Editorial

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# Metformin Based Dual-Combination Therapies in Drug Naïve Type 2 Diabetic Patients

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There is an explosive growth of type 2 diabetes mellitus (T2DM) in South Korea. According to Korea National Health and Nutritional Examination Survey performed in 2011, the prevalence of diabetes among the population of 30 years and old is 12.4%, and the number of patients with T2DM is expected to reach 6 million by 2050 [1].

Through studies such as UK Prospective Diabetes Study, it has been well established that aggressive glycemic control in patients with newly diagnosed T2DM reduces microvascular and macrovascular complications of the disease [2]. Therefore, it is important to diagnose and treat T2DM in early phase. Several institutions have suggested target glycemic goals—for instance, American Diabetes Association (ADA) has recommended glycated hemoglobin (HbA1c) to be controlled below 7% and stated that it should be maintained as close to normal level as possible in patients with short duration of T2DM, long life expectancy, and no cardiovascular disease [3,4]. Korean Diabetes Association (KDA) has recommended HbA1c below 6.5% as target glycemic goal [5]. In general, a regimen of single oral hypoglycemic agent reduces HbA1c by approximately 1.5%; therefore, a combination therapy is recommended as initial management in HbA1c greater than 8% [3-7]. The benefits of early combination therapy includes reduced glucotoxicity to β-cells through early normalization of blood glucose, reduced exposure time to hyperglycemia, and simultaneous blocking of multiple pathophysiology of T2DM [5,6].

The treatment guideline provided by ADA and European Association for the Study of Diabetes (EASD), as well as that by KDA, recommends metformin in addition to lifestyle modification in patients with newly diagnosed T2DM as long as there are no contraindications [3-5]. In the past, addition of oral hypoglycemic agents with different mechanism of action or insulin was indicated after failure of metformin monotherapy; however, since the recent recognition of importance of early aggressive glycemic control, metformin-based combination therapy has been widely employed in patients with HbA1c greater than 7.5% to 8% [3-6]. However, if combination of oral agents other than metformin is determined to be more effective based on several studies, an appropriate combination may be tailored to each patient depending not only on the mechanism, efficacy, side effect, and drug-drug interaction of each agent but also on individual lifestyle [3,6].

The major classes of hypoglycemic agents that may be combined with metformin include sulfonylurea (SU), thiazolidinedion (TZD), dipeptidyl-peptidase-4 inhibitor (DPP4-i), insulin, and glucagon-like peptide-1 (GLP-1) receptor agonist [6]. There is no clear guideline on the most effective combination regimen available for uncontrolled T2DM, and few studies investigated the effect of metformin-based early combination therapy.

SU acts on β-cells of the pancreas as an insulin secretagogue—it is the most commonly used drug in conjunction with metformin [5,7]. One study evaluated the efficacy and safety of glyburide/metformin combination regimen as initial

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therapy in drug-naïve T2DM patients over 2 years. The mean HbA1c at baseline and at 104 weeks after treatment was 8.4% and 6.8%, respectively. Combination with SU resulted in good glycemic control, but a significant increase in body weight and hypoglycemic episodes was noted [8]. While second generation SU (e.g., gliclazide, glimepiride) report lower incidence of hypoglycemic episodes compared to long acting SU (glyburide), it still needs to be taken into account in elderly patients [9]. In addition, another problem has been raised by a study entitled "A diabetes outcome progression trial (ADOPT)"—SU, when used as monotherapy agent, shows higher secondary failure rate compared to metformin or TZD [10]. Nonetheless, whether a similar result is observed when combined with metformin has not been reported as of yet.

Pioglitazone, a peroxisomal proliferator-activated receptor γ agonist, reduces insulin resistance in the liver and peripheral tissues, leading to increases in suppression of hepatic glucose production and glucose uptake in peripheral tissues [6,7]. One cohort follow-up study compared and analyzed the results of initial combination therapy consisting of metformin and pioglitazone and initial sequential monotherapy of metformin and pioglitazone in T2DM patients with HbA1c greater than 7%. This study found that initial combination therapy of metformin and pioglitazone was more effective than sequential combination therapy of metformin and pioglitazone in reaching and maintaining glycemic control, especially in subjects with HbA1c greater than 9% [11]. Although pioglitazone reduces the risk of death, myocardial infarction, and stroke, there is potential weight gain, and its long-term use is associated with elevated risk of other side effects, such as bone fracture [12,13].

DPP4 inhibits DPP4, an enzyme that degrades incretin hormone GLP-1, resulting in hypoglycemic effect [6,14]. Its combination with metformin is the subject of numerous recent studies.

Lim et al. [15] reported a decrease in mean HbA1c of approximately 1.5% in drug-naïve Korean T2DM patients who initially underwent 52 weeks of combination therapy with metformin and stagliptin—this efficacy was found to be greater in those with higher initial HbA1c after adjusting for BMI, insulin resistance, and other factors. In addition, it has suggested that DPP4-i may offer assistance in subjects with low β-cell function [15].

A series of recent studies have reported a combination regimen of metformin and DPP4-i to be associated with effective and safe glycemic control with no weight gain and low risk of hypoglycemia [16-18]. Nonetheless, there is a lack of studies on the effects of long-term DPP4-i use on cardiovascular disease, cancer, or the pancreas.

The study by Lee et al. [19] was designed to evaluate the efficacy of glycemic control in drug-naïve or newly detected Korean T2DM patients receiving metformin-based dual combination therapy with SU, pioglitazone, or DPP4-i, and they found similar hypoglycemic efficacy among SU, pioglitazone, and sitagliptin after 24 weeks of treatment in newly diagnosed T2DM subjects: this efficacy was similar or superior to that reported by other studies that combined SU, TZD, or DPP4-i to metformin [8,11,15-17]. Several studies have investigated which medications are more effective in Korean subjects [15,20,21]. In a study that reported more frequent β-cell dysfunction in Asian population compared to Westerners, combination therapy with SU could be effective in Korean [20]. DPP4-i was reported to be more effective in Asians than in Western [21]; however, in another study that included diabetes in early stages, TZD demonstrated equal hypoglycemic efficacy when compared to SU [22]. These findings imply that it is difficult to label a specific drug as superior to others.

Furthermore, patients with relatively high HbA1c at baseline responded well to combination oral hypoglycemic agent therapy [19]. Insulin therapy is the recommended treatment of choice in patients with HbA1c greater than 10% to 11% or with symptoms of hyperglycemia [3-6]; however, in this study, dual therapy was initiated in subjects with HbA1c greater than 11%. These patients showed a mean HbA1c below 6.5% after 24 weeks of treatment, demonstrating that oral hypoglycemic agents can achieve adequate glycemic control within 24 weeks in early diabetic patients with severe hyperglycemia [19]. As the authors have stated, this maybe be due to relatively spared pancreatic β-cell function, as well as due to lower insulin resistance compared to study groups of other researches.

The 2013 ADA/EASD guideline also recommended that glycemic target and control should be tailored to individuals [3]. In this study by Lee et al. [19], metformin-based dual therapies with SU, TZD, and DPP4-i all showed similar efficacy. This suggests that the choice of oral hypoglycemic agents should be based on side effects, compliance, cost, and other factors rather than relying on a specific class of drug. Nonetheless, the analysis included only 24 weeks of data since the initial diagnosis, requiring further studies that evaluates not only the continued hypoglycemic efficacy of the combination ther-

apy but also its side effects and its preventative effect on complications. A special attention should be paid in the future to the incidence of cardiovascular diseases and hypoglycemia in SU group, fracture and edema in TZD group, and pancreatitis, neoplasm, and cardiovascular disease in DPP4-i group.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## REFERENCES


1. Jeon JY, Ko SH, Kwon HS, Kim NH, Kim JH, Kim CS, Song KH, Won JC, Lim S, Choi SH, Jang MJ, Kim Y, Oh K, Kim DJ, Cha BY; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Prevalence of diabetes and prediabetes according to fasting plasma glucose and HbA1c. Diabetes Metab J 2013;37:349-57.
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
3. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia 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). Diabetes Care 2012;35:1364-79.
4. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, Davidson MB, Einhorn D, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez G, Davidson MH; American Association of Clinical Endocrinologists. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013;19:327-36.
5. Ko SH, Kim SR, Kim DJ, Oh SJ, Lee HJ, Shim KH, Woo MH, Kim JY, Kim NH, Kim JT, Kim CH, Kim HJ, Jeong IK, Hong EK, Cho JH, Mok JO, Yoon KH; Committee of Clinical Practice Guidelines, Korean Diabetes Association. 2011 Clinical practice guidelines for type 2 diabetes in Korea. Diabetes Metab J 2011;35:431-6.
6. Bailey T. Options for combination therapy in type 2 diabetes: comparison of the ADA/EASD position statement and AACE/ACE algorithm. Am J Med 2013;126(9 Suppl 1):S10-20.
7. Cheng AY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ 2005;172:213-26.
8. Gerich J, Raskin P, Jean-Louis L, Purkayastha D, Baron MA. PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. Diabetes Care 2005;28:2093-9.
9. Sinclair A, Morley JE, Rodriguez-Manas L, Paolisso G, Bayer T, Zeyfang A, Bourdel-Marchasson I, Vischer U, Woo J, Chapman I, Dunning T, Meneilly G, Rodriguez-Saldana J, Gutierrez Robledo LM, Cukierman-Yaffe T, Gadsby R, Schernthaner G, Lorig K. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc 2012;13:497-502.
10. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.
11. Pandya BJ, Bron M, McCall T, Yu AP, Chen KS, Mattson ME, Wu EQ. Achieving glycemic goal with initial versus sequential combination therapy using metformin and pioglitazone in type 2 diabetes mellitus. Curr Med Res Opin 2011;27:189-95.
12. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180-8.
13. Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M. Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. Diabetes Obes Metab 2010;12:716-21.
14. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet 2011;378:182-97.
15. Lim S, An JH, Shin H, Khang AR, Lee Y, Ahn HY, Yoon JW, Kang SM, Choi SH, Cho YM, Park KS, Jang HC. Factors predicting therapeutic efficacy of combination treatment with sitagliptin and metformin in type 2 diabetic patients: the COSMETIC study. Clin Endocrinol (Oxf) 2012;77:215-23.
16. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study. Int J Clin Pract 2013;67:

1283-93.
17. Pfutzner A, Paz-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab 2011;13:567-76.
18. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE; Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007;30:1979-87.
19. Lee YK, Song SO, Kim KJ, Cho Y, Choi Y, Yun Y, Lee BW, Kang ES, Cha BS, Lee HC. Glycemic effectiveness of metformin-based dual-combination therapies with sulphonylurea, pioglitazone, or dpp4-inhibitor in drug-naive Korean type 2 diabetic patients. Diabetes Metab J 2013;37:465-74.
20. Rhee SY, Chon S, Oh S, Kim SW, Kim JW, Kim YS, Woo JT. Insulin secretion and insulin resistance in newly diagnosed, drug naive prediabetes and type 2 diabetes patients with/without metabolic syndrome. Diabetes Res Clin Pract 2007;76:397-403.
21. Kim YG, Cho YM. Comparison of the efficacy of dipeptidyl-peptidase-4 inhibitors between Asian and non-Asian populations. J Korean Diabetes 2013;14:133-7.
22. Yoon KH, Shin JA, Kwon HS, Lee SH, Min KW, Ahn YB, Yoo SJ, Ahn KJ, Park SW, Lee KW, Sung YA, Park TS, Kim MS, Kim YK, Nam MS, Kim HS, Park IeB, Park JS, Woo JT, Son HY. Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in Korean drug-naive type 2 diabetic patients: the practical evidence of antidiabetic monotherapy study. Diabetes Metab J 2011;35:26-33.