTOI is indicated for T2DM patients if in combined treatment of minimally 2 types of OHAS (almost maximal dose) of different mechanisms prove unfruitful. Insulin dose should be started with 5 units intermediate insulin which can be given in the mornings and at bed time (the latter is preferable). OHAS should be stopped if insulin dosage is higher than 30 units /day, and twice injection of premixed insulin are recommended (two thirds in the morning and one third in the evening). Based on clinical experiences on CTOI (Tjokroprawiro 2003A, 2003B), Indications, Methods, the use of Formula One Third (1/3), Formula 5-5, Formula 2-2, and Formula 1-1 and Formula 1-2 will be shortly described.

INDICATIONS OF CTOI

Indication of CTOI (Tjokroprawiro 2003B) for out patients with T2DM can be divided into 2 categories:

I. Primary Indications of CTOI (almost similar with PERKENI-Consensus 2002):
   1. T2DM patients (with no infections and other metabolic stresses) who developed failure with appropriate dietary and lifestyle interventions even with 3 or 4 (almost) maximal dose of OHAS - combination of different mechanisms (especially those with AIC = 8%).
   2. T2DM patients Stage III A, III B, an IV A (see FIGURE-2).

II. Secondary Indications (Clinical Indication for Anabolic Property) are indicated for T2DM patients with:
   1. Bone Fractures
   2. Moderate, Severe, Hemodyalized Diabetic Nephropathy
   3. Advanced Pulmonary Tbc (Non-Obese Patients)
   4. Decompensated Liver Cirrhosis
   5. Rapid Body Weight Loss or Underweight Patients
   6. Specific Cases: Non-active Gangrene, etc.

COMBINED THERAPY OF GLIMEPIRIDE AND GLARGINE

(Clinical Experiences)

Based on clinical experiences, 3 Methods (A, B, and C) can be accepted by patients with diabetes mellitus based on their conveniences and life style.

1. Method-A

In Method-A GLIM-GLAR are both administered in the morning (morning and morning). Glimepiride (GLIM) in maximal dose 3-6 mg (titrated dose) is given 30 minutes before breakfast (pre-breakfast), and then Glargine (GLAR) injection (s.c.) in a doses of 10-30 units is administered, also 30 minutes pre-breakfast (Figure 1).

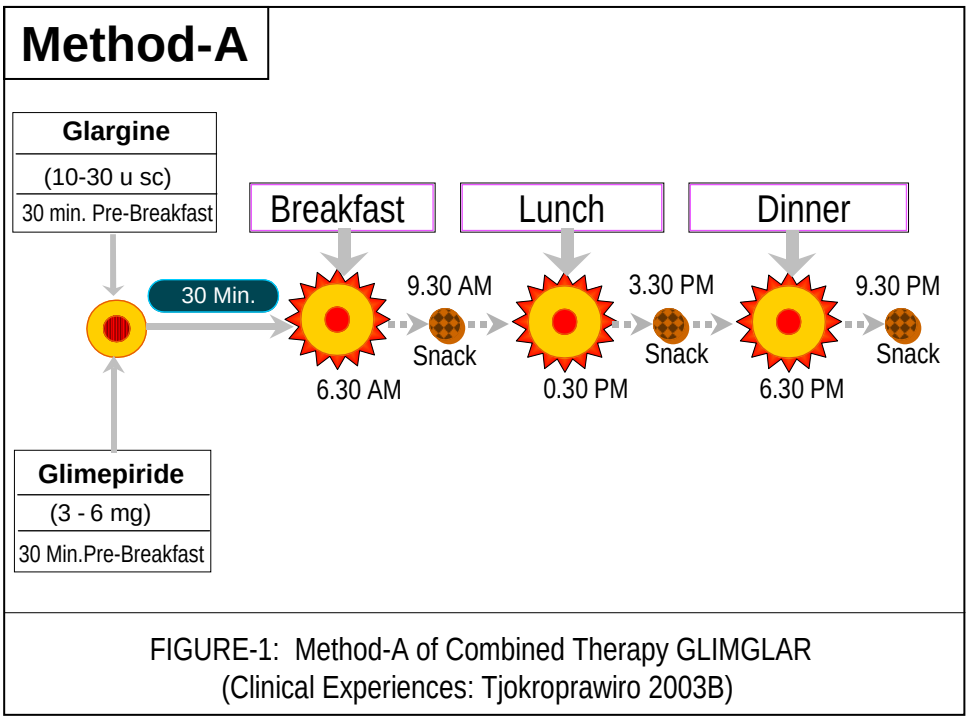

FIGURE-1: Method-A of Combined Therapy GLIMGLAR
(Clinical Experiences: Tjokroprawiro 2003B)

2. Method-B

In Method-B, GLAR-GLIM are separately administered (morning and evening). By this method, glargine (10-30 Units) is subcutaneously injected 30 minutes pre-breakfast, and glimepiride is given 30 minutes pre-dinner (Figure 2).

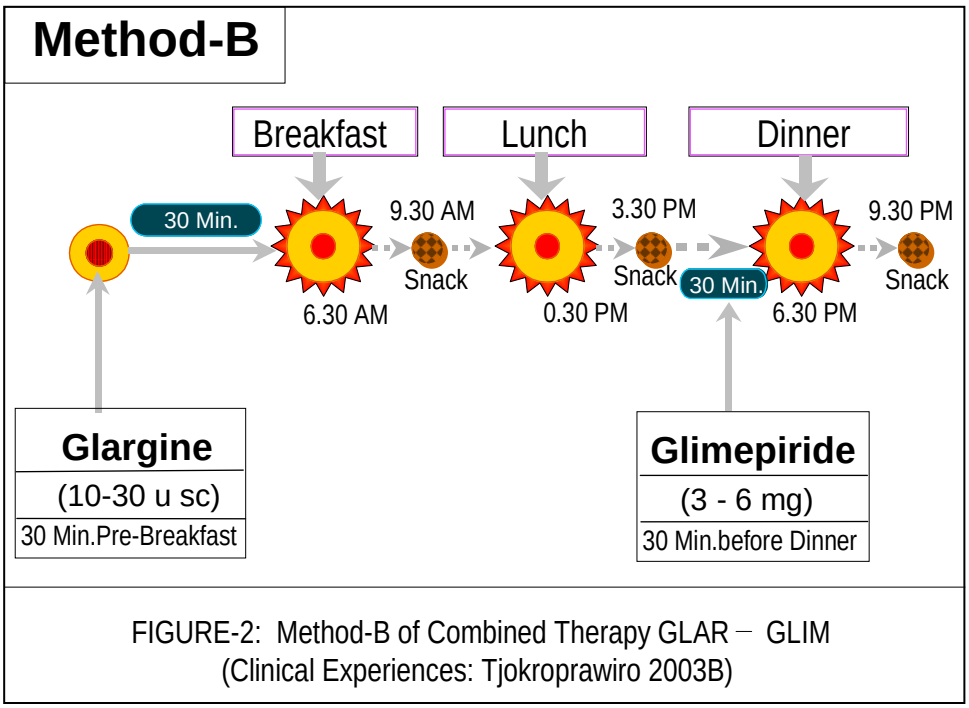

FIGURE-2: Method-B of Combined Therapy GLAR – GLIM
(Clinical Experiences: Tjokroprawiro 2003B)

3. Method-C

GLIM-GLAR are separately administered (morning and evening). Glimepiride is given 30 minutes before breakfast, and Glargine to be administered subcutaneously 30 minutes before dinner (Figure 3).

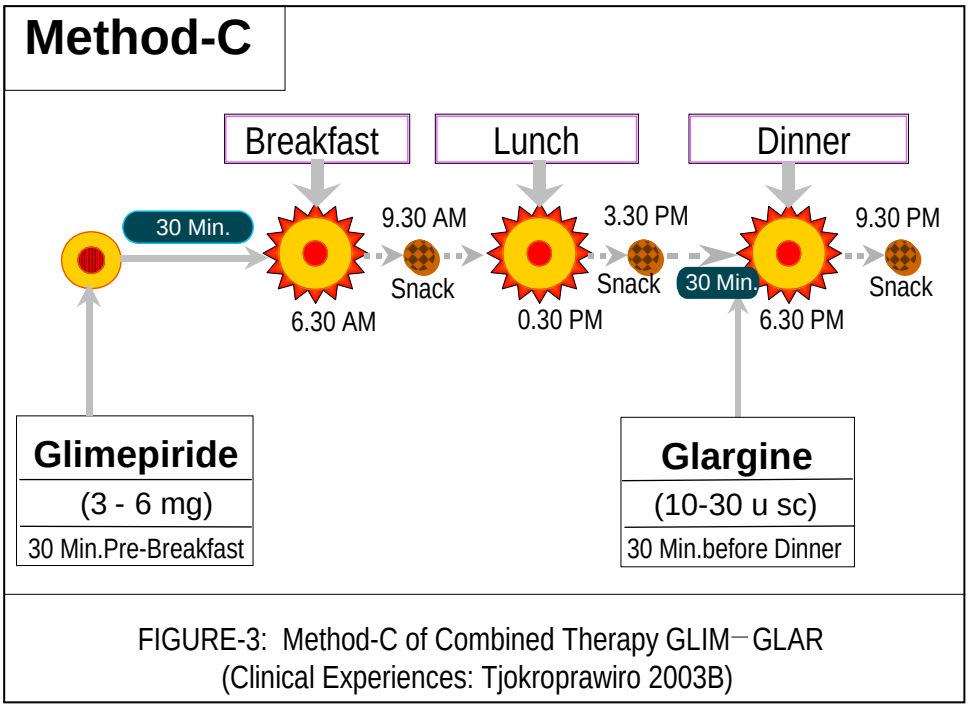

FIGURE-3: Method-C of Combined Therapy GLIM–GLAR
(Clinical Experiences: Tjokroprawiro 2003B)

On the basis of clinical experiences Method (A) is the most frequent one accepted by the patients with diabetes mellitus. However, either Method-A, B, or C shows the same glycemic control. For uneducated patients especially with autonomic diabetic neuropathy, Method-C may bring nocturnal hypoglycemic episode along with them.

COMBINED THERAPY OAD AND INSULIN (Formula 1/3, Formula 5-5, Formula 2-2, Formula 1-1 and Formula 1-2)

In clinical practice, CTOIS are frequently applied for T2DM-outpatients and T2DM-inpatients, in which CTOI of the latter is used for the discharged patients for home care (the conversion from three times injection of regular insulin / actrapid in the hospital to CTOI). The next description of CTOI-inpatients and CTOI-outpatients, Formula One Third (1/3), Formula 5-5, Formula 2-2, Formula 1-1, and Formula 1-2, will be used (based on clinical experiences of the author, Figure 4).

CTOI-inpatients (discharged patients): after T2DM-patients have been well controlled with actrapid (AR), f.e-20 units tid (60 units/day), those patients can be discharged with CTOI-inpatients, by Method-A, Method-B, or Method-C (see above description) using Formula-1/3, as illustrated below. CTOI - outpatients: the dose of insulin is depending on the level of 2-hour blood glucose level (2 h BG) of patients with T2DM who failed with almost maximal dose of OAD in combination with other 2 or more OADS. Example: 2 h BG = 360 mg/dl. Take Figure 36 (the first two of 360: 3 and 6), and apply Formula-1/3: 1/3 x 36 = 12, and use Method -A, Method - B, or Method - C thus:

a. Method-A:

1. GLAR: 12 units to be injected subcutaneously 30 minutes pre-breakfast.
2. GLIM is administered 30 minutes pre-breakfast

b. Method-B: - as mentioned in CTOI-In patients

Illustration of CTOI-Inpatients and CTOI-Outpatients can be seen in Figure 4.

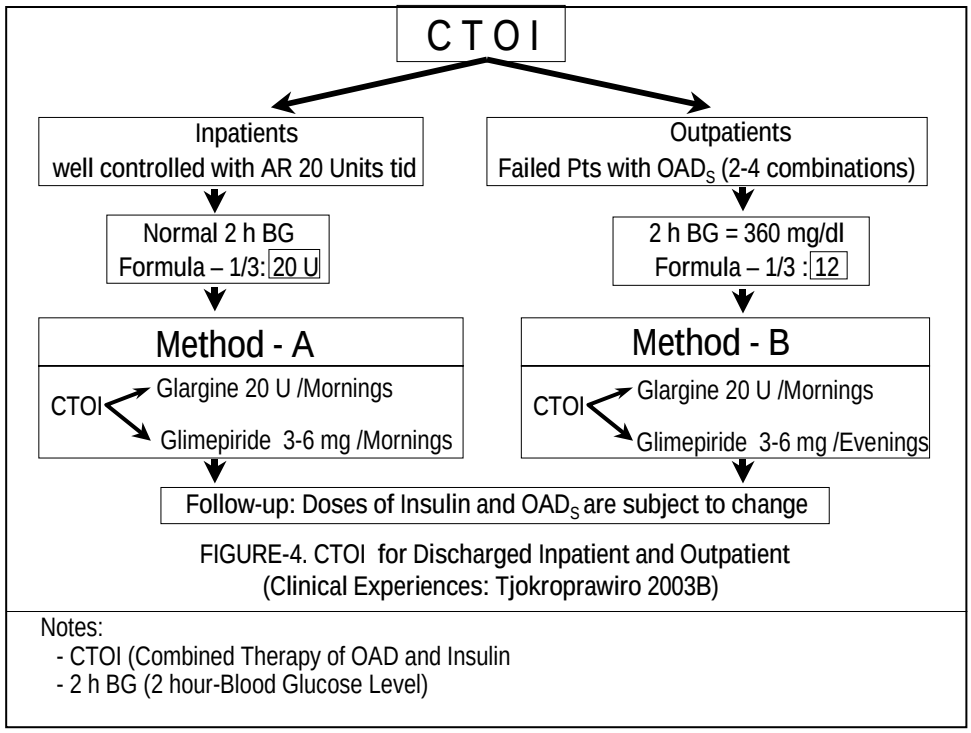

FIGURE-4. CTOI for Discharged Inpatient and Outpatient
(Clinical Experiences: Tjokroprawiro 2003B)

Notes:
- CTOI (Combined Therapy of OAD and Insulin
- 2 h BG (2 hour-Blood Glucose Level)

How to use Formula 5-5, Formula 2-2, Formula 1-1 and Formula 1-2 ? Formula 5-5 is used to increase the dose of insulin (5units) after 5 day-evaluation if the 2 h BG is still higher than 200 mg /dl. The increment of 2 units (PERKENI-Consensus 2002) insulin is frequently followed by the phenomena of dose-tolerance. Formula 2-2 is used to slow down the dose of insulin (2 units) every 2 day-evaluation (if the normal 2 h BG has been achieved). The application of this Formula- is aimed to minimize, or to stop, dose of insulin, while the dosages of OADS are increasing. The explanation of Formula 1-1: the slow down of the dose of insulin slowly is 1 (one)

unit everyday, and so on, until the last injection of insulin is ended. Formula 1-2 can be used by decreasing the insulin dose very slowly, 1 (one) unit every 2 (two) days, otherwise the dose of OAD should be increased optimally.

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