The impact of commercial drivers with type 2 diabetes on the risk for road traffic collisions in TBDCS study

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Research article

Abstract

Background : Identification of the relationship between diabetes mellitus (DM) and road traffic collision (RTC) that lead to hospital admissions and death in commercial motor vehicle (CMV) drivers is crucial to develop preventive strategies. A cohort study was used to follow up the outcomes of DM and receiving blood glucose-lowering therapy to assess the 6-year risk of RTCs in CMV drivers.

Methods: This cohort recruited 1,650 CMV drivers in 2005. Each subject completed the basic and working patterns questionnaire. Researchers found 84 DM cases in 2005, and 152 RTC events between 2005 and 2010. The data analysis was conducted in 2015. The Cox model and the extended Cox model were used to estimate the hazard ratio (HR) for first RTC events only and recurrent RTC events.

Results: Type 2 DM (T2DM) increased the 6-year RTC risks among CMV drivers (HR: 2.39, 95% CI: 1.35 to 4.24), after adjusting for confounders. The extended Cox models were used and showed that T2DM increased HR of the recurrent RTC events.

Conclusion: T2DM and oral antidiabetic drugs (OADs) used days pose possible risk factors for RTCs in CMV drivers. Labor or health care professionals and authorities should be aware of the risks and contribute in establishing effective RTC- prevention strategies for DM drivers with or without insulin treatment.

Key Messages

What is already known about this subject?

- Preliminary studies suggest that patients with diabetes mellitus (DM) might increase risk of road traffic collision (RTC), but the evidence-based conclusion is insufficient in commercial drivers.

What are the new findings?

- We used the cohort study to follow up the outcomes of DM and receiving blood glucose-lowering therapy, and found that the type 2 diabetes mellitus (T2DM) significantly increased the RTC risks among commercial drivers (HR: 2.39, 95% CI: 1.35 to 4.24).

How might it impact on clinical practice in the foreseeable future?

Commercial drivers with T2DM should be made more aware of the potential risks they have associate with driving, and regularly detect blood glucose under driving conditions of driving for reducing RTCs.

Background

The economic burden of diabetes mellitus (DM) on the global healthcare system and the broad global economy is significant. This burden includes direct medical costs, indirect expenditures resulting from

lost workdays, reduced productivity, early mortality, disability.[1] According to the global report on diabetes from the World Health Organization, the number of adults with DM has increased almost fourfold to 422 million adults since 1980. The prevalence of cases of diabetes among individuals aged over 18 years has risen from 4.7% in 1980 to 8.5% in 2014. This dramatic rise is mostly due to the rise in type 2 DM (T2DM).[1]

Several studies have mentioned that DM patients may have an elevated risk of road traffic collision (RTC), but results have been inconsistent.[2-9] Diabetes can weaken driving performance through short-term metabolic and longer-term complications, including those affecting vision, cognition and peripheral neural function.[10] Moreover, the common treatment with insulin and oral glucose-lowering medications causes rapid fluctuation in blood glucose and leads to impairment in cognitive functioning and driving performance.[11] For this reason, studies on the effect of DM and receiving blood glucose-lowering therapy in relation to RTC in CMV drivers are critical in supporting health services in setting up a program for detecting high-risk drivers.

However, reviewing papers in this research field revealed many problems, including the unclear time ordering, the absence of systematic traffic-accident data collection, the unreliability of self-reporting of diabetes status, and the poor control for confounding factors, such as working patterns and sleep apnea.[2 8 10 12] None of these studies dealt with the effect of recurrent RTC events and the percentage of patients who actually drove.

Therefore, the researchers used a large occupational cohort study of CMV drivers to observe the association between RTC risk and DM drivers, after controlling for RTC risk factors, and whether drivers who received blood glucose-lowering drugs had an elevated risk of first RTC only or repeated RTC events.

Methods

Participants

Supplementary figure 1 shows the detailed study procedures of the Taiwan Bus Driver Cohort Study (TBDCS). The researchers included 1,650. CMV drivers from a transportation company in Taiwan. We excluded CMV drivers whose true driving experience fallen short of 100 days during the first 3 years. The remaining 1014 drivers completed biochemistry indices such as blood lipids, blood pressure, and the overnight pulse oximeter survey as a sign of sleep-disordered breathing (SDB). The researchers excluded RTC events that were caused to cell phone use, alcohol use, and RTC event date before DM diagnosis date (n=17). Finally, the 135 non-fatal RTC cases and the 862 non-RTC drivers were used in the following analysis. This study was approved by the Institutional Review Board of the National Health Research Institutes, Taiwan (NIRB File Number: EC1060516-E). The constitution and operation of review board are formulated according to the guidelines of ICH-GCP. Authors confirm that all experiments were performed in accordance with relevant guidelines and regulations. Informed consent was obtained from each of the participants after a detailed explanation of the content.

Data Sources for RTC

Researchers used a Personal Identification Number (PIN) to identify new RTC cases and information of RTC among CMV drivers from National Traffic Accident Database (NTAD) from January 1st 2005 to December 31st 2010.

The Taiwan NTAD was set up by National Police Agency, Ministry of the Interior, Taiwan, in order to observe injuries and deaths of RTCs. It used a two-stage procedure to assess the reliability and completeness of the traffic accident report, and whether it can input the official system of NTAD.

Data Sources for DM and treatments

Information on cases of DM were obtained from the National Health Insurance Research Dataset (NHIRD), Ministry of Health and Welfare, Taiwan, to provide information to scientists in Taiwan for research purposes.[13] The NHIRD in Taiwan, with approximately 23 million insured, covers over 99% of Taiwan's population.

Using each worker's PIN, researchers were able to link DM cases (ICD-9-CM: 250) from CMV drivers to the NHIRD from 1 January 2005 to 31 December 2005. DM events including Type 1 DM (T1DM) (ICD-9 CM: 250.x1 and 250.x3), T2DM (ICD-9 CM: 250.x0 and 250.x2), and Hypoglycemia (ICD-9 CM: 251.2x) were solely investigated.

According to the Anatomical Therapeutic Chemical (ATC) system of the World Health Organization, the researchers identified incidents of receiving insulin injections (ATC code A10A) and oral antidiabetic drugs (OADs) (ATC code A10B). Insulin injection, insulin secretagogues of sulfonylureas and meglitinides, α-Glucosidase inhibitor, insulin sensitizers of Biguanide, Insulin sensitizers of Thiazolidinedione (TZD) or PPAR-γ agonists, and Dipeptidyl peptidase 4 inhibitor were included as outcome variables (Supplementary Table1). The researchers further counted follow-up periods in the use of OADs within the follow-up period, in order to assess the association between drug used days as a proxy for the severity of DM and the RTC risk among CMV drivers.

Overnight Oxygen Saturation Monitoring

A high-resolution pulse oximeter wristwatch (PULSOX-300i, Konica Minolta Sensing, Inc., Osaka, Japan) was used for monitoring overnight SpO_2 at home. The hourly average number of desaturation episodes, and cumulative time percentage with SpO_2 <88~90% were reading from the oximetry data. Oxygen

desaturation index (ODI) is defined as at least reducing a 3% or 4% in oxygen saturation from the average saturation in the preceding 120 seconds, and lasting > 10 seconds.

Statistical Analysis

This study used a Cox proportional hazards model and extended Cox regression models to assess the hazard ratio (HR) for RTC and repeated RTC events in CMV drivers. The counting process approach of Anderson and Gill intensity model and stratified Cox model approach of Prentice-Williams-Petersen model was to assess hazards of subsequent RTC events. The analysis was performed using SAS software (version 9.3; SAS Institute).

Results

During the 6-years of follow-up, there were 135 drivers (10.9%) who had RTC experience and 13 drivers who had more than one time RTC experience. (Supplementary Table 2) This is no difference of age, BMI, marriage status, education status, exercise, smoking, drinking, and chewing betel nut habits between the RTC and non-RTC drivers (p>0.05).

Associations between RTC and risk factors

The association between RTC and variables in CMV drivers is presented in Supplementary Table3. As shown in the univariate analysis, sleeping-pill use (HR= 3.18; 95%CI=1.18-8.60; p=0.02), caffeine drinks used (HR= 1.63; 95%CI=1.07-2.46; p=0.02), and ODI levels were related with elevated RTC risks. The negative association between bus-driving experience and RTC was found.

Associations between RTC and DM

This study found that RTC drivers had a significantly higher percentage of DM and T2DM compared to those without RTC. Moreover, the RTC drivers used a higher percentage of insulin secretagogue in comparison with non-RTC drivers (Table 1).

Supplementary figure 2 shows the probabilities of RTC survival as a function of the T2DM and DM treatment. Comparisons between survival curves were significant. The associations between RTC and DM in CMV drivers are presented in Table 2. After adjusting for confounders, the DM and T2DM were found to be associated with increased RTC risks among CMV drivers (Model 4: HR=2.40; 95%CI=1.37-4.21; p<0.01 and HR=2.39; 95%CI=1.35-4.24; p<0.01, respectively).

Associations between RTC and DM treatment

In Table 3, the drivers with DM treatment and OADs (insulin sensitizers) showed an increase of RTC risk (Model 4: HR=2.13 and 2.11; 95% CI: 1.13–4.02; p=0.02 and 1.07–4.17; p=0.03, respectively) than those without, after adjusted for confounders.

Associations between medication use and the risk of RTC in drivers with DM using time-dependent Cox model are shown in Table 3. DM drivers who were prescribed higher used days of insulin secretagogue as a proxy for the severity of DM were slight associated with an increased risk of RTC (Model 4: HR=2.76; 95% CI: 0.96–7.93; p=0.059) in compared to those less medication used days. DM drivers who were prescribed higher used days of insulin sensitizers were slight associated with increased risk of RTC (Model4: HR=2.36, 95% CI: 0.93–6.02; p=0.071).

DM and recurrent traffic collision events

The counting process approach and stratified Cox model approach both found that

DM and T2DM were both correlated with elevated repeated RTC risk in CMV drivers, regardless of the counting process approach (HR=2.64; 95%CI=1.46-4.76; p<0.01 and HR=2.58; 95%CI=1.57-4.24; p<0.01, respectively) or stratified Cox model approach used (HR=2.06; 95%CI=1.13-3.74; p=0.02 and HR=2.03; 95%CI=1.09-3.80; p=0.03, respectively). (Table 4) Moreover, CMV drivers who used medication with insulin secretagogue or insulin sensitizers increased the risk of recurrent RTCs (The proportional means model: HR=1.93; 95%CI=1.07-3.49; p=0.03 and HR=2.68; 95%CI=1.48-4.87; p<0.01, respectively) (The PWP total time model: HR=2.48; 95%CI=1.05-5.90; p=0.04 and HR=3.28; 95%CI=1.55-6.95; p<0.01, respectively).

Discussion

This 6-year follow-up study shows that significant elevated risks of both the first RTC event only and repeated RTC events for CMV drivers with T2DM are found. Drivers who used medication with insulin secretagogue or insulin sensitizers were related with increased risk of repeated RTC events. This finding clearly provides health policy evidence that recommendations for CMV drivers with insulin-treated diabetes and their medical attendants are needed. It used a prospective cohort study design, including the clear time ordering, information of DM and receiving blood glucose-lowering therapy, systematic traffic collisions data collection, consideration of recurrent traffic collision events, and control for confounding factors, especially for the percentages holding a driving license and sleep apnea.

RTC risk of diabetes and diabetes on insulin medications

Some studies have reported that elevated RTC risk appears in drivers with diabetes,[6 7 14-16] whereas other studies have reported no risk.[3-5 9 17] Among them, some studies recorded that accident rates in motor vehicle drivers with diabetes are reported to be a lower risk than those treated with oral antidiabetes agents.[7 14-18] A study combined a retinopathy screening and RTC data from police to assess RTC risk in drivers with or without DM. It did not find that drivers with insulin-treated diabetes were at increased risk.[17] However, this study has several deficiencies including incomplete recodes about actual percentage of situation for the time or the distance driven. This would produce biased misclassification. A Canadian study used health insurance coverage data and driving insurance programs to examine crash risk in older drivers.[15] This study observed a slightly elevated crash risk for older drivers with diabetes in insulin treatment (odds ratio=1.4, 95% CI:1.0-2.0) relative to non-users, and 1.3 times the odds ratio (95% CI: 1.0-1.7) for sulfonylurea and metformin combined. In another Canadian National Population Health Survey study, the authors used self-reporting of diabetes status and insulin treatment to assess the association for RTCs. It was not a significantly association between participants with diabetes treatment and self-reported a history of RTCs in the preceding 12 months.[9]

A study from Canadian evaluated DM drivers who had been reported driving accidents between 2005 and 2007 to their licensing authority.[16] This study provided the evidence that a history of severe hypoglycemia and diabetes diagnosis at later age were major risk factors for motor vehicle collision. The study showed that there was a 26% increase in the relative risk of a crash for each 1% reduction in HbA1c.

Cox et al. used case-control study design to compare drivers with T1DM, T2DM, and diabetes treatment with spouses of subjects with no diabetes on self-reporting crash accidents.[7] In the previous 2 years, the percentage of driver's accidents was 19% in drivers with T1DM, 12% in drivers with T2DM, and 8% in the spouses as controls. A higher rate of accident was observed in drivers with T1DM than in either of the other groups, but in drivers with T2DM was not different to controls. Moreover, drivers with T1DM presented an elevated risk of driving-related mishaps compared to drivers with T2DM, regardless of insulin treatment status.

A Norwegian study evaluated RTC risk in drivers with diabetes using the database for the completely adult population (3.1 million) over 2 years. It found over 170,000 were taking anti-diabetes medications. People with insulin-treated diabetes showed a standardized incidence ratio (SIR) of 1.4 (95%CI: 1.2-1.6), and 1.2 (95%CI: 1.0-1.3) for oral glucose-lowering agents.[14]

Signorovitch et al. assessed associations between hypoglycemia and risk of RTC among people with T2DM who were not being used insulin treatment from a national based employer claims database (1998–2010). The result showed that the risk of RTCs positive elevated (hazard ratio=1.82) in American

people with a history of treating a hypoglycemic episode, but the anti-diabetes medications being used were not reported.[19]

A meta-analysis included 15 case-control studies assess the risk of RTC rates in DM drivers.[8] This study did not find a significant elevated risk for drivers with diabetes. However, another meta-analysis of 25 studies showed a 1.56 times the relative risk of RTC for drivers with diabetes.[20] The researchers believe the inconsistent results may result from the considerable heterogeneity in the design of these studies, such as incomplete data of participants at risk of hypoglycemia (mainly those with insulin-treated diabetes) and participants with or without driving licenses. Our comprehensive and prospective cohort study may supply extra evidence regarding T2DM-related accidents.

Moreover, management of DM patients is progressively aiming at near normoglycaemia. However, the consequence of more aggressive treatment might cause more frequent hypoglycemic episodes in diabetic drivers.[11][21] The Swiss survey found a case fatality rate for sulfonylurea-induced hypoglycemia of 4.3% among 116 admissions.[21] The risk of sulfonylurea-induced hypoglycemia appears from the Swiss survey to be greater for some agents than for others. The UK Hypoglycemia Study Group recorded continuous glucose monitoring over a period of up to 1 year to test the hypothesis that diabetes type and duration of insulin treatment influence the risk of hypoglycemia. Severe hypoglycemia was relatively common in patients treated with a sulfonylurea, and gradually increased for prolonged duration of insulin treatment in T2DM. Moreover, it was the higher frequency in people with long-standing T1DM who had a rate of 3.1 episodes per year in a patient.[11] The principal reason is that the risk of hypoglycemia is related with glucose-lowering agents, particularly the insulin secretagogues, the sulfonylureas and glinides. This evidence supports our findings that the higher OADs dose levels with insulin secretagogue (sulfonylureas) or insulin sensitizers (biguanide) were associated with increased risk of RTCs.

Guidelines for Driving Licenses

According to experiences and methodologies between different regions of the world [2][22][23][24], the potential problems associated with driving and diabetes needs to be highlighted. Governments should be encouraged to adopt methods to assess and review medical fitness to drive for people who are being treated with insulin. Possible strategies include:

1. Legislative restrictions on driving licenses for medical disorders in order to remove those at intolerable high risk when driving.
2. Improve healthcare providers' awareness and knowledge about diabetes and driving mishaps. The last strategy is to teach this information to DM drivers to prevent future RTCs.
3. Transportation owner and drivers with diabetes should be made more aware of the potential risks they have associate with driving and have the opportunity to modify their approach to driving if they have drivers training education.

4. Transportation owner and drivers with diabetes should regularly monitor blood glucose before or under driving conditions of driving by using a glucose meter with a storing function to long-term keep levels of blood glucose.

Limitations

This study still has some limitations and unavoidable uncertainties in the methodology of this investigation. First, the study only included male CMV drivers; thus, it limits the interpretation of the results with female drivers. Second, this study did not assess the short-term effect of OADs intake for RTC risk, such as hypoglycemia events. It was not possible to directly assess blood glucose values in this long-term follow-up study. Third, the dosage of OADs had been only used as a proxy for the severity of DM in this study. The researchers cannot prove the direct relationship between the higher doses of OADs used and hypoglycemia events. Finally, this study did not assess the combined effect of different kinds of OADs.

Conclusion

An increased risk of RTC associated with T2DM and receiving blood glucose-lowering therapy (insulin secretagogue and insulin sensitizers) in CMV drivers were found. In the future, a regular screening guidelines or recommendation for CMV drivers with insulin-treated diabetes and their medical attendants should be established.

Declarations

Abbreviations

TBDCS: The Taiwan Bus Driver Cohort Study; DM: diabetes mellitus; RTC: road traffic collision; CMV: commercial motor vehicle; HR: the hazard ratio; T2DM: Type 2 DM; OADs: oral antidiabetic drugs; ODI: Oxygen desaturation index.

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Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

YCW designed the study, collected data, analysis, engaged in drafting the manuscript and revising it critically. YJL carried out acquisition of data, analysis, interpretation of data, and helped to draft the manuscript and revising it critically. TNW and SHL participated in data analysis, involved in drafting the manuscript. WTW conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request and only after approval from the Institutional Review Board of the National Health Research Institutes, Taiwan.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the National Health Research Institutes, Taiwan (NIRB File Number: EC1060516-E). Written informed consent was obtained from the parent or guardian of each subject prior to the subject's participation in this study

Consent for publication

Not applicable.

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Tables

Table 1. The diabetes mellitus (DM) distributions were compared between RTC drivers and non-RTC drivers

Variables	RTC drivers (N=135)		Non-RTC drivers (N=862)		
	n	*(%)*	*n*	*(%)*	*p-value*
DM					0.017
No	117	(86.7)	799	(92.7)	
Yes	18	(13.3)	63	(7.3)	
Type 2 DM					0.023
No	118	(87.4)	802	(93.0)	
Yes	17	(12.6)	60	(7.0)	
DM treatment (Injections & Oral antidiabetic drugs)					0.020
No	120	(88.9)	812	(94.2)	
Yes	15	(11.1)	50	(5.8)	
Injections					
Insulin injection					0.651
No	133	(98.5)	853	(99.0)	
Yes	#		9	(1.0)	
Oral antidiabetic drugs (OAD)					
1. Insulin secretagogue (Sulfonylurea & Meglitinde)					0.010
No	126	(93.3)	840	(97.4)	
Yes	9	(6.7)	22	(2.6)	
1. Alpha-glucisidase inhibitors (Acarbose & Miglitol)					0.492
No	135	(100.0)	859	(99.7)	
Yes	0	(0.0)	3	(0.3)	
1. Insulin sensitizers (Biguanide)					0.073
No	124	(91.9)	823	(95.5)	
Yes	11	(8.1)	39	(4.5)	
1. Others (Thiazolidinedione & DPP-4 inhibitor)					
No	135	(100.0)	862	(100.0)	
Yes	0	(0.0)	0	(0.0)	

The number of cases less than 3

Table 2. Hazard ratio and 95% CI for road traffic collision (RTC) by diabetes mellitus (DM) in CMV drivers from 2005 to 2010

Dependent: RTC event	Model 1 [a]				Model 2 [b]				Model 3 [c]				Model 4 [d]			
	HR	*95%CI*		*p-value*	*HR*	*95%CI*		*p-value*	*HR*	*95%CI*		*p-value*	*HR*	*95%CI*		*p-value*
Part I:																
DM (Yes vs. No)	1.95	1.56	3.26	0.012	1.91	1.14	3.20	0.014	2.36	1.35	4.13	0.003	2.40	1.37	4.21	0.002
Hypertension [e] (Yes vs. No)									1.21	0.78	1.89	0.391	1.22	0.78	1.90	0.387
LnODI4	1.27	1.06	1.51	0.009									1.27	1.03	1.56	0.022
LnODI3					1.33	1.08	1.63	0.007	1.34	1.06	1.69	0.014				
Part II:																
Type2 DM (Yes vs. No)	1.92	1.13	3.26	0.016	1.88	1.11	3.19	0.019	2.35	1.33	4.16	0.004	2.39	1.35	4.24	0.003
Hypertension [e] (Yes vs. No)									1.22	0.78	1.90	0.388	1.22	0.78	1.90	0.385
LnODI4	1.27	1.06	1.51	0.009									1.27	1.04	1.55	0.022
LnODI3					1.33	1.08	1.63	0.006	1.34	1.06	1.69	0.014				

[a] Adjusted for age, education, caffeine drinks used, sleeping pills used, bus-driving experience (years), shift work models, and ODI4 levels

[b] Adjusted for age, education, caffeine drinks used, sleeping pills used, bus-driving experience (years), shift work models, and ODI3 levels

[c] Adjusted for age, education, caffeine drinks used, sleeping pills used, bus-driving experience (years), shift work models, hypertension, and ODI3 levels

[d] Adjusted for age, education, caffeine drinks used, sleeping pills used, bus-driving experience (years), shift work models, hypertension, and ODI4 levels

[e] Hypertension: Baseline SBP≥140 or DBP≥90

Table 3. Hazard ratio and 95% CI for road traffic collision (RTC) by diabetes mellitus treatment, oral antidiabetic agents doses and used days in CMV drivers from 2005 to 2010

Independent variables [e.]	Model 1 [a.]			Model 2 [b.]			Model 3 [c.]			Model 4 [d.]		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
1 DM treatment (Yes vs. No)	2.02	1.17 3.49	0.012	2.28	1.22 4.27	0.010	2.08	1.10 3.91	0.024	2.13	1.13 4.02	0.019
2 Insulin injection (Yes vs. No)	1.37	0.34 5.57	0.658	1.00	0.14 7.21	0.996	0.85	0.12 6.17	0.869	0.84	0.12 6.13	0.864
3 OAD(Insulin secretagogue) (Yes vs. No)	2.56	1.29 5.08	0.007	2.61	1.19 5.73	0.017	2.21	0.99 4.92	0.053	2.19	0.98 4.89	0.055
4 OAD(Insulin sensitizers) (Yes vs. No)	1.80	0.97 3.36	0.064	2.24	1.14 4.38	0.019	2.04	1.04 4.02	0.039	2.11	1.07 4.17	0.031
5 Insulin secretagogue (ref. No used)												
Used days: ≤ 180 days	2.25	0.83 6.12	0.112	2.00	0.63 6.41	0.242	1.74	0.54 5.65	0.355	1.73	0.54 5.62	0.359
Used days: > 180 days	2.88	1.15 7.21	0.024	3.42	1.20 9.74	0.021	2.78	0.97 7.98	0.058	2.76	0.96 7.93	0.059
6 Insulin sensitizers (ref. No used)												
Used days: ≤ 300 days	1.79	0.73 4.40	0.163	2.26	0.90 5.69	0.083	1.86	0.73 4.75	0.192	1.91	0.75 4.86	0.175
Used days: > 300 days	1.81	0.79 4.17	0.163	2.21	0.85 5.57	0.094	2.25	0.89 5.71	0.088	2.36	0.93 6.02	0.071

[a.] Model 1: adjusted for education, caffeine drinks used, sleeping pills used, bus-driving experience (years)

[b.] Model 2: as Model 1 and additionally adjusted for hypertension

[c.] Model 3: as Model 2 and additionally adjusted for LnODI3

[d.] Model 3: as Model 2 and additionally adjusted for LnODI4

[e.] Each independent variable (1-8) was solely included in the models

Insulin secretagogue antidiabetics included Sulfonylureas and Meglitinides.

Insulin sensitizers antidiabetic included Biguanide.

Table 4. Analysis of survival analysis with recurrent RTC events by DM in CMV drivers from 2005 to 2010 [a.]

	DM			Type2 DM			DM treatment			Insulin secretagogue			Improving insulin sensitivity		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Counting Process Approach															
The intensity model (the model-based variance estimate)	2.64	1.46 4.76	0.001	2.58	1.40 4.75	0.002	2.72	1.35 5.49	0.005	1.93	0.81 4.57	0.137	2.68	1.27 5.66	0.010
The proportional means model (the robust sandwich variance estimate)	2.64	1.65 4.22	<0.001	2.58	1.57 4.24	<0.001	2.72	1.58 4.71	<0.001	1.93	1.07 3.49	0.030	2.68	1.48 4.87	0.001
Stratified Cox model approach (Conditional model)															
PWP total time model	2.06	1.13 3.75	0.019	2.03	1.09 3.80	0.027	3.45	1.70 7.03	<0.001	2.48	1.05 5.90	0.040	3.28	1.55 6.95	0.002
PWP gap time model	2.14	1.20 3.81	0.010	2.20	1.21 4.02	0.010	2.71	1.36 5.40	0.005	2.07	0.88 4.84	0.094	2.68	1.28 5.59	0.009

Adjusted for age, education, caffeine drinks used, sleeping pills used, bus-driving experience (years), hypertension, and LnODI4

Insulin secretagogue antidiabetics included Sulfonylureas and Meglitinides.

Insulin sensitizers antidiabetic included Biguanide.

Supplementary Files

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