

Review Article and Clinical Experience:

**NEW INSIGHTS INTO ORAL AGENTS IN THE TREATMENT OF T2DM
(THE ROLES OF FIXED-DOSE ORAL AGENTS COMBINATION)
(The Roles of Fixed-Dose Oral Agents Combination)**

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ABSTRACT

Recent advances in the development of strategies for the treatment of type 2 diabetes mellitus (T2DM) including a map of oral agents for diabetes (OADS) should be recognized. It has been widely reported that metformin, glimepiride, glinides, and gliclazide were 4(four) OADS which showed atheroprotective properties. Importantly, as reported by the landmark UKPDS in 1998, metformin has proven to be more than an OAD beyond its antihyperglycemia effects. Its pleiotropic effects, such as antiatherogenic properties, inhibitor of glycation processes, and reducer of microvascular dysfunction may result in cardiovascular benefits. Moreover, 21 metabolic and endocrine effects of metformin are summarized in this paper. Type 2 diabetes mellitus (T2DM) may range from predominantly insulin resistance (IR) with relative insulin deficiency to predominantly secretory defect (impaired acute insulin response = impaired AIR or impaired first phase of insulin secretion) with insulin resistance. Thus, the dual endocrine defects are involved in T2DM. Rationally, metformin and glibenclamide address directly such dual endocrine defects (IR and impaired AIR). As reported in UKPDS-1998, both metformin and glibenclamide decreased significantly the risk of diabetic vascular complications: diabetes-related death 42%, all cause mortality 36%, all diabetes-related end point 32 %, myocardial infarction 39%, and stroke 41%. Glucovance is the ideal combination of metformin and glibenclamide formulated and engineered for optimal drug delivery. Earlier absorption of glibenclamide from a freely-soluble metformin matrix in glucovance taken with meals may help to deal with the postprandial hyperglycemia. Glucovance is therefore optimized to cope with both fasting and postprandial hyperglycemia. Many reports (2001-2003) are in favour of glucovance showing metabolic and potential cardiovascular benefits. One of them (2003) showed that one year treatment with this new drug was associated with durable improvement in AIC (-1.7%), fasting plasma glucose = FPG (-55 mg/dl), improvement in lipid profiles (Total Cholesterol, LDL-Cholesterol, Slightly HDL-Cholesterol) but TG was unaffected, and no increase in body weight. These changes imply a modest improvement in cardiovascular risk profile. Conclusions: The pathophysiology of T2DM and the dual endocrine defects of T2DM (IR and impaired AIR) should be well recognized. The first strong indication of a potentially beneficial effect of fixed combination of metformin and glibenclamide on the cardiovascular system comes from the landmark UKPDS. Such a fixed combination engineered for optimal release called glucovance, therefore, can be used as new strategy for the treatment of T2DM if no contraindications (especially for metformin) exist.

Keywords: oral agents, type 2 diabetes mellitus, metformin, glibenclamide, UKPDS, glucovance

INTRODUCTION

Before starting to study on oral agents for diabetes (OADS), a map of such drugs should be recognized. For a clinical practice point of view, since the year 1996, Tjokroprawiro has composed a map of OADS (TABLE 3). As seen in TABLE 3, there are 4 OADS in which each shows atheroprotective properties, f.e.: metformin, glimepiride, glinide group, and gliclazide.

Importantly, landmark longitudinal study has proven with many significant clinical results (UKPDS 1998). Metformin is more than an OAD; beyond its antihyperglycemic effect, metformin has recently been known having many cardiovascular benefits through many pleiotropic effects, such as: antiatherogenic properties (Mamputu et al 2003), inhibitor of glycation processes (Beisswenger 2003), and reducer of microvascular dysfunction (Wiernsperger et al 2003), etc.

Acute and chronic hyperglycemia in patients with type 2 diabetes mellitus (T2DM) confer a sharply increased risk of microvascular diabetic complications, including retinopathy, peripheral neurology, nephropathy, and increased risk of cardiovascular events. Both dual endocrine effects (insulin resistance and β -cell

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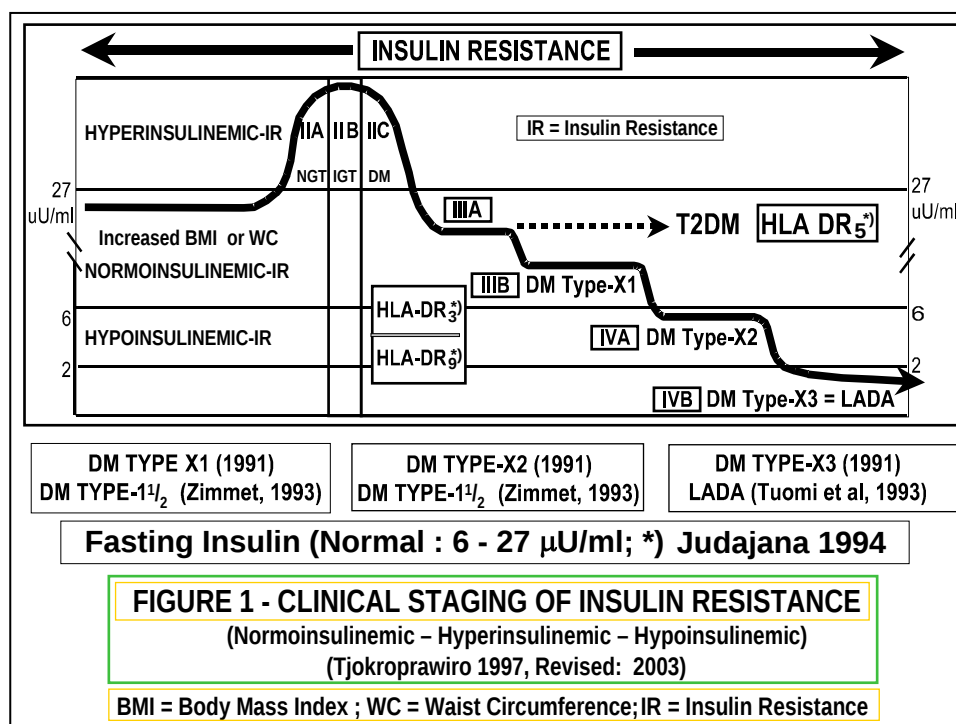
dysfunction) of T2DM become a major current status of T2DM care. Based on such descriptions, a new strategy for the treatment of T2DM is directed to both the insulin resistance and the β -cell dysfunctions.

Glucovance is a combination of metformin and glibenclamide formulated within a single tablet that is engineered for optimal drug delivery. Each Glucovance tablet contains glibenclamide particles in a precisely controlled range of particle sizes within a freely soluble metformin matrix. Glucovance is therefore optimized to support efficacy against both fasting (chronic) and postprandial (acute) hyperglycemia.

The aim of this paper and presentation is to transfer the basic recent knowledge and clinical experiences on T2DM, OADS esp. metformin and glucovance with clinical and cardiovascular benefits, to GPS, Residents, Internists, and associated Specialists.

CLINICAL STAGING OF INSULIN RESISTANCE

Based on clinical experiences, by the year 1997, Tjokropawiro (2003A) hypothesized the link between Insulin Resistance - Obesity - Pre-DM (IFG and IGT), and T2DM, and it was termed as Clinical Classification Staging of Insulin Resistance (Figure 1).



The Classification of Insulin Resistance - Linked Obesity, Pre-DM (IFG and IGT) and T2DM can be categorized into 4 Stages; this classification has been already hypothesized by the author since 1997 and revised in the years 2001, and 2003 (Tjokropawiro 2003).

Stage -I: Normo insulin with Insulin Resistance
(Insulin Resistant, Normoinsulinemic Individuals: Obesity, Pre-DM)

In clinical practice, the Homeostasis Model Assessment = HOMA, has been suggested as method to assess Insulin Resistance (HOMA-R) and Insulin Secretion of

pancreatic β -cell (HOMA-B) from the fasting glucose and insulin concentrations (Mathews et al 1985). However, this method has not been extensively evaluated, particularly in different ethnic groups. Patients with Stage-I (Obesity, Pre-DM) still have normal insulin (normoinsulinemic IR) blood levels, whereas Insulin Resistance (IR) may be detected by Euglycemic Clamp or HOMA-R; Stage-I may happen in patients with BMI ≥ 30 kg /m² or Visceral Obesity or Pre-DM (IFG, IGT).

Stage-II: Stage-IIA, IIB, and IIC (Insulin Resistant, Hyperinsulinemic Individuals)

1. Stage-IIA: Hyperinsulinemia with normal Glucose Tolerance, usually with BMI³ 30 or Visceral Obesity, or Pre-DM (IFG and IGT)
2. Stage-IIB: Hyperinsulinemia plus Glucose Intolerance BMI³ 30 or Visceral Obesity
3. Stage-IIC : Hyperinsulinemia plus T2DM and BMI³ 30 or Visceral Obesity

Stage-III: Stage-IIIA and Stage-IIIB (Insulin Resistant, Normoinsulinemic Individuals)

- a. Stage-IIIA: Normoinsulinemia plus T2DM, and BMI is usually less than 30, Visceral Obesity is still present but less prominent
- b. Stage-IIIB: Low Normoinsulinemia plus Type-X1 DM. (Type 2-DM with poor response of b Cell to glucose stimulation, but fasting C-peptide level is still > 0.8 mU/ml)

Type X1-DM (firstly coined by the author in 1991) is identical with Type 1½ -DM as coined by Zimmet in 1993

Stage-IV: Stage-IVA and Stage-IVB (Insulin Resistant, Hypoinsulinemic Individuals)

- a. Stage-IVA : Hypoinsulinemia (fasting insulin < 6 mU/ml, normal : 6 - 27 mU/ml plus Type X2-DM or Type 1½-DM but fasting C-peptide become lower (0-6-0.8 mU/ml)
- b. Stage- IVB : Hypoinsulinemia plus Type X3-DM or LADA (as coined by Tuomi in 1993) and fasting C peptide level < 0.6 mU/ml.

This patient (Type X3-DM) become totally insulin dependent but more resistant to ketoacidosis compared with Type 1-DM. The investigation of Judajana in Surabaya in the year 1994 showed that patients with HLA-DR3 and HLA-DR9 are prone to develop DM-Type X-3 (LADA), whereas those with HLA-DR5 do not (or resistant to insulin dependent). The summarized short description of the Classification of Insulin Resistance can be seen in Table 1.

TABLE 1 - Insulin Resistance - IFG - IGT - T2DM - DM-Type X (Clinical Experiences : Tjokroprawiro 1997,2003)	
Stage	IFG - IGT - T2DM - DM-Type X1, DM-Type-X2, DM-Type-X3
Stage I	IFG : BMI* $\geq$ 30, Normoinsulinemia
Stage IIA	IFG : BMI* $\geq$ 30, Hyperinsulinemia
Stage IIB	IGT : BMI* $\geq$ 30, Hyperinsulinemia
Stage IIC	T2DM : BMI* $\geq$ 30, Hyperinsulinemia, Oral Treatment
Stage IIIA (HLA-DR ₅)	T2DM : BMI* < 30, Normoinsulinemia, CTOI, Reversible
Stage IIIB (HLA-DR ₃ & HLA-DR ₉)	DM-Type X1 = DM-Type1½ : BMI* < 30, Low Normal Insulin, Fasting C-peptide $\geq$ 0.8 ng/ml, Post Prandial C-peptide : Poorly Response, CTOI, Partially Insulin Dependent
Stage IVA (HLA-DR ₃ & HLA-DR ₉)	DM-Type X2 = DM-Type 1½ : BMI* < 30, Subnormal Insulin (C-peptide 0.6-0.8 ng/ml), CTOI, Partially Insulin Dependent
Stage IVB (HLA-DR ₃ & HLA-DR ₉)	DM-Type X3 = LADA : BMI* < 30, Fasting and 2 PP C-peptides : < 0.5 ng/ml each. Totally Insulin Dependent: CTOI is not indicated

Normal Values: - Fasting C-peptide: 0.8 - 4.0 ng/ml
- 2 PP C-peptide: 1.1 - 5.0 ng/ml

LADA = Latent Autoimmune Diabetes of Adult. HLA-DR5 = Resistant to DM-Type X; HLA-DR3 & HLA-DR9 = Susceptible to DM-Type X. As seen in Figure 1 and Table 1, CTOI can be started to treat patients with T2DM Stage IIIA, IIIB, and Stage IVA, whereas patients with Stage IV-B should be treated with insulin

only (totally insulin dependent-T2DM = DM-Type X3 = LADA)

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

As reported by ADA (2003), etiologic classification of diabetes mellitus can be summarized and is depicted in

TABLE 2 (Tjokroprawiro 2004). Type 2 diabetes mellitus (T2DM) may range from predominantly insulin resistance (measured by HOMA-R) with relative insulin deficiency to predominantly "secretory defect of the β -cell" (by HOMA - B) with insulin resistance. Hypothetically, the latter may begin from impaired fasting glucose (IFG) or Phase-1, through impaired glucose tolerance = IGT or Phase-2, and finally followed by T2DM ("advanced secretory defect") or Phase-3.

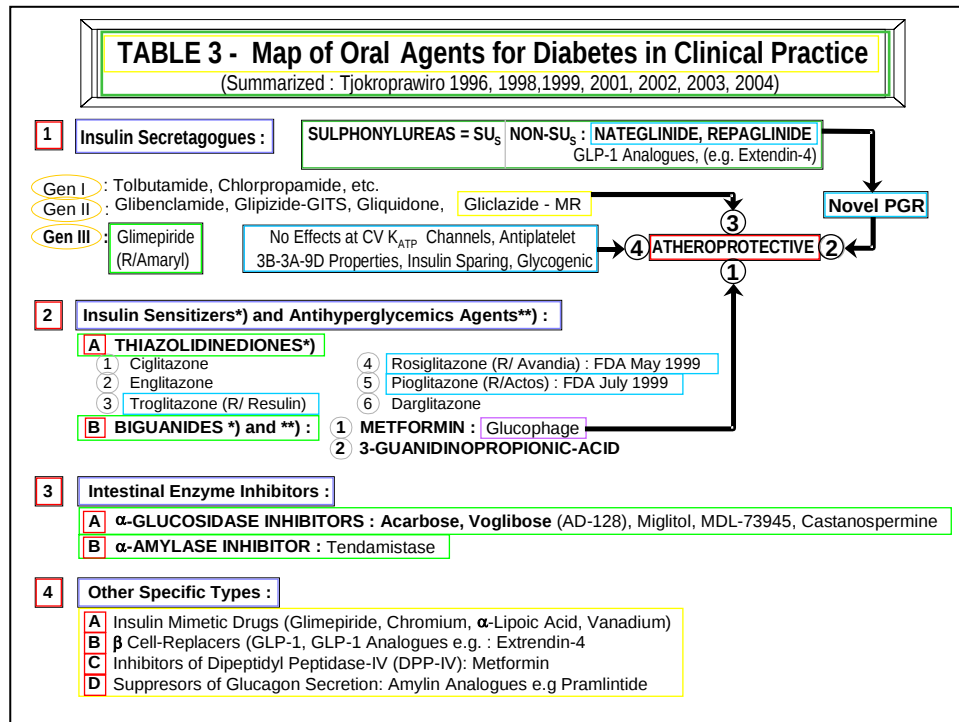
In conclusion, T2DM has dual endocrine defects: insulin resistance (IR) and advanced secretory defects of the β -cell or impaired first phase of secretion, or advanced impaired acute insulin response (AIR). In other words, T2DM (or Phase-3) is a result of IR and impaired AIR or: T2DM is the sum of IR and impaired AIR (Table 2); Phase-1 is manifested by IFG, whereas Phase-2 by IGT and Phase-3 by T2DM.

TABLE 2 - Etiologic Classification of Diabetes Mellitus (ADA-2003, Summarized : Tjokroprawiro 2003)	
I	T1DM : A - Immune Mediated B - Idiopathic
II	T2DM : From IR (HOMA-R) with relative Insulin Deficiency (HOMA-B) to Secretory Defect of AIR*of β Cell (HOMA -B) with IR (HOMA-R) Suggestion : Phase ① : HOMA-R to HOMA-B or IFG Phase ② : HOMA-B with HOMA-R or IGT Phase ③ : Advanced Secretory Defect or T2DM * AIR (Acute Insulin Response = First Phase) T2DM = IR + Impaired AIR
III	Other Specific Types : A, B, C, D, E, F, G, H
IV	Gestational Diabetes Mellitus (GDM)
IFG = Impaired Fasting Glucose; IGT = Impaired Glucose Tolerance T2DM = Type 2 Diabetes Mellitus; HOMA = Homeostasis Model Assessment HOMA-B for β -cell Dysfunction; HOMA-R for Insulin resistance; IR = Insulin Resistance	

MAP OF ORAL AGENTS FOR DIABETES IN CLINICAL PRACTICE (Focus on Metformin)

Since 1996, Tjokroprawiro (2004) has summarized a map of Oral Agents for Diabetes (OADS), which is renewed annually based on clinical experiences. Other specific types of OADS are also selectively depicted (Table 3). To date, four OADS are claimed to have

atheroprotective properties, f.e: glimepiride, gliclazide, glinides and metformin. Metformin has been used in the treatment of T2DM for more than 40 years, and its antihyperglycemic effect and insulin sensitizer properties are well-established. It has recently been shown that treatment with metformin may delay or prevent the manifestation of T2DM in subjects with IFG or IGT, who are at high risk of developing T2DM.



Mounting evidence indicates that metformin may reduce the risk of vascular complications in patients with T2DM, and 7 (seven) articles reported several cardiovascular benefits of this drug, such as:

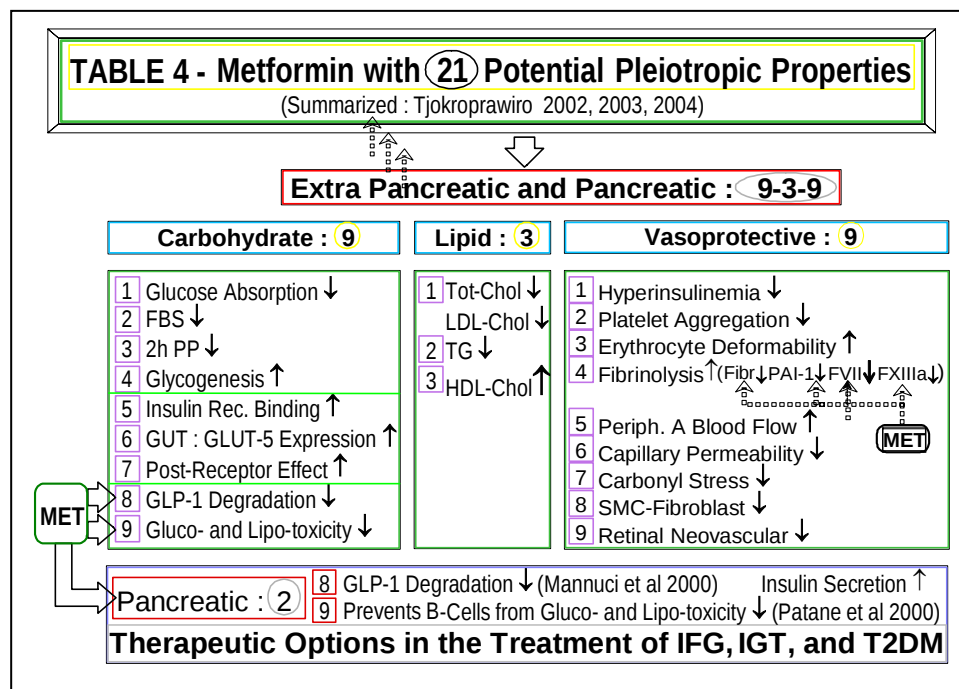
1. reducing insulin resistance (Glannarelli et al 2003)
2. beneficial effects on homeostasis and vascular function (Grant 2003)
3. potential contribution to the management of the metabolic syndrome and type 2 diabetes mellitus (Després 2003)
4. antiatherogenic properties (Mamputu et al 2003).
5. inhibition of glycation processes (Beisswenger et al 2003)
6. vascular protection (Garber 2003, Libby 2003)
7. prevention of type 2 diabetes mellitus and cardiovascular complications in high-risk subjects (Standle 2003).

Since 1994, Tjokropawiro (2004) has collected and summarized 21 metabolic and vasoprotective properties of metformin (TABLE 4). Interestingly, triple effects of metformin in fibrinolysis are reported: to decrease serum levels of fibrinogen, PAI-1 and Factor-XIIIa. It 3.

has been known that Factor-XIIIa is a potent stabilizer of fibrin in which the latter may cause coronary atherosclerosis or acute thrombosis. The outcome of intensive glycemic therapy reported by UKPDS in 1998 showed significant decreases in risk (compared with conventional therapy), f.e.: diabetes-related death (42%, p. 0.017), all cause mortality (36%, p. 0.011), any diabetes-related endpoint (32%, p. 0.0023), myocardial infarction (39%, p. 0.01), and stroke (41%, p. 0.013).

The Diabetes Prevention Program (DPP) recently reported (2002) that the incidence of diabetes in people with IGT was reduced by 58% with lifestyle modification and by 31% with metformin after a mean duration of 2.8 years of intervention. Garber (2003) concluded and categorized 10 (ten) pleiotropic effects of metformin in reducing the risk of cardiovascular diseases into 2 groups.

1. Improved: (Insulin Sensitivity, Fibrinolysis, Nutritive Capillary Flow, Hemorheology, Postischemic Flow).
2. Reduced: (Hypertriglyceridemia, AGE-formation, Cross-linked Fibrin, Neovascularization, Oxidative Stress).



THE FIXED-DOSE ORAL AGENT COMBINATION

Based on the dual endocrine defects of T2DM, a combination (fixed-dose or free combination) of two Oral Agents for Diabetes (OADs) may be prescribed to address such defects. Metformin (insulin sensitizer) directed to improve insulin resistance (IR), can be combined with one of various secretagogues (glibenclamide, glimepiride, gliclazide, or glipizide) to improve impaired AIR (acute insulin response) or impaired first phase of insulin secretion. Both metformin and glibenclamide reduce significantly the risk of diabetic complications as reported in the landmark UK Prospective Diabetes Study (UKPDS 1998). Rationally, metformin and glibenclamide may directly address the dual endocrine defects (IR and impaired AIR) which occur in T2DM.

The summarized information about glucovance are listed below.

1. Glucovance tablet is engineered for optimal drug delivery
2. Each glucovance tablet contains glibenclamide particles in a precisely controlled range of particle sizes within a freely soluble matrix of metformin.
3. The pharmacokinetics (AUC and Cmax) of metformin and glibenclamide from glucovance are comparable with those of co-administered or free combination of metformin and glibenclamide.

4. Glibenclamide within glucovance, however, is absorbed more rapidly from glucovance than from standard glibenclamide tablets.
5. Earlier absorption of glibenclamide from glucovance taken with meals helps to deal with the postprandial glucose surge.
6. Glucovance is therefore optimized to cope with both fasting and postprandial hyperglycemia.
7. The absorption of glibenclamide from the gastrointestinal tract is limited by its solubility, which is in turn depends critically on the size of glibenclamide particles (Scheen et al 1987).
8. All these technical designs have important clinical applications for the therapeutic benefit of glucovance.

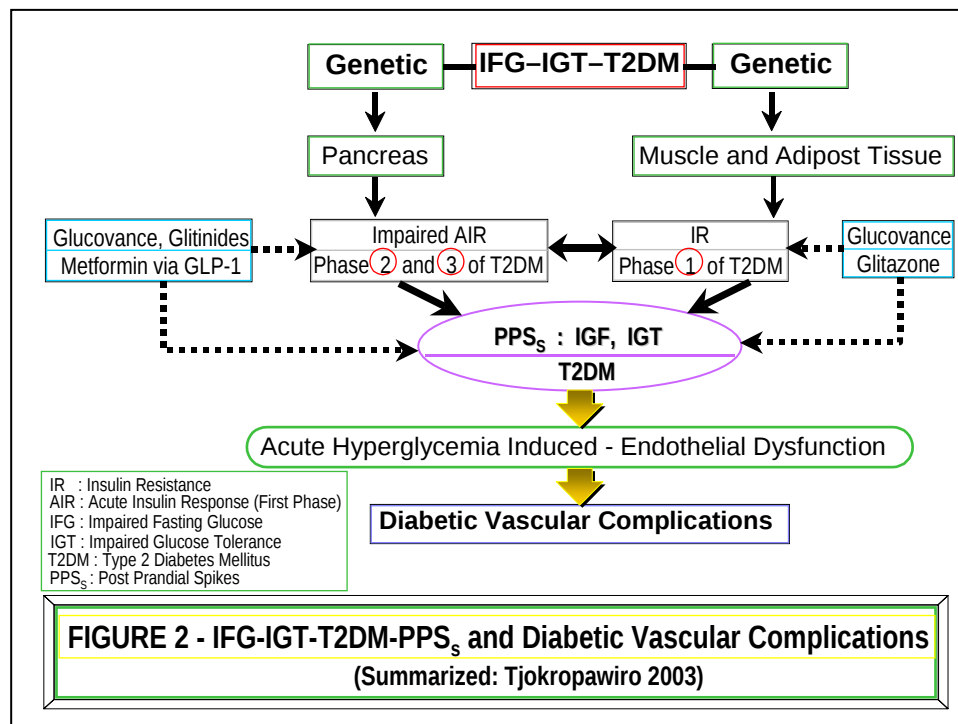
THE ROLES OF FIXED-DOSE ORAL AGENT COMBINATION (Focus on Glucovance)

A. Hypothetical Mechanisms of the pathophysiology of T2DM

Back to the pathogenesis of T2DM through Phase-I, Phase-2, and Phase-3 as described in (TABLE-2), the dual endocrine defects occurring in T2DM are IR and impaired AIR (Tjokroprawiro 2004). Hypothetically (Tjokroprawiro 2004), as seen in FIGURE 2, IR and mild secretory defect of β -cell may happen in the Phase-2 (clinically = IGT); T2DM may occur in the Phase-3 in which the secretory function of the β -cell has been

severely impaired. Insulin resistance can be treated with insulin sensitizers (metformin or glitazone), whereas impaired AIR or secretory defect can be improved with secretagogues (glibenclamide, glimepiride, glitinides, etc). Recently, it was reported that metformin may increase the release of GLP-1 from ileal L-Cells, which is in turn via GLP-1 receptor in the pancreatic β -cell, the

next reaction then is followed with the activation of PKA, and finally PKA may stimulate the insulin release. In other words (Tjokropawiro 2004): theoretically, metformin has a hypoglycemic action (via GLP-1 release) beyond its antihyperglycemic effect (insulin sensitizer) especially in the susceptible individuals.

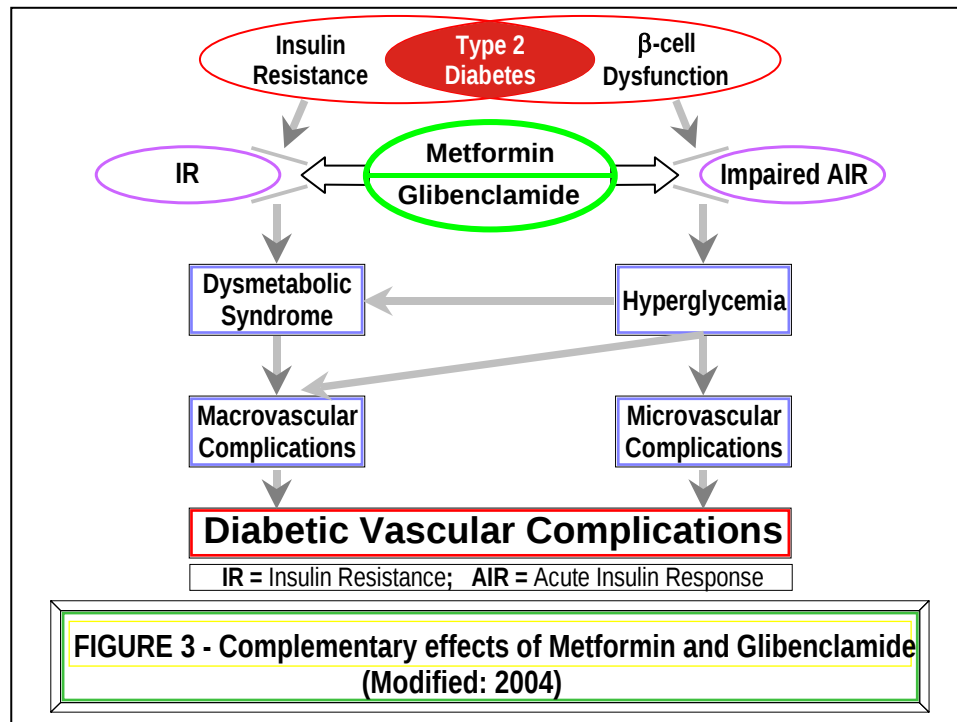


B. Complementary Effect of Metformin and Glibenclamide

Metformin and glibenclamide markedly reduced the incidence of macrovascular and microvascular complications, respectively as reported by the landmark UKPDS in 1998. Barriers to successful treatment outcomes arise from the complex pathophysiology of T2DM (Reasner et al 2002), the limitations of available treatment, the way of treatments applied, and also poor patient compliance with the regimen of therapy given.

As previously described (Tjokropawiro 2004), IR and impaired AIR (β -cell dysfunction) are both the dual endocrine defects of T2DM. As seen in Figure 3, glucovance (fixed dose tablet of metformin and

glibenclamide) may address both of the dual endocrine defects. Specifically, glibenclamide within glucovance is absorbed more rapidly from glucovance than from standard glibenclamide tablets. This earlier absorption of glibenclamide from glucovance taken during meals will be able to cope with the postprandial glucose spike. It is recommended that glucovance should be taken with meals, so that the earlier absorption of glibenclamide is ideally timed to coincide with the postprandial glucose. Hence, glucovance is engineered to optimize drug delivery to support efficacy against both fasting and postprandial hyperglycemia. In conclusion, Figure 3: glucovance has potential contribution to the management of cardiovascular disease risk in patients with the metabolic syndrome and T2DM.



GLUCOVANCE AND METFORMIN: INFORMATION AND RELEVANT CLINICAL OUTCOMES (from 2000 through 2003)

- I. Epidemiological analysis of the UKPDS (2000) reported that greater decreases in A1C provide greater protection against diabetic complications: every 1% reduction in A1C may reduce risks in (each with $p < 0.0001$): deaths from diabetes -21%, heart attacks -14%, microvascular complications -37%, and peripheral vascular disorder -43%.
- II. In 16 weeks, randomized, active-control study in diet-failed patients (Garber et al 2002) resulted in decreases of (significant, each with $p < 0.05$): A1C -2.3% (baseline 8.8%), fasting plasma glucose -61.2 mg/dl (baseline 190.8 mg/dl), and postprandial plasma glucose -82 mg/dl (baseline 246.6 mg/dl). About 80% patients reach A1C < 7%. Treatment discontinuation: gastrointestinal disturbances 1%, hypoglycemia 2%.
- III. In a US retrospective Analysis of patients new to pharmacological therapy (Merck Data on File 2003) reported decreases in A1C (Difference, $p < 0.001$): metformin plus glibenclamide group ($n = 74$) -1.9%, and glucovance group -3.2% ($n = 397$).
- IV. Blonde et al (ADA 2001): demonstrated durable antidiabetic effects and favorable effect of glucovance (G/M) as Second-line Therapy for

T2DM (52-weeks, multicenter, open label trial). A1C < 9% received G/M 2.5 bid and A1C > 9% receive G/M 5.0 bid.

- V. Garber et al (ADA 2001): Durable (52-weeks) efficacy and positive impact on lipid profile of G/M as first-line Therapy for T2DM. Overall, a decrease in A1C to 6.8% after 13 weeks from a baseline of 8.7%. A mean A1C 7.0% was maintained at 52 weeks. A1C < 9% received G/M 1.25 bid and A1C > 9% receive G/M 2.5 bid.
- VI. Blonde et al (ADA 2001): G/M tablets provide a significantly greater reduction in A1C (-2.02%) with lower drug doses than do Glib + Met (-1.49%, $p < 0.0001$), especially when baseline A1C > 8% (Study period: 76 - 194 days). Conclusion: T2DM patients with A1C > 8% on Glibenclamide + Metformin experienced significant A1C reductions by switching to comparable doses of G/M.
- VII. Goldstein et al (ADA 2002): the addition of Rosiglitazone (4 mg od and titrated to 4 mg bid) to an established regimen of G/M effectively lowered glucose parameters in T2DM patients not adequately controlled with optimum doses of G/M alone (Triple-Combination). It provides to insulin therapy or CTOI (Bruce et al ADA 2002).
- VIII. Allavoine et al (IDF 2003): Long-term (one year) treatment with G/M was associated with durable improvement in A1C (-1.7%), FPG (-55 mg/dl), and improvements in lipid profiles (Total

Cholesterol, LDL Cholesterol, Slightly HDL but Triglyceride was unaffected), and no increase in Body Weight. These changes imply a modest improvement in cardiovascular risk profile.

- IX. Porte et al (IDF 2003): Single-tablet G/M enhanced Postprandial Insulin Release (PPI), without affecting Fasting Insulin (FI). Glibenclamide increased PPI and FI. The differences in insulin secretion may result from earlier absorption of glibenclamide, or enhanced Beta-cell function following greater improvements in glycemia with the single-tablet G/M
- X. Beneficial effects of metformin on homeostasis and vascular function in man have been summarized (from several studies) by Grant in 2003.
 1. PAI-1 (marked reduction)
 2. Factor VII (reduction)
 3. Fibrinogen (some studies report reduction, others no effects).
 4. Factor XIII (reduces A and B subunit)
 5. Fibrin (alters structure) function
 6. C-reactive protein (reduction)
 7. Platelets (reduction PF4 and β TG, stabilizes platelet, antioxidant effects)
 8. Blood Flow (increases hemodynamic response to L-arginine, lowers asymmetric dimethyl arginine, improves post ischemic blood flow, improves blood flow in both skeletal muscle and adipose tissue).
- XI. Després (2003) showed the potential contribution of the selective loss of visceral adipose tissue to the beneficial effects of metformin on the features of the metabolic syndrome. Metformin has been shown not only contribute to a better glycemic control but also to induce some weight loss especially in the visceral depot.
- XII. A substantial database of clinical evidence, including the reports of UKPDS in 1998, underpins the place of metformin both as an effective oral antihyperglycemic agent and for reducing the risk of morbid cardiovascular events. The latter can be achieved through 10 potential beneficial effects of metformin (Garber 2003).
 - A. Improved:
 1. Insulin sensitivity
 2. Fibrinolysis
 3. Nutritive capillary flow
 4. Hemorheology
 5. Postischemia Flow
 - B. Reduced:
 1. Hypertriglyceride
 2. AGE formation
 3. Cross-link fibrin

4. Neovascularization
5. Oxidative Stress

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