Published in final edited form as:

Ophthalmology. 2009 March ; 116(3): 497–503. doi:10.1016/j.ophtha.2008.10.016.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII. The Twenty-Five-Year Incidence of Macular Edema in Persons with Type 1 Diabetes

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Abstract

Objective—To examine the 25-year cumulative incidence of macular edema (ME) and its relation to various risk factors.

Design—Population-based study.

Participants—Nine hundred and fifty-five insulin-taking persons living in an 11-county area in southern Wisconsin with type 1 diabetes diagnosed before age 30 years who participated at baseline (1980-1982) and at least one of 4 follow-up (4-, 10-, 14-, and 25-year) examinations (n=891) or died before the first follow-up examination (n=64).

Methods—Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme. Competing risk of death was included in statistical models.

Main Outcome Measures—Incidence of ME and clinically significant ME (CSME).

Results—The 25-year cumulative incidence of ME was 29% and for CSME it was 17%. Annualized incidence of ME were 2.3, 2.1, 2.3, and 0.9%, respectively, in the 1st, 2nd, 3rd, and 4th follow-up periods of the study. In univariate analyses, the incidence of ME was associated with more severe diabetic retinopathy, being male, having higher glycosylated hemoglobin, proteinuria, higher systolic and diastolic blood pressure, and having smoked more pack years. Multivariate analyses showed that the incidence of ME was related to higher baseline glycosylated hemoglobin (Hazard Ratio [HR] per 1% 1.17, 95% Confidence Interval [CI] 1.10, 1.25, $P<0.001$) and higher systolic blood pressure (HR per 10 mmHg 1.15, 95% CI 1.04, 1.26, $P=0.004$) and marginally to proteinuria (HR 1.43, 95% CI 0.99, 2.08, $P=0.06$).

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None of the authors have any proprietary interests.

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Conclusions—These data show that relatively high 25-year cumulative rates of incidence of ME were related to glycemia and blood pressure. The lower risk of incident ME in the last period of the study may reflect recent improvement in care.

Macular edema (ME) is an important cause of visual impairment in persons with diabetes.¹⁻³ While a number of studies have described the incidence of ME and its relationship to various risk factors such as glycemia and blood pressure, few have been in cohorts of persons with type 1 diabetes followed over a long period.⁴⁻¹⁷ Recent changes in incidence of ME would be expected with the more widespread use of intensive glycemic and blood pressure control.^{1,18-21} In this report, we extend our previous observations by describing the 25-year incidence of ME and changes in the prevalence and incidence of ME in a large cohort of persons with type 1 diabetes mellitus participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).⁸⁻¹⁰

METHODS AND MATERIALS

Study Population

The population, which has been described in previous reports,^{10,22-28} consisted of a sample selected from 10,135 diabetic patients who received primary care in an 11-county area in southern Wisconsin from 1979 to 1980. This sample was composed of all “younger-onset” and a duration stratified sample of “older-onset” persons. The analyses in this report are limited to the group of younger-onset persons, all of whom were taking insulin and had been diagnosed before 30 years of age ($n = 1210$). There were 996 persons in this group who participated in the baseline examination (1980 to 1982),²³ 903 in the 4-year follow-up,²⁵ 816 in the 10-year follow-up,²⁶ 667 in the 14-year follow-up,²⁶ 567 in the 20-year follow-up,²⁷ and 520 in the 25-year follow-up.²⁸ The reasons for nonparticipation and comparisons between participants and nonparticipants at baseline and the 4-, 10-, and 14- and 20-year follow-ups have been presented elsewhere.^{10,23,25-27} Retinopathy data were not collected at the 20-year follow-up, so information from that examination is not included in this report. For the 25-year follow-up, the reasons for nonparticipation have been presented elsewhere.²⁸

Procedures

The baseline and follow-up examinations were performed in a mobile examination van in or near the city where the participants resided. All examinations followed a similar protocol that was approved by the institutional human subjects committee of the University of Wisconsin and conformed to the tenets of the Declaration of Helsinki. The pertinent parts of the ocular and physical examinations included measuring weight, height, and blood pressure,²⁹ dilating the pupils, taking stereoscopic color fundus photographs of seven standard fields^{30,31} (not done at 20-year follow-up), performing a semiquantitative determination of protein levels in the urine using Labstix (Ames, Elkhart, IN), and determining blood glucose and glycosylated hemoglobin A1 levels from a capillary blood sample at the baseline, 4-, 10- and 14-year follow-ups and glycosylated hemoglobin A1c from venous blood at the 20- and 25-year follow-ups (Quick Step Fast Hemoglobin Test System. Akron, OH: Isolab).^{32,33} The normal range for glycosylated hemoglobin A1 was 4.6% to 7.9%. Its intra-assay coefficient of variation was 2.4%. The WESDR glycosylated hemoglobin A1 microcolumn results compare with the Diabetes Control and Complications Trial (DCCT) glycosylated hemoglobin A1c results as follows: $DCCT = 0.003 + 0.935$ (WESDR).³²

A structured interview was conducted by the examiners that included questions about specific medications for control of hyperglycemia and blood pressure, the number of aspirin used during the 30 days before the baseline examination, and smoking history. If there was any question about medication usage, it was verified by a physician's report.

Grading Protocol

Grading protocols have been described in detail elsewhere^{25,34} and are modifications of the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification of diabetic retinopathy (DR).^{35,36} Interobserver and intraobserver variations and the validity of the systems have been evaluated, and the results have been presented elsewhere.^{25,34,36,37}

Definitions

For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the “retinopathy levels”. This has been described in detail elsewhere.^{26,36} In brief, 13 levels of increasing DR severity from none to end-stage proliferative diabetic retinopathy (PDR) with loss of vision (10, 21, 31, 37, 43, 47, 53, 60, 61, 65, 71, 75, 85) were assigned to each. The DR level for a participant was derived by concatenating the levels for the two eyes, giving the eye with the higher level greater weight. This scheme provided a 15-step scale (10/10, 21/<21, 21/21, 31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60+/<60+, and 60+/60+) when all levels of PDR are grouped as one level. For purposes of classification, if the DR severity could not be graded in an eye, it was considered to have a score equivalent to that in the other eye.

Macular edema was defined as retinal thickening in the macular area while clinically significant macular edema (CSME) was defined according to the Early Treatment Diabetic Retinopathy Study classification protocol as the presence of retinal thickening at or within 500 μm of the center of the macula or hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina and/or zones of retinal thickening 1 disc area in size, at least part of which being within 1 disc diameter of the center. The cumulative incidence of ME was estimated from all persons who had no ME while the cumulative incidence of CSME was estimated from all persons who had no CSME at the baseline who participated in the follow-up examination(s).

Age was defined as the age at the time of the baseline examination. Age at diagnosis of diabetes was defined as the age at the time the diagnosis was first recorded by a physician on the patient’s chart or in a hospital record. The duration of diabetes was that period between the age at diagnosis and the age at the baseline examination.

Systolic and diastolic blood pressures were the average of the two measurements taken according to the protocol of the Hypertension Detection and Follow-Up Program protocol.²⁹ Hypertension was defined as a mean systolic blood pressure ≥ 160 mmHg, a mean diastolic blood pressure ≥ 95 mmHg, or a history of antihypertensive medication at the time of examination for individuals ≥ 25 years of age and a mean systolic blood pressure of ≥ 140 mmHg, a mean diastolic blood pressure of ≥ 90 mmHg, or a history of antihypertensive medication at the time of examination in younger persons.

A person was classified as a never smoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime, as an ex-smoker if he/she smoked more than this number of cigarettes in his/her lifetime but had stopped smoking before the examination, and as a current smoker if he/she had not stopped. Pack-years smoked was calculated as the number of cigarettes smoked per day divided by 20, multiplied by the number of years of smoking from the time of diagnosis of diabetes. Body mass index (BMI) was defined as weight in kg divided by the height in m^2 . Proteinuria was defined as urine protein concentration of 30 mg/dL or greater as measured by Labstix.

Statistical Methods

Cumulative 25-year incidence rates were calculated with a competing risk approach (a modification of the Kaplan-Meier approach) to account for censored observations due to missed examinations and the competing risk of death.³⁸ Estimated incidence between examinations were converted to an average annual rate using the formula: $1-(1-p_n)^{1/n}$, where n is the number of years between examinations and p_n is the cumulative incidence between examinations.

For multivariable analyses, we used a generalized linear model for the binary outcomes (incidence during the examination interval) with the complementary log-log link function to estimate an underlying continuous-time proportional hazard model while accounting for the varying follow-up times between examinations. For these analyses, duration of diabetes was the time variable and the baseline hazard was assumed to be piecewise constant within 5-year bands of diabetes duration starting at 10 years and continuing to > 40 years. Hazard ratios estimates were calculated by exponentiation of estimated coefficients. PROC NLMIXED of SAS version 9.1 (Cary, NC) was used for these analyses.

Variables included in the multivariable analyses were selected in stepwise fashion from the following list: age at diagnosis, sex, glycosylated hemoglobin, systolic and diastolic blood pressure, hypertension, gross proteinuria, and BMI. These models were rerun including severity of retinopathy at baseline. Continuous variables were included as linear terms. Two sets of models were considered: 1) models including only baseline characteristics; and 2) models using time-varying covariates updated at each follow-up examination (i.e., for each time interval in which a subject participated, the values of the risk factors at the beginning of the interval were used).³⁹

RESULTS

Characteristics of the Cohort

Characteristics at the baseline examination of those who participated in the 25-year follow-up, those who did not participate because they could not be located or they refused, and those who had died in the 11-year interval between the 14- and 25-year examinations have been presented elsewhere.²⁸ With the exception of less education, there were no significant differences in characteristics of those who participated compared to those who survived but did not participate. The 120 younger-onset persons who had died in the interval between the 14- and 25-year follow-up examination were older and had longer duration of diabetes, higher glycosylated hemoglobin, proteinuria, higher systolic blood pressure, greater BMI, more pack years smoked, more severe retinopathy, and poorer visual acuity than those who participated (data not shown). The frequency of focal and macular grid photocoagulation was not significantly different in those that died compared to those who participated (data not shown).

Factors Associated with the Cumulative Incidence of ME

The 25-year cumulative incidence of ME in the population accounting for the competing risk of death was 29% (95% CI 25, 32) and the 25-year cumulative incidence of CSME was 17% (95% CI 14, 19). Cumulative incidence of ME was not linearly related to age and duration of diabetes at baseline (Table 1). The competing risk of death increased with age and duration at baseline (Table 1).

The estimates of the annual incidence of ME and CSME over the four study intervals are presented in Figure 1. The annualized estimates were lowest in the last period of observation.

In univariate analyses, having more severe DR, being male, having higher glycosylated hemoglobin, proteinuria, higher systolic and diastolic blood pressure, and history of having smoked more pack years at baseline were significantly associated with the incidence of ME (Table 2). Hypertension, body mass index, smoking status, history of aspirin use (data not shown), history of diuretics use (data not shown), and education level at baseline were not associated with incidence of ME (Table 2). Multivariate analyses showed that having a higher glycosylated hemoglobin and higher systolic blood pressure were statistically significantly related and proteinuria marginally related to the incidence of ME (Table 2). When DR severity was added to the model, only glycosylated hemoglobin (Hazard ratio [HR] per % increase 1.15, 95% CI 1.08, 1.23, $P < 0.001$) and DR severity (HR per 2 step increase 1.19, 95% CI 1.12, 1.29, $P < 0.001$) were associated with the incidence of ME over a 25 year period. While controlling for baseline glycosylated hemoglobin and retinopathy severity, only a change in glycosylated hemoglobin (HR per 1% 1.22, 95% CI 1.14, 1.31, $P < 0.001$) between baseline and the 4-year follow-up was associated with ME over a 21 year period.

Time-varying covariate analyses generally showed similar associations to those found with analyses using only baseline covariates. Glycosylated hemoglobin (HR per 1% 1.37, 95% CI 1.29, 1.45, $P < .001$), proteinuria (HR 1.56, 95% CI 1.13, 2.14, $P = 0.006$), systolic blood pressure (HR per 10 mmHg 1.15, 95% CI 1.06, 1.25, $P = 0.001$), and diastolic blood pressure (HR per 10 mmHg 1.24, 95% CI 1.09, 1.42, $P < 0.001$) were associated with incident ME but not hypertension (HR 1.31, 95% CI 0.94, 1.81, $P = 0.11$), smoking status (HR past vs never 0.98, 95% CI 0.68, 1.41, $P = 0.90$ and HR current vs never 1.16, 95% CI 0.84, 1.59, $P = 0.37$) or body mass index (HR per 1 kg/m² 0.93, 95% CI 0.81, 1.07, $P = 0.32$).

Changes in Prevalence of ME and CSME by Year at Diagnosis

There was no statistically significant relation of prevalence of ME or CSME by year of diabetes diagnosis and duration of diabetes in the cohort (data not shown).

DISCUSSION

The data reported herein provide long-term population-based information regarding the 25-year cumulative incidence of ME and its relationship to glycemia, blood pressure, proteinuria, and other factors in persons with type 1 diabetes mellitus. The 25-year incidence of ME (29%) and CSME (17%) were high and the strongest and most consistent associations were with glycemia and to a lesser extent, systolic and diastolic blood pressure and nephropathy as manifest by gross proteinuria. Lower annualized incidence of ME and CSME was found in the last period of follow-up compared to earlier periods of follow-up.

Based on our findings, we would estimate that over a 25-year study period, of the 515,000 to 1.3 million Americans thought at present to have type 1 diabetes, that approximately 149,000 to 377,000 will develop ME and 88,000 to 221,000 will develop CSME (NIDDK Clearing House <http://www.medhelp.org/NIHlib/GF-254.html#four> accessed September 16, 2008). The decline in estimated annualized incidence of ME and CSME between the 1994-95 and 2005-06 examinations from earlier periods suggest the possibility that applying these figures to persons who currently have type 1 diabetes may overestimate the number of persons who will develop ME over the next 25 years. There are few other population-based studies in which incidence data collected over a long period of time employing objective measures have been used to detect changes in incidence of ME. Data from a clinic-based study in Denmark showed a decline in the incidence of ME in persons who were more recently diagnosed to have diabetes.¹⁸ This decline was associated with statistically significant trends of decreasing glycosylated hemoglobin, mean arterial blood pressure levels, and earlier treatment of hypertension. In the WESDR, a reason for the decline in incident CSME may involve better glycemic control.⁴⁰ This is suggested by lower levels of mean glycosylated hemoglobin A1 (from 10.7% in first

period to 9.4% in 4th period) in those at risk of developing ME in more recent compared to earlier periods of the study (Klein R, unpublished data June 30, 2008). This is likely the result of data from randomized clinical control trials demonstrating a beneficial effect of intensive glycemic control on reducing the incidence of ME in persons with type 1 diabetes.¹² However, changes in levels of mean systolic blood pressure (from 120.4 mmHg in first period to 124.4 mmHg in the 4th period) in those at risk of developing ME in more recent compared to earlier periods of the WESDR were unlikely to explain the reduction of incidence of ME in persons with type 1 diabetes in more recent periods (Klein R, unpublished data June 30, 2008). Alternatively, the decline in incidence of ME in the latest period of the WESDR may be a result of death leading to selection of the healthiest. This is suggested by the finding that those who had died in the interval between the 14- and 25-year follow-up examination were older and had longer duration of diabetes, higher glycosylated hemoglobin, proteinuria, higher systolic blood pressure, greater BMI, more pack years smoked, more severe retinopathy, and poorer visual acuity than those who participated. This information is important in planning for counseling and rehabilitative services, projecting costs, measuring temporal trends, developing causal inferences, and providing sample size estimates for conducting clinical trials. For example, if there is a “true” decrease in the incidence or CSME in persons with type 1 diabetes, there may be a need for fewer health care resources to detect and treat these individuals with focal or macular grid photocoagulation. It is also important to emphasize caution when using these data to estimate samples sizes needed to evaluate efficacy of new treatments in reducing the incidence of ME in clinical trials. Our WESDR population, first examined nearly 30 years ago in 1980-1982, is likely to not be representative of contemporary populations of persons newly diagnosed with type 1 diabetes because more emphasis today is placed on intensive control of glycemia, blood pressure, lipids, and more aggressive management of renal disease.

Hyperglycemia, at baseline and throughout the study period, was strongly associated with the incidence of ME. This was not surprising given our earlier findings and those from the DCCT/EDIC and other studies.^{8-13,41} In our study, hyperglycemia was similarly associated with incidence of ME at all examinations suggesting that lower levels of glycosylated hemoglobin were associated with lower incidence regardless of duration of diabetes. An increase of 1% in the glycosylated hemoglobin between baseline and follow-up was associated with a 22% increase in the 21-year cumulative incidence of ME. This is consistent with data from the DCCT that found that in people with type 1 diabetes, intensive glycemic control was associated with 46% reduction in the incidence of ME at the end of the trial and a 58% reduction 4 years later compared to those in the conventional group.¹²

In our study, systolic blood pressure but not the presence of hypertension was associated with the incidence of ME. Blood pressure has inconsistently been found to be associated with prevalence and incidence of ME in persons with type 1 diabetes.^{8-11,13,16,41} Selective mortality may be attenuating the relationship of blood pressure and hypertension to the incidence of ME in the current study, that is, participants with high blood pressure who developed ME may have died in the 11-year interval between the 14 and 25-year examinations before being examined.

Proteinuria, independent of glycemia and blood pressure, was found to be marginally associated with the incidence of ME in the WESDR. This is consistent with data from most studies that showed associations between the prevalence of diabetic nephropathy, as manifest by microalbuminuria or gross proteinuria, and the incidence and progression of DR.^{23,26,42-48} There are also anecdotal reports of patients with renal failure having more severe ME that improves after dialysis or renal transplantation. Rheological, lipid, and platelet abnormalities associated with nephropathy may be involved in the pathogenesis of ME.

We had hypothesized that smoking, through its affect on coagulation and inflammatory pathways leading to hypoxia and exudation, would increase the risk of developing ME.⁴⁹⁻⁵² While we found a univariate relation of higher incidence of ME in those with a history of the highest amount of smoking exposure (≥ 15 pack years smoked after diagnosis of diabetes) in the WESDR, this relationship was attenuated and no longer statistically significant in multivariate analyses. This is consistent with our earlier findings and with those from others showing no relationship of smoking to incidence and progression of DR or ME.^{48,53-55} The reasons for not finding a relation are not known. Regardless, smoking should be avoided due to its relation to increased risk of death and other systemic complications.

There are many strengths of the study including a large cohort with a broad distribution of severity of retinopathy at baseline, a low refusal rate, and use of standardized protocols of measurement which included objective recording of ME using stereoscopic fundus photographs of seven standard fields. However, caution should be observed when interpreting the findings from our study. Mortality may affect the relation of risk factors to incidence of endpoints. Because glycosylated hemoglobin, blood pressure, gross proteinuria, and retinopathy severity level are significantly associated with incidence of ME and decreased survival,⁴⁰ it is likely that the effect of death would diminish the strength of these relationships. Also, serum lipids were not measured at baseline limiting our ability to examine the relation of this risk factor to the 25-year cumulative incidence of ME.

In summary, our data suggest that better glycemic and blood pressure control at baseline and throughout the study, may be beneficial in reducing the incidence of ME. In addition, our data show a reduction in the incidence of ME in the latest period of follow-up, suggesting a possible benefit of recent changes in management of diabetes on the incidence of ME, although it may, in part, reflect survival of the healthiest.

Acknowledgments

This research is supported by National Institutes of Health grant EY03083 and EY016379 (Ronald Klein, MD, MPH, Barbara E.K. Klein, MD, MPH) and, in part, by the Research to Prevent Blindness (R. Klein and BEK Klein, Senior Scientific Investigator Awards), New York, NY. The National Eye Institute provided funding for entire study including collection and analyses and of data; RPB provided further additional support for data analyses.

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Figure 1. Estimated annual rates for incidence of macular edema for four periods of the Wisconsin Epidemiologic Study of Diabetic Retinopathy.

25-year Cumulative Incidence of Macular Edema and Clinically Significant Macular Edema (CSME) by Age and Duration of Diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Incidence of Macular Edema				Incidence of CSME				
	No. at Risk	No. Events	Cumulative Incidence (%)		No. at Risk	No. Events	Cumulative Incidence (%)	
			Event	Risk of Dying Prior to Event			Event	Risk of Dying Prior to Event
All groups	818	213	28.6	25.3	841	128	16.6	29.0
Age								
0-9 years	24	4	23.2	0.0	24	4	23.2	0.0
10-14 years	77	18	28.8	10.4	77	12	19.0	12.4
15-19 years	142	34	26.1	13.7	143	23	17.7	15.2
20-24 years	141	39	29.7	11.9	143	25	18.4	13.5
25-29 years	111	40	39.9	15.7	117	23	21.1	21.3
30-34 years	122	33	29.9	21.0	125	19	16.5	25.1
35+ years	201	45	23.4	57.5	212	22	11.0	63.0
Diabetes Duration								
0-2 years	74	11	17.7	9.6	74	6	10.2	11.5
3-4 years	80	19	29.2	10.0	80	10	14.4	11.9
5-9 years	234	72	34.0	9.3	235	56	26.4	11.8
10-14 years	142	50	37.7	14.1	146	25	18.1	16.0
15-19 years	100	24	26.1	30.2	103	12	12.3	35.1
20-24 years	60	20	36.0	38.8	68	12	19.5	45.0
25-29 years	54	10	19.1	59.8	57	6	10.7	63.6
30+ years	74	7	9.6	82.8	78	1	1.3	88.3

Table 2

Associations with Incidence of Macular Edema.

Risk variable	Level	Univariate			Multivariate*		
		HR	95% CI	P	HR	95% CI	P
Sex	Male	1.32	1.02, 1.72	0.04			
Age at diagnosis	10-19 yrs vs <10 yrs	1.32	0.96, 1.82	0.09			
	20-29 yrs vs <10 yrs	1.32	0.92, 1.90	0.13			
	Per 1%	1.17	1.10, 1.25	<0.001	1.17	1.10, 1.25	<0.001
Glycosylated hemoglobin A _{1c}	9.5-10.5 vs <9.5%	1.54	1.00, 2.39	0.05			
Glycosylated hemoglobin A _{1c} quartiles	10.6-12.0 vs <9.5%	2.17	1.46, 3.22	<0.001			
	12.1-19.5 vs <9.5%	2.50	1.67, 3.72	<0.001			
	Present	1.68	1.19, 2.37	0.003			
Proteinuria	21 vs 10	1.52	1.00, 2.32	0.05			
Retinopathy severity	31-37 vs 10	2.71	1.85, 3.95	<0.001			
	43-53 vs 10	3.26	2.08, 5.11	<0.001			
	60+ vs 10	3.40	2.06, 5.62	<0.001			
	Per 10 mmHg	1.15	1.06, 1.25	0.001	1.15	1.04, 1.26	0.004
	Per 10 mmHg	1.16	1.02, 1.32	0.02			
Systolic Blood Pressure	Present	1.20	0.83, 1.74	0.34			
Hypertension	Past vs never	0.72	0.44, 1.17	0.18			
	Current vs never	1.03	0.74, 1.45	0.85			
	<5 pack-years	0.85	0.55, 1.32	0.47			
Pack Years Smoked†	5-14 pack-years vs never	0.94	0.58, 1.53	0.81			
	≥15 pack-years vs never	1.67	1.03, 2.69	0.04			
	Per 4 years	1.15	1.00, 1.32	0.06			
Education	Per 4 kg/m ²	1.09	0.97, 1.23	0.16			

* All variables except retinopathy severity not included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.

† Univariate model additionally controls for age

Abbreviations: HR=hazard ratio; CI=confidence interval