Original Article

Differences in Mortality Rate by Anti-hyperglycemic Regimens among Patients in the Thailand Diabetic Registry Project

Thongchai Pratipanawatr MD[1], On behalf of the Thailand Diabetic Registry Working Group

[1] Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Background: The present study was conducted in order to determine the impact of different regimens of anti-hyperglycemic agents on all-cause mortality.

Materials and Methods: The Thailand diabetes registry cohort was a prospective 3-year follow-up of the Thai Diabetes Registry project, registered 9,419 diabetes from 10 diabetic clinics in tertiary medical centers in Bangkok and the major provinces between April, 2003 and February, 2006. The authors included type 2 diabetic patients over 30 year-old. Patients whose serum creatinine was >3 mg/dl were excluded to avoid a bias of choosing insulin and metformin. Since few patients took glinide or alpha-glucosidase inhibitors, our 8,109 (86.09%) patients were classified by their respective regimen of anti-hyperglycemic agents: i.e., whether sulfonylurea monotherapy (1,151; 14.2%); metformin monotherapy (794; 9.8%); sulfonylurea combined with metformin (3,665; 45.2%); thiazolidinedione [TZD] monotherapy or combined with anti-hyperglycemic agents (393; 4.9%); insulin treatment combined with metformin or TZD (1,273; 15.7%); or, insulin treatment without metformin or TZD (833; 12.6%).

Results: The mortality rate for those who received insulin treatment without metformin or TZD combination (49.3 per 1,000 patient-years) were the highest among anti-hyperglycemic treatment regimens followed by sulfonylurea monotherapy (22.7 per 1,000 patient-years), insulin treatment combined with metformin or TZD (13.6 per 1,000 patient-years), sulfonylurea combined with metformin (12.2 per 1,000 patient-years), TZD (8.1 per 1,000 patient-years) and metformin monotherapy (7.0 per 1,000 patient-years). Compared with patients who received sulfonylurea monotherapy, those who received metformin monotherapy, TZD, sulfonylurea combined with metformin had a respective lower mortality rate of 53% (adjusted hazard ratio [HR] 0.47 (0.25 to 0.88)), 56% (adjusted HR 0.44 (0.19 to 1.00)), and 31% (adjusted HR 0.69 (0.50 to 0.95)). The mortality of patients who received insulin treatment without metformin or TZD combination was increased by 53% (adjusted HR 1.58 (1.10 to 2.28)), while the harmful effects of insulin was reduced when combined with metformin or TZD (adjusted HR 0.83 (0.53 to 1.29)).

Keywords: Diabetes, Anti-hyperglycemic agents, Metformin, Sulfonylurea, Insulin, Thiazolidinedione, Mortality rate, Death rate

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An intensive treatment protocol that tightens glycemic control has been demonstrated to prevent diabetic complications[1,2]. These benefits or "legacy effects" can persist for as long as ten years[3,4]. Metformin, acrabose, and pioglitazone are the primary anti-hyperglycemic agents, but only a few randomized control trial studies have evaluated which provides consistent desirable clinical outcomes, especially vis-a-vis mortality.

The UK Prospective Diabetes Study showed that metformin monotherapy reduced diabetic-related endpoint among obese type 2 diabetics[5]. Observational studies also reported metformin monotherapy significantly decreased diabetic-related endpoints when compared with sulfonylurea

Correspondence to:
Pratipanawatr T, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand
Phone: +66-43-363665
E-mail: thongcha@kku.ac.th

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monotherapy[6]. The beneficial effects of metformin on diabetic complications were not, however, consistent. The addition of metformin to sulfonylurea was associated with an increase in diabetic-related endpoint compared with sulfonylurea alone[5]. Observational studies reported significantly increased mortality associated with metformin[7] and metformin combined with sulfonylurea[8].

Acrabose is an alpha-glucosidase inhibitor. The STOP NIDDM study was designed to demonstrate the diabetes prevention effect of acrabose in glucose intolerant patients. Acrabose also significantly decreased the diabetic-related endpoint when compared with placebo[9].

Pioglitazone is the only thiazolidinedione available. The PROCATIVE study demonstrated that pioglitazone plus other anti-hyperglycemic agents decreased composite cardiovascular outcomes; including acute myocardial infarction, cerebrovascular accident, and death in high cardiovascular risk type 2 diabetes[10]. The benefits of Pioglitazone were confirmed through a systematic review and meta-analysis[11].

We previously reported the risk of death among Thai diabetics[12]. Metformin was one of factors associated with a lower risk of death. By contrast, diabetic patients who were taking insulin at time of registration had almost double the risk of death. Those findings, however, were not classified by regimens of anti-hyperglycemic agent combinations which might affect mortality.

Herein are presented the findings of a longitudinal study of Thai type 2 diabetic patients. The aim of the study was to examine the effect of various anti-hyperglycemic treatment regimens on all-cause mortality.

Materials and Methods

Setting and subjects

The detailed methods used by the Thailand Diabetic Registry have been published[12]. Diabetic patients (9,419) attending the diabetic clinics of 10 tertiary care hospitals across Thailand were registered. Elements of the study prospectively registered included: (a) demographic data, (b) pertinent parts of physical examinations, (c) laboratory examinations performed within 12 months prior to recruitment (d) medications including insulin, oral anti-hyperglycemic agents, anti-hypertensive agents, lipid lowering agents and aspirin, and, (e) diabetic complications verified by physician's reports. The subject was thus diabetic patients being treated in these clinics. All subjects provided informed consent before participating in the registry. The study was approved by the ethics committee at each hospital.

This analysis included patients over 30 with type 2 diabetes. Patients who had a serum creatinine >3 mg/dl were excluded in order to avoid the bias of choosing between insulin and metformin. Since only a few of the patients were on glinide and alpha-glucosidase inhibitors, both of these anti-hyperglycemic agents were excluded from the analysis. Based on information recorded during the registry (i.e., between April 2003 and December 2003), anti-hyperglycemic therapy regimens were classified into 6 common treatment regimens: 1) sulfonylurea monotherapy; 2) metformin monotherapy; 3) sulfonylurea combined with metforminl; 4) thiazolidinediones [TZD] either monotherapy or combined with other anti-hyperglycemic agents; 5) insulin treatment together with metformin or TZD; and, 6) insulin treatment without metformin or TZD combination.

The respective type of health care plan, based on the registry data, was categorized as Universal Coverage, Social Security Welfare, or Civil Service health plan. A number of patients paid the hospital charges out-of-pocket and some by private health insurance. The Civil Service health plan is for government employees and their family members. The Civil Service plan pays for all health care costs and is considered the best plan in the country. Social Security Welfare is the plan for workers and is supported by employer contributions. Universal Coverage is the government health plan for all Thais not covered by any other health care plan: it covers only essential health care so is considered the least desirable coverage. At the end of February 2006, the respective vital status of 99.5% of the diabetic patients (9,370) was determined using the database of each of the participating hospitals as well as The Bureau of Registration Administration, The Ministry of Interior. The primary outcome was death from any cause (i.e., all-cause mortality).

Statistical methods

The patients were divided into 6 groups according to their anti-hyperglycemic treatment regimen. The proportions of studied variables were compared using the Chi-squared test and the Fisher's exact test. Differences in the means of the studied variables were compared using ANOVA with Bonferroni correction and the Kruskall-Wallis test.

Cox proportional hazard models were used to calculate hazard ratios [HR] for all-cause mortality vis-a-vis anti-hyperglycemic treatment regimens. Cox proportional hazard models were adjusted in 3 models; viz., Model 1 which was adjusted for age and sex; Model 2 which adjusted for age, sex, serum creatinine group, and previous history of coronary artery and cerebrovascular disease; and, Model 3 which adjusted for all important covariates factors (as follows). Important covariate factors were determined according to an applied multiple Cox regression model with backward elimination. Whenever two variables were similar and/or had multi-co-linearity, only one was included in the model, and thus the final Cox proportional hazard model-assessment of model adequacy-was constructed. The proportional hazard assumption and goodness-of-fit were tested.

Statistical analyses were performed using STATA version 13.0 (Stata Corporation, College Station TX, US).

Results

Based on the complete information of 9,370 enrollees, 8,109 were included in the analysis. These were then divided into 6 groups; according to the anti-hyperglycemic treatment regimen-viz., sulfonylurea monotherapy (1,151; 14.2%), metformin monotherapy (794; 9.8%), sulfonylurea combined with metformin (3,665; 45.2%), thiazolidinediones (monotherapy or combined with anti-hyperglycemic agents (393; 4.9%), insulin treatment combined with metformin or TZD (1,273; 15.7%), and insulin treatment without metformin or TZD (833; 12.6%).

The baseline characteristics of each group are presented in Table 1. Differences in treatment between each group are presented in Table 2. The mortality rate is presented in Table 3. Table 4 presents the hazard ratios of all 5 treatment regimens compared with the mortality rate of sulfonylurea monotherapy (i.e., 22.7 per 1,000 patient-years) that was assigned as the reference group. In Figure 1, for each anti-hyperglycemic treatment regimen, the all-cause unadjusted mortality Kaplan-Meier survival estimates are illustrated in the follow-up period.

Mortality rate, hazard ratios of metformin treatment regimens

Metformin monotherapy had the lowest mortality rate among the 6 regimens. The crude all-cause-mortality rate was 7.0 per 1,000 patient-years (Table 3). Both the unadjusted HR and adjusted HR for all-cause mortality in the metformin monotherapy group was significantly lower than the control sulfonylurea monotherapy (HR unadjusted 0.39 (0.17 to 0.55)) and the HR adjusted model 3 0.47 (0.25 to 0.88)).

Mortality rate, hazard ratios for the sulfonylurea and metformin treatment regimens

The crude mortality rate in the sulfonylurea combined with metformin group (12.2 per 1,000 patient-years) ranked between the metformin and sulfonylurea monotherapy. The unadjusted hazard ratio of the sulfonylurea combined with metformin group was 0.54 (0.40 to 0.73), compared to 0.69 (0.50 to 0.95) for the adjusted hazard ratio of Model 3.

Mortality rate, hazard ratios of thiazolidinediones treatment regimens

At registration, only 393 (4.9%) patients were taking TZD in 4 different combinations: (a) TZD monotherapy (7; 1.8%), (b) TZD with metformin (29; 7.4%), (c) TZD with sulfonylurea (61; 15.5%), and (d) TZD with sulfonylurea and metformin (296; 75.3%). Analysis of all 4 TZD combinations revealed that the crude mortality rate of TZD users (8.1 per 1,000 patient-years) was lower than sulfonylurea monotherapy with an unadjusted HR of 0.36 (0.17 to 0.75) vs. an adjusted HR of 0.44 (0.19 to 1.00) for Model 3.

Focusing on the triple oral anti-hyperglycemic agent combination (i.e., the TZD combination with sulfonylurea and metformin), the benefit of TZD vis-a-vis mortality was even more prominent with an unadjusted HR of 0.12 (0.03 to 0.48) vs. an adjusted HR of 0.21 (0.05 to 0.88) for Model 3.

Mortality rate, hazard ratios of insulin treatment regimens

Insulin treatment was divided into 2 regimens; whether or not combined with insulin sensitizers (metformin or TZD). Compared with sulfonylurea monotherapy, the group that was taking insulin without metformin or TZD had the highest mortality among all 6 anti-hyperglycemic treatment regimens (49.3 per 1,000 patient-years) with a respective unadjusted and adjusted hazard ratio of 2.18 (1.59 to 2.99) and 1.58 (1.10 to 2.28).

A group of 1,273 insulin-treated patients was also given either metformin or TZD (i.e., only metformin (665; 52.2%); sulfonylurea and metformin (527; 41.4%); metformin and TZD (38; 3.0%); sulfonylurea and metformin and TZD (20; 1.6%); or, only TZD (18; 1.4%)). The combination of either metformin or

Table 1. Patient demographic data at entry classified by anti-hyperglycemic treatment regimen

	Sulfonylurea	Metformin	Sulfonylurea with metformin	TZD or combined with others	Insulin with metformin or TZD	Insulin without metformin or TZD	*p*-value
n	1,151	794	3,665	393	1,273	833	
Age (years)	64.2±11.4	58.5±12.5	60.5±10.9	61.0±10.1	58.9±11.1	63.5±12.2	<0.01
Female (%)	707 (61.42)	556 (69.5)	2,487 (67.86)	227 (57.76)	926 (72.74)	492 (59.06)	<0.01
Duration of diabetes (years)[a]	6.9 (0.1 to 44.1)	4.6 (0.1 to 45.4)	8.9 (0.1 to 45.4)	11.0 (0.3 to 46.4)	13.2 (0.1 to 46.1)	13.3 (0.1 to 46.5)	<0.01
Height (cm)	156.8±8.3	157.3±8.3	157.5±8.3	160.4±8.8	157.7±8.4	157.7±8.4	<0.01
Weight (kg)	60.7±11.5	66.8±13.4	63.3±11.9	69.5±12.8	66.8±12.2	62.8±12.9	<0.01
BMI (kg/m^2)	24.6±4.0	26.9±4.7	25.5±4.1	26.9±4.3	26.8±4.4	25.1±4.3	<0.01
SBP (mmHg)	144.0±23.3	140.4±20.2	142.9±21.5	144.6±19.2	143.7±21.9	146.1±26.1	<0.01
DBP (mmHg)	77.7±11.9	80.6±10.6	79.6±10.9	79.6±10.2	79.2±10.7	77.0±12.0	<0.01
FBS (mg/dl)	142.9±43.3	131.5±31.1	152.9±46.2	155.8±51.0	169.1±71.2	166.5±75.3	<0.01
HbA1c (%)	7.6±1.7	7.1±1.3	8.0±1.6	8.4±1.6	9.3±2.0	9.2±2.2	<0.01
Cholesterol (mg/dl)	199.1±40.4	196.1±39.2	196.0±40.0	193.2±36.6	194.4±40.5	201.6±51.0	<0.01
Triglyceride (mg/dl)	147.6±89.1	146.7±78.4	150.5±90.1	142.9±75.1	158.0±109.7	158.0±111.2	<0.01
HDL(mg/dl)	54.0±20.4	52.3±21.6	51.8±21.3	54.8±16.3	50.6±20.7	52.2±27.1	<0.01
LDL(mg/dl)	115.5±34.5	113.8±34.0	114.2±34.7	110.0±31.6	112.1±35.6	118.0±39.6	<0.01
Smoking status (%)							<0.01
Non-smoker	887 (77.06)	656 (82.62)	2,980 (81.31)	319 (81.17)	1,031 (80.99)	612 (73.47)	
Ex-smoker	206 (17.90)	94 (11.84)	463 (12.63)	56 (14.25)	174 (13.67)	163 (19.57)	
Current-smoker	58 (5.04)	44 (5.54)	222 (6.06)	18 (4.58)	68 (5.34)	58 (6.96)	
Health care plan (%)							<0.01
Civil Service	713 (61.95)	481 (60.58)	2,088 (56.97)	210 (53.44)	710 (55.46)	499 (59.91)	
Self-pay& Insurance	252 (21.89)	214 (26.95)	1,009 (27.53)	171 (43.51)	361 (28.56)	209 (25.09)	
Social welfare	49 (4.26)	54 (6.80)	204 (5.57)	5 (1.27)	84 (6.65)	40 (4.80)	
Universal coverage	137 (11.90)	45 (5.67)	364 (9.93)	7 (1.78)	118 (9.33)	85 (10.20)	
History of coronary artery disease (%)	96 (8.38)	47 (5.94)	256 (7.02)	24 (6.14)	122 (9.67)	133 (16.16)	<0.01
History of cerebrovascular disease (%)	61 (5.30)	30 (3.78)	155 (4.23)	9 (2.29)	50 (3.93)	66 (7.92)	NS
Hypertension (%)	896 (77.85)	561 (70.65)	2,795 (76.26)	298 (75.83)	1,024 (80.44)	674 (80.91)	<0.01
Serum Cr >1.5 mg/dl	231 (20.07)	40 (5.04)	325 (8.87)	40 (10.18)	107 (8.41)	375 (45.02)	<0.01

TZD = Thiazolidinedione; BMI = Body mass index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; FBS = Fasting Blood Sugar; HDL = High density lipoprotein; LDL = Low density lipoprotein; Cr = creatinine; NS = not significant (p>0.05)

[a] median (min-max)

Table 2. Treatment at entry subdivided by each anti-hyperglycemic treatment regimen and treatment with anti-hypertensive agent, lipid-lowering agent, and aspirin

	Sulfonylurea	Metformin	Sulfonylurea with metformin	TZD or combined with others	Insulin with metformin or TZD	Insulin without metformin or TZD	*p*-value
n	1,151	794	3,665	393	1,273	833	
Anti-hypertensive agent							
ACEi (%)	437 (37.97)	250 (31.49)	1,424 (38.85)	99 (25.19)	532 (41.79)	281 (33.73)	<0.01
ARB (%)	84 (7.30)	47 (5.92)	271 (7.39)	70 (17.81)	122 (9.58)	102 (12.24)	<0.01
Beta-blocker (%)	212 (18.42)	152 (19.14)	698 (19.05)	71 (18.07)	283 (22.23)	210 (25.21)	<0.01
Alpha-blocker (%)	40 (3.48)	14 (1.76)	106 (2.89)	12 (3.05)	45 (3.53)	44 (5.28)	<0.01
Calcium channel blocker (%)	240 (20.85)	155(19.52)	732 (19.97)	82 (20.87)	342 (26.87)	278 (33.37)	<0.01
Diuretic (%)	315 (27.37)	19 (24.69)	980 (26.74)	112 (28.50)	432 (33.94)	339 (40.7)	<0.01
Lipid-lowering agent							
Statin (%)	484 (42.05)	325(40.93)	1,613 (44.01)	207 (52.67)	669 (52.55)	434 (52.1)	<0.01
Fibrate (%)	150 (13.03)	97 (12.22)	500 (13.64)	67 (17.05)	194 (15.24)	104 (12.48)	NS
Aspirin (%)	430 (37.36)	244 (30.73)	1,344 (36.67)	126 (32.0)	540 (42.42)	340 (40.82)	<0.01

TZD = Thiazolidinedione; ACEi = Angiotensin converting enzyme inhibitors; ARB = Angiotensin II receptor blockers; NS = not significant ($p>0.05$)

Table 3. Time at risk, death and mortality rate, by anti-hyperglycemic treatment regimen

	Time at risk (patient-years)	Death (n)	Mortality rate (1,000 patient-years)
Sulfonylurea	2,821.5	64	22.7
Metformin	1,987.8	14	7.0
Sulfonylurea and Metformin	9,090.9	111	12.2
TZD or combined with others	958.8	8	8.1
Insulin with metformin or TZD	3,165.6	43	13.6
Insulin without metformin or TZD	1,987.1	98	49.3

TZD = Thiazolidinedione

Table 4. Unadjusted hazard ratios, adjusted hazard ratios and their 95% CI from multivariate Cox models; as used to identify mortality according to anti-hyperglycemic treatment regimens

Treatment regimens	Unadjusted HR (95% CI)	Adjusted HR (95% CI)		
		Model 1[a]	Model 2[b]	Model 3[c]
Sulfonylurea	1	1	1	1
Metformin	0.31 (0.17 to 0.55)	0.41 (0.23 to 0.74)	0.46 (0.26 to 0.83)	0.47 (0.25 to 0.88)
Sulfonylurea and metformin	0.54 (0.40 to 0.73)	0.67 (0.49 to 0.91)	0.73 (0.53 to 0.99)	0.69 (0.50 to 0.95)
TZD	0.36 (0.17 to 0.75)	0.44 (0.21 to 0.91)	0.48 (0.23 to 0.99)	0.44 (0.19 to 1.00)
Insulin with metformin or TZD	0.60 (0.41 to 0.88)	0.82 (0.55 to 1.21)	0.86 (0.58 to 1.28)	0.83 (0.53 to 1.29)
Insulin without metformin or TZD	2.18 (1.59 to 2.99)	2.25 (1.64 to 3.09)	1.80 (1.30 to 2.49)	1.58 (1.10 to 2.28)

TZD = Thiazolidinedione
[a] Adjusted for age and sex
[b] Adjusted for age, sex, serum creatinine, history of coronary and cerebrovascular disease
[c] Adjusted for age, sex, duration of diabetes, HbA1c, serum creatinine, BMI, health care plan, occupation, use of lipid lowering agents, current smoking, history of coronary and cerebrovascular disease

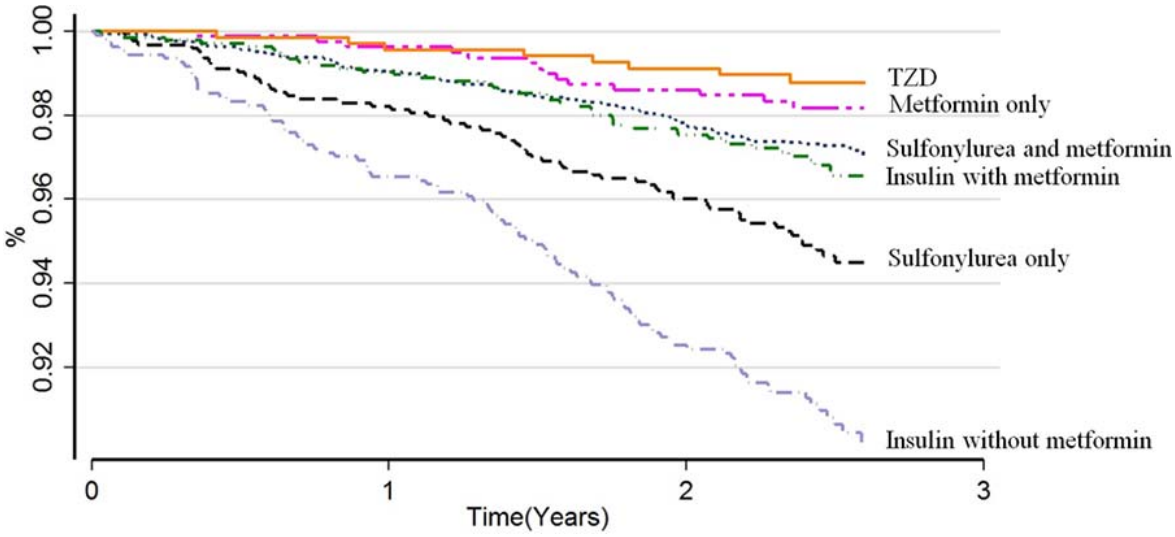

Figure 1. Kaplan-Meier all-cause survival estimate curves by anti-hyperglycemic treatment regimens.

TZD with insulin had a lower mortality rate (13.6 per 1,000 patient-years) than insulin without metformin or TZD. The respective unadjusted and adjusted HR of insulin therapy with metformin or TZD was 0.60 (0.40 to 0.88) and 0.83 (0.53 to 1.29) when compared with sulfonylurea monotherapy.

Comparing between two insulin treatment regimens, insulin without metformin had about 2 to 3 times higher mortality than insulin treatment with either metformin or TZD (unadjusted HR 3.65 (2.55 to 5.21)) and adjusted HR Model 3 1.94 (1.25 to 3.02)).

Discussion

The current study showed the difference in mortality among 6 common anti-hyperglycemic treatment regimens. Metformin-containing regimens, metformin alone, and metformin combined with sulfonylurea had lower mortality rates than sulfonylurea alone. Even though less common, the TZD regimen had about half the mortality rate of sulfonylurea treatment alone. Insulin-containing regimens had highest mortality among common treatment regimens; however, combining metformin or TZD with insulin decreased the mortality rate to the same rate as sulfonylurea and even lower than insulin treatment without metformin or TZD (i.e., by about 2 to 3 times).

The reduction of mortality associated with metformin observed in the current study agreed with results from UKPDS and previous observational studies. Our findings also had similar results as the Clinical Practice Research Database [CPRD] in the UK[13]. The results of the current study and those of the CPRD were similar in magnitude vis-a-vis the effect of metformin compared with sulfonylurea monotherapy. Our results also agreed with a previous observational study of the Danish diabetic population[14].

In contrast to the UKPDS, in the current study sulfonylurea combined with metformin reduced the mortality risk over against sulfonylurea alone. The mortality rate of sulfonylurea combined with metformin lay between metformin monotherapy and sulfonylurea monotherapy. Adding sulfonylurea seemed to dilute the beneficial effect of metformin (i.e., reducing mortality (HR 0.69 (0.50 to 0.95)). Our findings agreed with a previous report although we used a different reference group[15]. The current study used sulfonylurea monotherapy, while Morgan et al[15] used sulfonylurea combined with metformin as a reference group, but both results conveyed a similar message.

Insulin-containing treatment regimens were the worst mortality outcome. This finding agrees with observational data from Saskatchewan, Canada[16] and Third French MONICA survey[17]. The mortality hazard ratio for insulin treatment was 2 to 3 time higher than the sulfonylurea treated diabetic population compared with non-diabetic control subjects.

Combining metformin or TZD and insulin treated diabetic patients decreased the mortality rate by about 2 to 3 times form diabetic patients who received insulin treatment without combination with metformin and TZD. This finding demonstrated the benefit of metformin and TZD in a broad range of diabetic patients (i.e., whether they received oral anti-hyperglycemic agents or insulin treatment). It also suggests that all diabetic patients should receive metformin (or TZD) with every combination regimen.

Thiazolidinedione showed reduce mortality in the same magnitude as metformin. The findings of the current paper support a PROACTIVE study[10] and Meta-analysis[11]. These findings are consistent with data from the UK-based General Practice Research Database[15].

Most (75.3%) of the patients receiving TZD were prescribed triple oral anti-hyperglycemic agents which was always chosen for patients who failed sulfonylurea and metformin regimens and refused to start insulin injection. The current study indicated that triple oral anti-hyperglycemic agents seemed to be the best at reducing mortality with an adjusted HR of 0.21 (0.05 to 0.88). The current findings showed that patients who failed sulfonylurea and metformin regimens trended to add TZD than start insulin injection.

The mechanisms underlying the mortality rate increase among those taking sulfonylurea and insulin may be partly explained by two theories. Theory 1 may be explained as a treatment bias; as sulfonylurea and insulin were prescribed to the high-risk population (i.e., those with more severe disease: (a) longer duration of diabetes; (b) higher prevalence of chronic kidney disease [serum creatinine >1.5 mg/dl]; and, (c) previous history of coronary artery disease. A hazard ratio analysis (plus adjustment) was performed for all covariates. Theory 2 may be explained as the direct harmful effects of sulfonylurea and insulin. For example, the binding of sulfonylurea to receptors in the cardiac muscle may interfere with ischemic preconditioning[18], which is a protective mechanism against ischemia or hypoxia; thereby increasing the severity of any subsequent infarction[19,20].

Hypoglycemia is a well-known serious side-effect of sulfonylurea and insulin. Severe

hypoglycemia has been linked with an increased risk of cardiovascular events[21,22], and both cardiovascular and all-cause mortality[23,24].

Hyperinsulinemia is also known to promote cell proliferation via the MAP kinase activation pathway[25], which promotes both atherosclerosis and proliferation of cancer cells. Many observational studies have reported the association between insulin treatment and cancer mortality. Insulin sensitizers (viz., metformin and TZD) improve insulin action and reduce the level of serum insulin, which may explain why insulin sensitizers reduce cancer and cardiovascular mortality.

The limitation of the current study was that the analysis was based on treatments and clinical parameters at registration, which means that changes in treatment (s) or clinical parameters during follow-up were not taken into account.

Conclusion

The current longitudinal study demonstrated that metformin and TZD-containing regimens reduced mortality compared with sulfonylurea monotherapy. Insulin-containing regimens were shown to be harmful as they increased mortality by ~60%. In cases of no contraindication to metformin or TZD, patients who fare poorly on sulfonylurea and/or metformin regimens should add TZD before resorting to insulin treatment. Insulin treatment regimens should start only after failure of triple oral anti-hyperglycemic agent regimen and must be combined with metformin or TZD together with insulin injection regimens.

What is already known on this topic?

Previous studies reported that metformin decreased mortality among sufferers of type 2 diabetes and insulin increased mortality compared to using sulfonylurea treatment alone.

What this study adds?

The current longitudinal study demonstrated the effect of different anti-hyperglycemic regimens on mortality among Thai patients with type 2 diabetes. Thiazolidinedione added to the regimen significantly decreased mortality compared with using sulfonyurea alone. Supplementing metformin or thiazolidinedione to insulin treatment decreased mortality compared to using insulin treatment alone. Adding metformin or thiazolidinedione to an insulin treatment regimen is a better approach than using insulin treatment only.

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Appendix

On behalf of the Thailand Diabetic Registry Working Group; Thongchai Pratipanawatr MD (Department of Medicine, Faculty of Medicine, Khon Kaen University), Thanya Chetthakul MD (Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University), Pongamorn Bunnag MD (Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University), Chardpraorn Ngarmukos MD (Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University), Yupin Benjasuratwong MD (Department of Medicine, Phramongkutklao Hospital), Rattana Leelawatana MD (Department of Medicine, Prince of Songkla University), Natapong Kosachunhanun MD (Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University), Nattachet Plengvidhya MD (Department of Medicine, Faculty of Medicine, Chiang Mai University), Chaicharn Deerochanawong MD (Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University), Sompongse Suwanwalaikorn MD (Department of Medicine, Faculty of Medicine, Chulalongkorn University), Sirinate Krittiyawong MD (Department of Medicine, Bangkok Metropolitan Medical College and Vajira Hospital), Petch Rawdaree MD (Department of Medicine, Bangkok Metropolitan Medical College and Vajira Hospital), Sirima Mongkolsomlit BS (Faculty of Public Health, Thumasart University), Chulaluk Komoltri PhD (Department of Research and Development, Faculty of Medicine, Siriraj Hospital, Mahidol University).

Potential conflicts of interest

The authors declare no conflicts of interest.

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