EXPERT OPINION

Acarbose plus metformin fixed-dose combination in the management of type 2 diabetes

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Introduction: The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. Concerns in the management of diabetes include drug-induced hypoglycemia, poor control of postprandial blood glucose level and weight gain. A carbohydrate-rich diet can cause more load on the intestinal cells producing α-glucosidase. Many patients need combination treatment based on their level of glycemic control and other associated parameters. In such cases, a therapy that provides effective glycemic control with minimal or no risk of adverse events like hypoglycemia or weight gain is highly desired. The chances of cardiovascular events are high in diabetes patients; hence, medicines providing benefits beyond glycemic control such as reduced cardiovascular risk factors may be ideal in such patients.

Areas covered: Current available data are related to the rationale and clinical trials on the fixed-dose combination of acarbose plus metformin in management of type 2 diabetes.

Expert opinion: Combination therapy is routinely prescribed in the management of T2DM. Drugs with complimentary mechanisms should be used to maximize the efficacy of combination therapy. The combination of metformin and acarbose is a rational therapy because of their different and complimentary mechanisms of action, which provides effective glycemic control with additional cardiovascular benefits and minimizes adverse events.

Keywords: acarbose, efficacy, fixed-dose combination, metformin, pharmacotherapy, tolerability

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1. Introduction

Diabetes mellitus is a growing concern across the world, including in India. In type 2 diabetes mellitus (T2DM), when lifestyle interventions alone are not effective, pharmacotherapy is started [1]. American Association of Clinical Endocrinologists (AACE) consensus statement recommends treatment with single drug in addition to therapeutic lifestyle changes for the recent onset of T2DM or mild hyperglycemia, that is, glycosylated hemoglobin (HbA1c) < 7.5%. Metformin as a first-line treatment offers advantages of less hypoglycemia, modest weight loss and long-term effect on blood glucose with remarkable cardiovascular safety. Patients with inadequate control of target HbA1c level with metformin monotherapy and those presenting with HbA1c > 7.5% need add-on agent to metformin [2]. Similarly, Korean Diabetes Association treatment guidelines for diabetes recommends oral hypoglycemic combination therapy for HbA1c between 8 and 10% [3]. The early use of combination is being practiced by Indian physicians for > 40 years [4]. For combination therapy, drugs with complementary mechanisms of action should be used [5].

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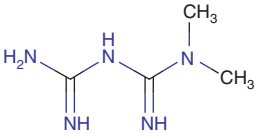
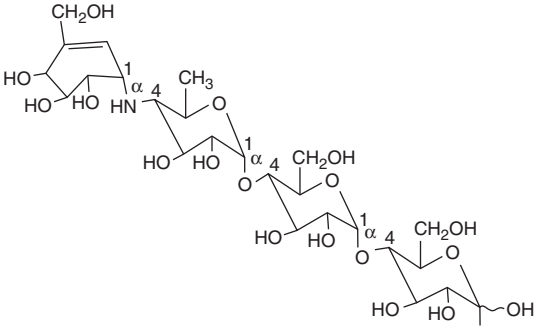
Box 1. Drug summary.

Drug name (generic)	Acarbose plus metformin combination
Phase (for indication under discussion)	Marketed
Indication (specific to discussion)	Type 2 diabetes mellitus
Pharmacology description/mechanism of action	Metformin primarily controls fasting blood glucose, while acarbose controls postprandial blood glucose level
Route of administration	Oral
Chemical structures	Metformin



Metformin

Acarbose



Acarbose

Pivotal trial (s)	[27,36]

2. Body of review

2.1 Overview of the market

Management of T2DM involves a multidimensional approach to improve metabolic control, reduce blood glucose and modify factors known to damage blood vessels. The U.K. Prospective Diabetes Study found that ~ 50% of patients needed > 1 pharmacological agent after 3 years of treatment because monotherapy did not achieve HbA1c target values [6]. Twelve drug classes are currently available for the treatment of T2DM [2,7]. Some oral agents work by primarily reducing fasting blood glucose (FBG), whereas few by primarily reducing postprandial blood glucose (PPG). The International Diabetes Federation (IDF) recommends targeting both PPG and FBG as an important strategy for achieving optimal glycemic control [8], whereas AACE recommends the use of drugs with complementary mode of action [2]. Availability, approved indications and clinical usage of drugs vary from country to country. For example, alfa-glucosidase inhibitors are widely used in Asia, whereas metformin is ubiquitously used elsewhere in the world. In addition, with favorable results on glycemic control, low risk of hypoglycemia, and body weight and reduction in risk for cardiovascular events, (**Box 1**) acarbose and metformin provide a good option for combination therapy.

2.2 Introduction to the compound

2.2.1 Acarbose

Acarbose, α-glucosidase inhibitor, is effective as a first-line drug in T2DM patients in whom blood glucose is not controlled by diet alone [9].

Acarbose augments release of glucagon-like peptide (GLP-1), by retarding/inhibiting carbohydrate absorption (**Figure 1**) [10] and increases GLP-1 activity [11].

It also has beneficial cardiovascular effects like reduction in blood pressure, improved triglyceride level and the downregulation of biomarkers of low-grade inflammation. Acarbose intake is associated with reduction of cardiovascular events and has a beneficial effect on weight [12]. It provides short-term benefits by reducing blood glucose level and in the long term by reducing HbA1c levels, with higher benefits on early initiation in the course of disease. Beneficial effects are also seen on postprandial triglyceride levels, elevated cholesterol, hyperinsulinemia [6] and postprandial hyperglycemia.

A meta-analysis of seven placebo-controlled clinical studies in T2DM patients with a minimum treatment duration of 52 weeks involving 1248 patients in acarbose group versus 932 patients in placebo group demonstrated that acarbose can prevent myocardial infarction and cardiovascular events. The benefit could have been due to the reduction of

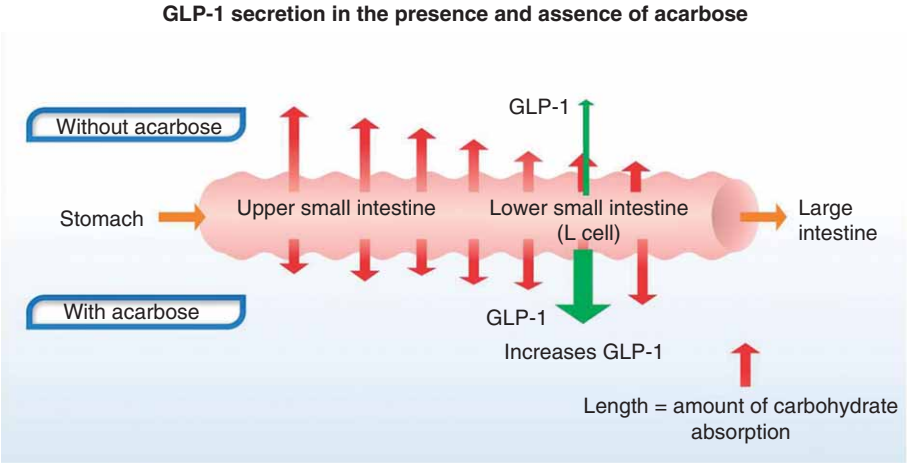


Figure 1. Effect of acarbose on GLP-1.
GLP-1: Glucagon-like peptide.

postprandial hyperglycemia and improvement in the other parameters of the metabolic syndrome [13].

Acarbose is superior to metformin in improving lipid levels. In a comparative study, increase in low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio by 14.4% was seen in the placebo group, use of acarbose resulted in reduction by 26.7%, while no effect was seen with metformin [14].

Initially, acarbose use may be associated with adverse events due to its local effect on the gastrointestinal tract; however, these effects last for short term and reduce over time. Importantly, it is devoid of systemic toxicity and does not cause hypoglycemia or weight gain [9].

Acarbose was launched worldwide for the treatment of T2DM as monotherapy and combination therapy in 1990. It was first approved as a diabetes prevention therapy (impaired glucose tolerance) in China in 2002 and India in 2006 [15]. Acarbose is currently approved for treatment of impaired glucose tolerance/prevention of diabetes in 25 countries [12].

2.2.2 *Metformin*

Metformin is an old [16] and established first-line anti-diabetic medicine for the management of T2DM [17]. Therapeutic benefits, including glycemic control, effects on endothelial dysfunction, hemostasis, oxidative stress, insulin resistance, fat redistribution, reduced LDL and triglyceride contributing to better cardiovascular outcomes and safety advantages like minimal risk of hypoglycemia and rare drug interactions make metformin the best treatment for T2DM [16].

Metformin provides beneficial effects on lipid metabolism and insulin resistance. It improves changes in coagulation and fibrinolytic pathways in patients having insulin resistance [18]. United Kingdom prospective diabetes study 35 results have shown that the risk for cardiovascular disease events, stroke and all-cause mortality was closely linked to glycemic control in diabetes. Every reduction of 1% HbA1c was associated with benefits, including reduction in diabetes-related mortality, myocardial infarction, heart failure and stroke. Despite equal reduction in HbA1c, metformin was more effective than sulfonylurea or insulin in reducing diabetes-related efficacy parameters, all-cause mortality and stroke [19].

Elevated plasma GLP-1 levels are seen in diabetic patients who are on chronic metformin therapy. Metformin does not cause weight gain [20]. As a first-line therapy, risk of death in patients receiving metformin is significantly less compared to those receiving sulfonylurea [21]. Type 2 diabetes patients have increased risk of various cancers. Reduced incidence of different cancers and cancer-related mortality has been reported in patients receiving metformin [16].

2.2.3 *Rationale of combination of acarbose plus metformin*

Metformin and α-glucosidase inhibitors (e.g., acarbose) are recommended as the first-line treatment either as monotherapy or in combination therapy, in case one of the agents fails to control glycemia [22].

Acarbose retards the digestion and absorption of carbohydrates by inhibiting α-glucosidase enzyme, and reduces postprandial hyperglycemia without risk of hypoglycemia, which is an important feature in early diabetes [23,24].

Metformin, a biguanide, acts by different mechanisms compared to other agents. Metformin increases insulin sensitivity, improves peripheral uptake of glucose and reduces hepatic glucose output. It reduces blood glucose level without weight gain and has minimal risk of hypoglycemia [25].

Many striking similarities between two molecules, including oral use, administration with meals, insulin sparing action, proven cardiovascular safety, beneficial effect on body weight and low risk of hypoglycemia make this combination justified [26].

Patients presenting with HbA1c > 7.5% need add-on agent to metformin. Similarly, patients who are not able to control HbA1c target with metformin alone should be given

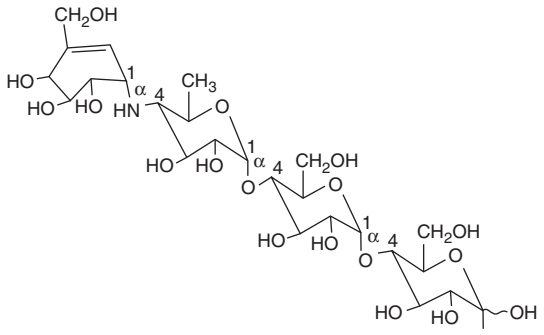


Figure 2. Chemical structure of acarbose.

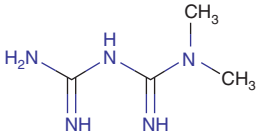


Figure 3. Chemical structure of metformin.

combination treatment [2]. T2DM patients may spend > 50% of time in the postprandial state. High carbohydrate in the diet causes more exposure of carbohydrates to the L-cell of the intestine and intestinal brush border, which synthesizes GLP-1. Because of these pathophysiological mechanisms, special measures for management of glucose excursions are required in Indian patients [11].

2.2.4 *Fixed-dose combinations in diabetes mellitus*

Diabetes being a chronic, complex and progressive disease may need complex treatments as the treatment progress. Reducing number of tablets to be taken per day provides an opportunity for better glycemic control. Rational fixed-dose combination (FDC) could be of use in this regard [27].

FDCs have the potential to increase treatment adherence because of reduced pill burden. Improved compliance can result in better glycemic control and less disease management costs. Availability of FDC in different dose–strength formulation also offers an added advantage of dose flexibility [5].

2.3 Chemistry

Chemical structure of acarbose and metformin is given in **Figures 2** and **3**.

2.4 Pharmacodynamics

The mechanisms of action of metformin and acarbose are different and complimentary that is, metformin primarily controls FBG, while acarbose controls PPG levels [28]. (**Figure 4**) Thus, the combination of acarbose and metformin is beneficial in providing better efficacy than monotherapy without risk of side effects.

2.5 Pharmacokinetics and metabolism

Bioequivalence of the acarbose–metformin 50/500 mg FDC versus loose combination of acarbose and metformin 500 mg: Bioequivalence is usually evaluated by pharmacokinetic comparisons. However, in case of acarbose it is difficult because of its poor absorption. Hence, pharmacodynamic parameters like plasma levels of glucose and insulin after sucrose test are commonly used methods for establishing bioequivalence. A randomized, non-blinded single-dose, four-way crossover study in 40 healthy male volunteers between 18 and 45 years has demonstrated bioequivalence between acarbose metformin FDC and loose combination of 50 mg acarbose and 500 mg metformin. No drug interactions on glucose absorption were seen when acarbose and metformin were given simultaneously. A slight but clinically non-relevant decrease in metformin bioavailability was seen [29].

2.6 Clinical efficacy

2.6.1 α-*glucosidase inhibitor as an add-on treatment*

Chiasson *et al.* [30] showed that acarbose improves long-term glycemic control in T2DM regardless of other concomitant anti-diabetic drug therapy. In this study, acarbose or placebo was added to the existing regimen, which included either diet alone, diet and metformin, diet and sulfonylurea, or diet and insulin. These results show beneficial effects with acarbose as an add-on treatment to existing therapy. The addition resulted in significant improvement in glycemic control. Because of different mechanism of action from other classes of drugs, acarbose is a suitable add-on option to sulfonylurea, metformin or insulin [30].

The summary of studies with combination of acarbose and metformin in T2DM patients is given in **Table 1**.

2.6.2 *Free-dose combination*

Rosenstock *et al.* [31] demonstrated that the addition of acarbose to metformin in T2DM patients inadequately controlled with diet and metformin is safe and well tolerated. The combination is effective in reducing HbA1c and fasting and PPG levels.

Halimi *et al.* [32] conducted a double-blind, placebo-controlled, randomized, parallel-group study wherein acarbose was given to overweight patients with inadequate control on metformin monotherapy. In this 6-month study, acarbose was found to be significantly effective in controlling glycemic parameters (HbA1c, FBG and PPG level). Acarbose is useful add-on therapy in overweight patients with uncontrolled blood glucose with metformin monotherapy.

Similarly, Phillips *et al.* [33] also evaluated the efficacy and safety of add-on acarbose or placebo to metformin in overweight T2DM uncontrolled on metformin monotherapy in a randomized, double-blind, placebo-controlled, parallel

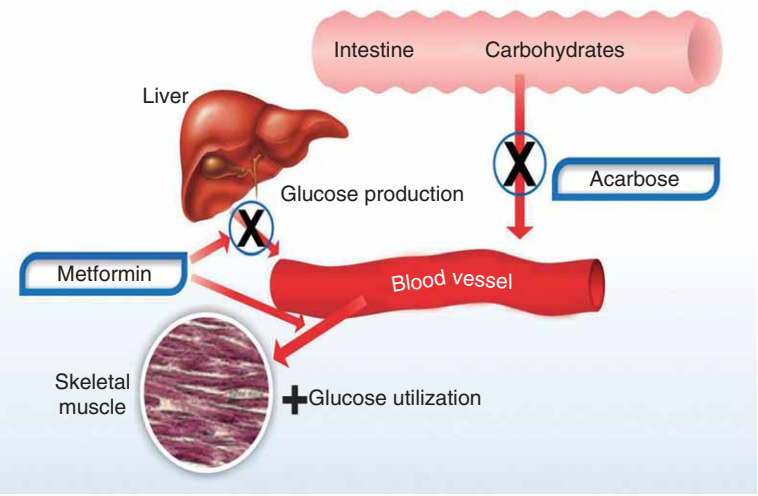


Figure 4. Complimentary and distinct mechanism of action of acarbose and metformin.

Table 1. Studies with combination of acarbose and metformin.

Author	Number of patients	Interventions	Patient population
Rosenstock *et al.* (1988) [31]	168	Acarbose and metformin or placebo and metformin	Patients inadequately controlled on metformin, HbA1c between 7 and 10%
Phillips *et al.* (2003) [33]	82	Acarbose or placebo as add-on therapy to metformin	Overweight type 2 patients inadequately controlled with metformin
Halimi *et al.* (2000) [32]	152	Addition of acarbose or placebo to metformin	Overweight patients inadequately controlled with metformin
Jayaram *et al.* (2010) [28]	229	Fixed-dose combination of acarbose and metformin versus metformin alone	Drug naive type 2 diabetes with BMI > 25 kg/m2; HbA1c between 7.5 and 10% at screening, those on acarbose and required metformin or those on metformin requiring acarbose
Wang *et al.* (2013) [37]	233	Fixed-dose combination of acarbose and metformin versus acarbose alone	Type 2 diabetes patients with BMI < 35 kg/m^2, with HbA1c between 7and 10% within 3 months prior to study

BMI: Body mass index; HbA1c: Glycosylated hemoglobin.

group study for 24 weeks. Acarbose was significantly effective in reducing FBG and PPG levels. Significantly higher number of patients were classified as responders with acarbose compared with placebo (47 vs. 14%, p = 0.001).

A recently published study [34] from India evaluated the efficacy and tolerability of acarbose as add-on or monotherapy in T2DM. Out of 1996 patients, 44.2% received acarbose monotherapy, while the remaining received combination therapies. Combination of acarbose and biguanides were received by 20.7%. Acarbose reduced FBG as well as PPG and HbA1c level. Use of acarbose resulted in mean decrease in weight by 1.4 kg, while the waist circumference reduced by 1.6 cm. The incidence of adverse events was 2.74%, while drug-related adverse events were seen in only 2.19%. Close to 20% of the study population also received biguanides, mostly metformin. Though the study did not analyze the effect of metformin plus acarbose combination separately, reviewing the results of the total study population, it could be concluded that the combination of metformin plus acarbose was effective and well tolerated. Subgroup analysis may provide more results about safety and effectiveness of the combination.

An analysis of 27 randomized controlled clinical trials involving 1198 patients showed addition of all noninsulin anti-diabetic drugs to metformin therapy, resulted in similar reduction in HbA1c. However, there was difference in weight gain and risk of hypoglycemia. Thiazolidinediones, sulfonylureas and glinides were associated with weight gain, while sulfonylurea and glinides use was associated with increased risk of hypoglycemia. α-glucosidase inhibitors were associated with no change in weight and was not associated with increased risk of hypoglycemia [35].

n	233	229	147	81	152
Comparator	Acarbose monotherapy	Metformin monotherapy	Placebo plus metformin	Metformin plus placebo	Metformin plus placebo
P value (between groups)	< 0.0001	< 0.0001	≤ 0.0036	0.0001	0.0001

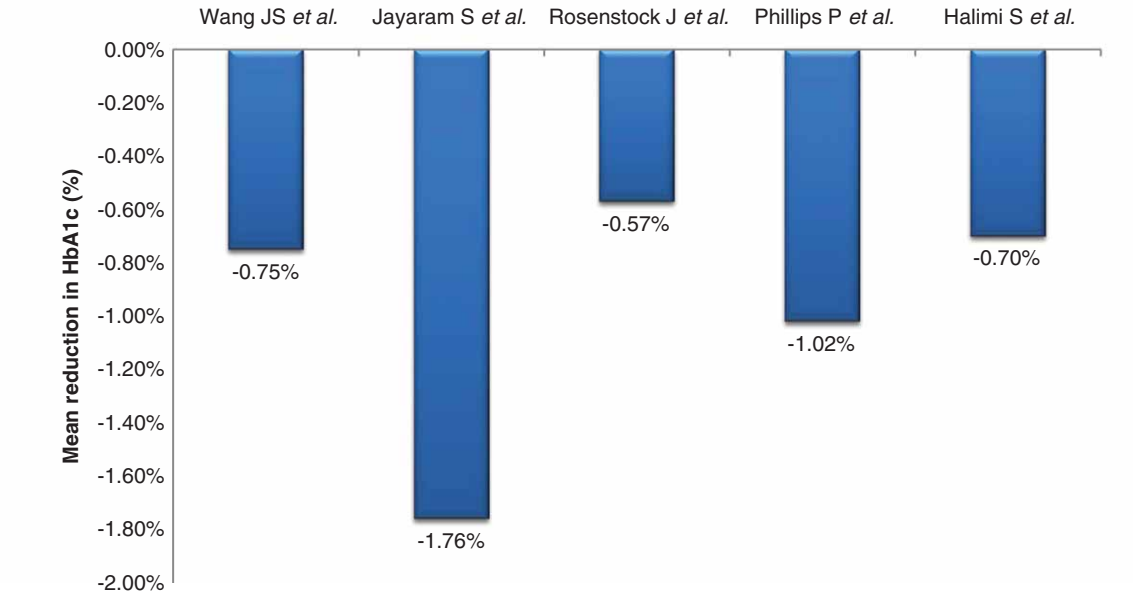


Figure 5. Reduction in glycosylated hemoglobin with combination treatment.

Patient compliance is an important aspect of diabetes management. Patients on monotherapy requiring an additional therapy show significantly better adherence when they are switched to FDC compared with free-dose combination therapy [36]. Hence a well-studied FDC if available; it will be a welcome option for the patients requiring treatment with acarbose and metformin.

The efficacy and safety of the FDC of acarbose plus metformin monotherapy have been evaluated in two comparative studies.

2.6.3 Studies with FDC

FDC of acarbose plus metformin and metformin monotherapy were significantly effective in reducing FBG and PPG and HbA1c in Indian patients [28]. The combination of acarbose and metformin was more effective in reducing all three parameters compared to metformin monotherapy. The study included drug naive adults with T2DM in whom combination of treatment was required for adequate glycemic control and also patients who were uncontrolled with acarbose or metformin monotherapy.

Recently, Wang *et al.* [37] compared the efficacy and safety of acarbose plus metformin FDC versus acarbose monotherapy for 16 weeks in Taiwanese T2DM patients. FDC was effective in significantly lowering all the glycemic control parameters that is, HbA1c, FBG and PPG from baseline. The difference between groups was significant for all parameters favoring FDC therapy (all $p < 0.0001$).

The large post-marketing study [38] evaluated the safety and effectiveness of FDC in T2DM under day-to-day real-life conditions in India involving 9364 patients. Mean changes in FBG (-42.4 mg/dl, CI 95%; 41.73, 43.14), PPG (-80.2 mg/dl, CI 95%; 79.09, 81.23) and HbA1c (-1.0%. CI 95%; 0.98, 1.02), body weight (-1.7 kg, CI 95%; 1.65, 1.75) between baseline and 12 weeks were statistically significant ($p < 0.0001$ for all). The physician assessment of efficacy was rated as excellent to good in 89% of patients. The patients with known history of T2DM and who were newly diagnosed with T2DM showed similar significant decreased in PPG, FBG and HbA1c ($p < 0.0001$).

All studies with acarbose plus metformin therapy resulted in reduction in HbA1c as shown in figure below (**Figure 5**).

Similarly, all studies with acarbose plus metformin therapy resulted in reduction in both FBG and PPG level except one as shown in **Figure 6** [33]. In the Phillips *et al.* [29] study, the mean increase in FBG level with placebo was 24.48 mg/dl, while with acarbose there was only slight increase (1.44 mg/dl) in FBG. Phillips *et al.* did not evaluate the change in PBG level with addition of acarbose or placebo to metformin therapy.

Combination of acarbose with metformin does not cause weight gain (**Figure 7**). In fact, some amount of weight

n	233	229	168	152
Comparator	Acarbose monotherapy	Metformin monotherapy	Placebo plus metformin	Metformin plus placebo
Fasting (p value)	< 0.0001	< 0.0001	0.0213	0.0001
PPG (p value)	< 0.0001	< 0.0001	0.0001	0.0001

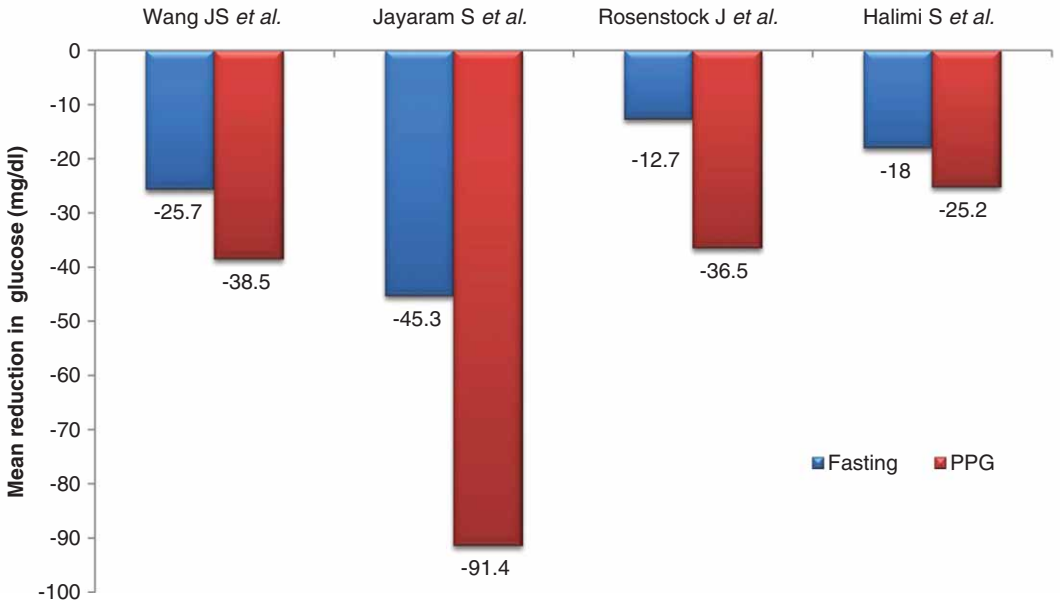


Figure 6. Reduction in fasting and postprandial glucose level with combination treatment.

n	233	229	168	83
Comparator	Acarbose monotherapy	Metformin monotherapy	Placebo plus metformin	Metformin plus placebo
P value (between groups)	< 0.01	0.189	0.08108	0.13

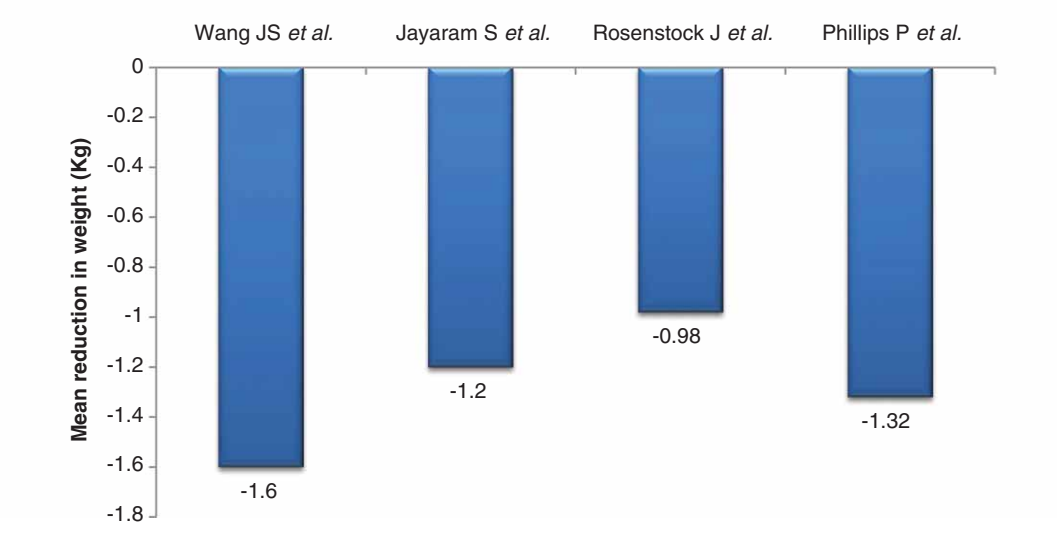


Figure 7. Reduction in body weight with combination treatment.

Table 2. Safety of acarbose plus metformin fixed-dose combination.

Acarbose	Metformin	Combination of acarbose plus metformin
Mild-to-moderate gastrointestinal side effects	Mild-to-moderate gastrointestinal side effects	Gastrointestinal adverse effects are not additive or synergistic
No risk of hypoglycemia	Low risk of hypoglycemia	No/low risk of hypoglycemia
Beneficial effect on weight	Beneficial effect on weight	Beneficial effect on weight

Table 3. Place of acarbose plus metformin combination in clinical practice.

	International Diabetes Federation 2012 guideline (IDF 2012) [15]	AACE consensus statement (2013) [2]
Monotherapy	Generally metformin is first choice	Entry HbA1c < 7.5% (metformin is first choice)
Dual therapy (metformin plus acarbose)	Failure of monotherapy (metformin or acarbose)	Entry HbA1c ≥ 7.5%
Three drug combination	Unsatisfactory control on dual therapy	Entry HbA1c ≥ 9%

AACE: American Association of Clinical Endocrinologists; HbA1c: Glycosylated hemoglobin.

reduction occurred with this combination, which is beneficial for obese diabetic patients.

2.7 Safety and tolerability

The safety and tolerability data from published clinical studies with free-dose combination and FDC and clinical experience with FDC available in India do not raise any new safety concern. Acarbose and metformin both can cause gastrointestinal adverse events; however, additive or synergistic gastrointestinal adverse events do not occur with combination. No significant difference in the gastrointestinal adverse events was seen between the FDC of acarbose plus metformin versus metformin alone [28]. The incidence of adverse events was 8.7 and 7.9% in patients receiving FDC and metformin monotherapy, respectively. All adverse events were gastrointestinal and mild-to-moderate in nature, which disappeared with continuation of treatment without any intervention. No patient dropped out because of adverse events or no hypoglycemic event in the study reflects the well-tolerated safety profile of combination. In the Taiwan study [33], both the acarbose monotherapy and FDC of acarbose and metformin significantly reduced bodyweight ($p < 0.0001$). The mean weight reduction with FDC was 0.6 kg more compared to acarbose monotherapy ($p < 0.01$). There were no cases of hypoglycemia reported with either treatment group. Similar to Indian study, there was no difference in the incidence of other adverse events between the groups. Other studies in different populations have also corroborated the observation [31,32]. Beneficial additive effects of both the agents are seen on body weight and triglyceride levels [12]. Only 2.06% patients reported adverse events in a noninterventional, prospective study, while 1.43% patients had adverse events related to the study drug [38]. All three clinical trials have shown that the FDC was well tolerated without any significant safety issue (**Table 2**).

2.8 Regulatory affairs

In India, acarbose plus metformin FDC (Glucobay M®, Bayer Healthcare Pharmaceuticals) has received regulatory approval in 2009 for the treatment of T2DM, when diet, exercise and single agent do not result in adequate glycemic control. Furthermore, in Taiwan this FDC has recently (July 2013) obtained license. The recommended dosage should be one tablet (25/50 mg acarbose; 500 mg metformin HCl) given 3 times daily and should be given with the first mouthful of meal. The daily dosage should be individualized for each patient on the basis of both effectiveness and tolerance. The maximum recommended daily dosage is 5 tablets per day (= 250 mg acarbose; 2500 mg metformin HCl). The combination is contraindicated in chronic intestinal disorders, renal failure or renal dysfunction (creatinine clearance < 60 ml/min) and hepatic insufficiency. The package insert lists other warnings and precautions, including hypoglycemia, lactic acidosis and liver enzyme monitoring during the first 6 – 12 months of treatment [15].

3. Conclusion

The combination of acarbose and metformin is well studied with separate tablets and in a FDC. The combination offers beneficial effects on glycemic control without additive risk of gastrointestinal adverse events. FDC is convenient to use and offers potential for improvement of compliance.

4. Expert opinion

As the diabetes pandemic continues to grow, so does the need for novel therapeutic regimens and strategies. The development of new drugs, however, is constrained by concerns related to cardiovascular safety, pancreatic safety and other issues.

Existing molecules, with well-proven safety and tolerability track record, represent an attractive strategy for management of diabetes. The use of FDC is another method of improving glucose control by increasing patient acceptability and adherence.

The combination of metformin and acarbose is a rational one, based upon a synergistic effect created by complimentary mechanisms of action, which work on synergy to reduce fasting and postprandial glycemia. Proven efficacy is matched by safety, tolerability and beneficial effects on cardiovascular health. Both molecules have demonstrated efficacy in enhancing GLP-1 levels.

Use of metformin and acarbose combination is bound to grow in future. Existing guidelines support the use of this combination as first-line therapy in persons with HbA1c > 7.5%, and as second-line treatment in persons not responding to either drug as monotherapy (Table 3). The proven safety, tolerability and pleiotropic benefits of these synergistic drugs should encourage earlier, timely use of the combination. Recent trends toward pharmacotherapy of prediabetes are relevant in the context of this discussion; both metformin and acarbose are used in the management of prediabetes and their combination may find utility in this indication, in select individuals.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Rosak C, Mertes G. Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. Diabetes Metab Syndr Obes 2012;5:357-67
2. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. Endocr Pract 2013;19(Suppl 2):1-48
3. Korean Diabetes Association. 2011 Clinical practice guidelines for type 2 diabetes in Korea. J Korean Diabetes Assoc 2011;12:71
4. Kalra S, Sahay BK, Rao MS. Fixed dose combinations in diabetes: indian innovation, Indian pride. Indian J Endocrinol Metab 2012;16:4-5
5. Blonde L, San Juan ZT. Fixed-dose combinations for treatment of type 2 diabetes mellitus. Adv Ther 2012;29:1-13
6. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) group. JAMA 1999;281:2005-12
7. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;35:1364-79
8. International Diabetes Federation. 2011 guideline for management of postmeal glucose in diabetes. IDF; Brussels: 2011
9. Hanefeld M. The role of acarbose in the treatment of non-insulin-dependent diabetes mellitus. J Diabetes Complications 1998;12:228-37
10. Enc FY, Imeryuz N, Akin L, et al. Inhibition of gastric emptying by acarbose is correlated with GLP-1 response and accompanied by CCK release. Am J Physiol Gastrointest Liver Physiol 2001;281:G752-63
11. Joshi SR. Post-prandial carbohydrate modulation via gut-Indian perspective. J Assoc Physicians India 2010;58:665
• **Editorial on the Phase-III study report on acarbose plus metformin fixed dose combination and rationalizing the clinical role of this Fixed dose combination (FDC) in Indian diabetes population.**
12. Hanefeld M, Schaper F. Acarbose: oral anti-diabetes drug with additional cardiovascular benefits. Expert Rev Cardiovasc Ther 2008;6:153-63
13. Hanefeld M, Cagatay M, Petrowitsch T, et al. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. Eur Heart J 2004;25:10-16
14. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. Am J Med 1997;103:483-90
15. Bayer Healthcare Pharmaceutical Ltd. Data on file 2014
16. Rojas LB, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr 2013;5:6
17. Scarpella JH, Howlett HC. Metformin therapy and clinical uses. Diab Vasc Dis Res 2008;5:157-67
18. Klachko D, Whaley-Connell A. Use of metformin in patients with kidney and cardiovascular diseases. Cardiorenal Med 2011;1:87-95
19. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12
20. Kappe C, Patrone C, Holst JJ, et al. Metformin protects against lipoapoptosis and enhances GLP-1 secretion from GLP-1-producing cells. J Gastroenteol 2013;48:322-32
21. Jenkins-Jones S, Currie CJ, Mukherjee J, et al. Association between first-line monotherapy with sulfonylurea versus metformin and risk of all-cause mortality

[abstract #201]. EASD, Barcelona, Spain; September 2013

22. Clinical Guidelines Task Force. Global guideline for type 2 diabetes. International Diabetes Federation. 2012;1-117. Available online at: www.idf.org/sites/default/files/IDF%20T2DM%20Guideline.pdf. Accessed on 17 June 2014
23. Monnier L, Colette C, Dunseath GJ, et al. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care 2007;30:263-9
24. Clissold SP, Acarbose EC. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1988;35:214-43
25. Holman R. Metformin as first choice in oral diabetes treatment: the UKPDS experience. Journ Annu Diabetol Hotel Dieu 2007;13-20
26. Kalra S, Chadha M, Sharma SK, Unnikrishnan AG. Untapped diamonds for untamed diabetes: the alpha-glucosidase inhibitors. Indian J Endocr Metab 2014;18:138-41

• **Highlights the under-utilization of α-glucosidase inhibitors in clinical practice.**

27. Miccoli R, Penno G, Del S. Multidrug treatment of type 2 diabetes. A challenge for compliance. Diabetes Care 2011;34(Suppl 2):s231-5
28. Jayaram S, Hariharan RS, Madhavan R, et al. A prospective, parallel group, open labelled, comparative, multicentric, active controlled study to evaluate the safety, tolerability, and benefits of fixed dose combination of acarbose and metformin versus metformin alone in type 2 diabetes. J Assoc Physicians India 2010;58:679-87

•• **Pivotal Phase-III clinical study data from Indian patients (first clinical study report on FDC of acarbose and metformin).**

29. Bayer Healthcare Pharmaceuticals Ltd. Data on file; Clinical study report: Glucobay M FDC BE study 15420 (Unpublished data)
30. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Ann Intern Med 1994;121:928-35
31. Rosenstock J, Brown A, Fischer J, et al. Efficacy and safety of acarbose in metformin treated patients with type 2 diabetes. Diabetes Care 1998;21:2050-5
32. Halimi S, Le Berre MA, Grange V. Efficacy and safety of acarbose add on therapy in the treatment of overweight patients with type 2 diabetes inadequately controlled with metformin: a double blind, placebo controlled study. Diabetes Res Clin Pract 2000;50:49-56
33. Phillips P, Karrasch J, Scott R, et al. Acarbose improves glycemic control in overweight type 2 diabetic patients insufficiently treated with metformin. Diabetes Care 2003;26:269-73
34. Philip E, Sundaram ML, Das R, et al. Acarbose improves glycemic control as add-on or monotherapy in Indian type-2 diabetes: findings from the GlucoVIP multinational observational study. Indian J Endocrinol Metab 2013;17:S674-9
35. Phung OJ, Scholle JM, Talwar M, et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010;303:1410-18
36. Melikian C, White TJ, Vanderplas A, et al. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 2002;24:460-7
37. Wang JS, Huang CN, Hung YJ, et al. Acarbose plus metformin fixed-dose combination outperforms acarbose monotherapy for type 2 diabetes. Diabetes Res Clin Pract 2013;102:16-24

•• **Second pivotal Phase-III clinical study data from Taiwanese patients (clinical study report on FDC of acarbose and metformin).**

38. Bayer Healthcare Pharmaceuticals Ltd. Data on file. Clinical study report (PH37466): Glucobay M FDC phase IV study 2013 (unpublished data)

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