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The Risk for Stroke and Myocardial Infarction After Herpes Zoster in Older Adults in a US Community Population

Barbara P. Yawn, MD, MSc, **Peter Wollan, PhD**, **Maria A. Nagel, MD**, and **Don Gilden, MD**

Department of Research, Olmsted Medical Center, Rochester, Minnesota (Yawn, Wollan); Department of Neurology, Univerity of Colorado School of Medicine, Aurora, Colorado (Gilden, Nagel); Department of Immunology and Microbiology, University of Colorado School of Medicine, Aurora, Colorado (Gilden)

Abstract

OBJECTIVE—To assess risk of stroke and MI after zoster in a U.S. community population of older adults.

DESIGN—A community cohort study (1986–2011) comparing risk for stroke and MI in adults ≥50 with and without zoster. Odds ratios are presented for MI and stroke at 3, 6, 12 and 36 months after index zoster plus hazard ratios for long-term risk (up to 28.6 years).

SETTING—Olmsted County, Minnesota.

PARTICIPANTS—All adult residents of Olmsted County, aged ≥50 at the time of medical record confirmed zoster (n = 4,862) and 19,433 sex and age matched individuals with no history of zoster.

EXPOSURE—Zoster.

MAIN OUTCOMES—Incident MI and stroke.

RESULTS—Overall, individuals with zoster had more risk or confounding factors for MI and stroke, suggesting that they had worse health status overall. When controlling for the multiple risk factors, those with zoster were at increased for stroke at 3 months post zoster compared to those without a history of zoster (OR 1.53 (95% confidence interval (CI95) 1.10–2.33, $P = .04$. The association between zoster and MI at 3 months was not robust across analytic methods. Zoster was not associated with an increased risk for either stroke or MI at any point beyond 3 months.

CONCLUSIONS AND RELEVANCE—Zoster was associated with only a short- term increased risk of stroke which may be preventable with prevention of zoster.

Corresponding Author: Barbara P. Yawn, MD, MSc, Department of Research, Olmsted Medical Center, Rochester, MN; telephone: 507-287-2758; byawn@olmmed.org.

Conflict of Interest Disclosures:

All authors report no conflict of interest.

Introduction

Varicella zoster virus (VZV) causes varicella (chickenpox) after which virus becomes latent in neurons of ganglia along the entire neuraxis.[1,2] As VZV-specific cell-mediated immunity declines in older and immunocompromised individuals, VZV reactivates to produce zoster (shingles). More than 95% of the world's adult population is infected with VZV[3,4] and up to one-third will develop zoster in their lifetime.[5,6] Zoster can be complicated by myelitis, meningoencephalitis, vasculopathy, multiple ocular disorders[7–19] and giant cell arteritis.[10]

Epidemiological studies outside the U.S. have suggested an increased risk of stroke and myocardial infarction (MI) after zoster.[11–16] Those studies used national or regional administrative databases, assessing the association at time points ranging from weeks[11,13,14,15] to years[12] after zoster. None used medical record confirmation, most relying on zoster diagnostic codes,[11–13,15], while one used antiviral prescriptions as a proxy for zoster.[14] No similar studies of the U.S. population have been reported.

Herein, we assessed the risk of stroke and MI in a U.S. community-based population comparing outcomes among patients 50 years and older with medical record confirmed episodes of zoster and age and sex matched control patients without zoster. We assessed the risk of zoster-associated stroke or MI at 3, 6, 12 and 36 months as well as 20 years after zoster, adjusting for several known stroke and MI risk factors..

Methods

Study Design

This is a retrospective study of a population-based cohort of older adults with zoster comparing their rates of post zoster myocardial infarction (MI) and stroke to a cohort of age and sex matched individuals from the same community who had no medical record history of zoster. Patients were followed for a mean of 7.1 years (range 0–28.6 years). All adults aged 50 years and older with a confirmed zoster episode between January 1, 1986 and October 1, 2011 (N= 4,862) were included in the zoster cohort.. The no zoster cohort, (N= 19,433, included approximately 4 individuals matched by birthdate (+/− 1 year) and sex to the individuals in the zoster cohort. All patients had not refused medical record research authorization as required by Minnesota Statute.[16,17] The study was approved by Institutional Review Boards of the Olmsted Medical Center and the Mayo Clinic. Risks for stroke and MI were assessed separately.

Participants, Data Collection and Adjudication of Cases of Zoster

Patients with zoster were identified using resources of the Rochester Epidemiology Project (REP), an electronic database that collects and links medical diagnoses for all patients receiving care in Olmsted County, MN.[18–21] Diagnostic code and visit data are collected and linked by patient across two large systems (the Mayo Clinic and the Olmsted Medical Center) as well as three small clinics with one to three clinicians. Capture is estimated to be over 98% of each Olmsted County, MN community resident's medical events.[18]

The zoster cohort was identified using a broad group of zoster related diagnostic codes (International Classification of Diseases version 9, ICD-9).[6,9,22–24] The broad spectrum of codes increased sensitivity of electronic identification, and medical record review of each potential case assured specificity of the diagnosis. Confirmation required documentation of acute pain and dermatomal or rarely disseminated rash or organ damage consistent with zoster.[25] Individuals with recurrent zoster were included since we have previously reported that recurrent zoster is not rare[24] and our medical record review removed individuals with recurrent herpes simplex infection. Zoster patients included in the stroke analyses had no history of stroke before their index date and those included in the MI analyses had no history of MI before their index date.

The patients in the no zoster cohort were also selected using REP resources by matching each zoster patient with four patients whose birthdate was ± 1 year, who were of the same sex and had no zoster diagnoses in the five years prior to their inclusion in the cohort. All individuals in both cohorts lived in Olmsted County and most receive care from each of the two medical systems.[18–20] Individuals included in the MI analyses had no history of prior MI and those in the stroke analyses had no history of prior stroke.

Stroke and MI

Our primary outcome was incident (first event) stroke or MI after the index date which was the date of zoster in the zoster cohort members and for the “matched” zoster individuals in community cohort patients. Transient ischemic attacks (TIA) were not included as an outcome since TIA is often not a definitive event.[12,14] Conversely, a previous study in the Olmsted County population reported that diagnoses of stroke and MI have high clinical accuracy when the diagnostic code in the REP is taken from hospital discharge data or death certificates.[26]

The occurrence of a stroke or MI was assessed using the codes listed in Supplemental eTable 1. For each case and control, all stroke or MI events were identified using the date associated with the earliest available stroke or MI code as the event date. All strokes and MIs were included as events of interest if they occurred 30 days or less before the index date of zoster through the follow-up period since replication and spread of VZV begins before zoster rash.[27]

Covariates

Diagnostic codes used to adjust analyses for multiple other morbidities were obtained for each case using the REP diagnostic index which records all diagnoses for each medical encounter. Overall, 92% of cases and all control patients had at least 5 years of health care data to search for covariates before their index date. Only diagnoses before the individual’s index date were included as risk or confounding factors for that patient. Data on current and former smoking status and obesity were poorly recorded in the diagnostic coding data and were therefore not included in analyses.

To enhance the list of diagnostic codes used to identify potential risk factors for stroke and MI, we used the list of factors published by the US Department of Health and Human Services Taskforce (US-DHHS) in 2010.[28–30] The list includes diagnostic codes for the

major risk factors for MI and stroke such as hypertension, dyslipidemia, coronary artery disease (including MI for stroke), cardiac arrhythmias, congestive heart failure, diabetes, vasculopathies and stroke (for MI), depression and chronic obstructive pulmonary disease. (See Supplemental eTable 2.)

The REP diagnostic code data for all visits for each patient were searched electronically to identify all visits with any ICD-9 codes for the risk and confounding factors from their first visit to any Olmsted County health care facility until the last visit 30 days before the index date. The ICD-9 codes were then pooled into the risk factor domains: hypertension, dyslipidemia, coronary artery disease (includes MI), arrhythmias, congestive heart failure, diabetes, depression, chronic obstructive pulmonary disease, vasculopathies and stroke as proposed by the US DHHS.[28–30] We added a domain of "anxiety"[31] based on recent work suggesting that it is a risk factor for MI.[32] To decrease the risk of false-positive diagnoses for any condition, we required that a patient received two codes for a given condition separated by more than 30 days for that condition to be considered present.[33,34]

Statistical Analyses

Only individuals with no MI before the zoster index date were included in zoster and MI analyses. Similarly, only individuals with no stroke before the index date were included in zoster and stroke analyses.

The zoster and no zoster cohorts were compared for demographic and co-morbidity frequency using Chi-squared tests. We examined the effect of HZ on risk for stroke using 3 methods: 1) univariate and multi-variate logistic regression analysis of the unpaired subjects, including age and sex as predictors with a step-down method, deleting non-significant variables to reduce the number of co-morbidity predictors, 2) conditional logistic regression for matched pairs, and 3) survival analyses (time to stroke or MI) presented using Kaplan-Meier curves, and Cox proportional hazards models for the full follow-up period, with case status, age, sex, and other co-morbidities, as predictors.[35] The S-Plus statistics package v. 7.0.6 (Tibco Software) was used for all computations.

Results

The 4,862 patients with zoster and 19,433 patients with no zoster patients had substantial rates of morbidity and multi-morbidity diagnosed before the index date (Table 1). The rates of chronic conditions were higher among the zoster cohort than among the no zoster cohort patients when stratifying by 1–3 or more chronic conditions: 1 condition, 24.7% vs. 23.1%; 2 conditions, 21.3% vs 17.5%; and for 3 or more conditions 27.7% vs 21.7% for cases and controls respectively; $P < .001$. The sex ratio of cases and controls did not differ. The average age of the patients for the stroke analyses differed by 0.7 years (P=<.001) and by 0.5 years for the MI analyses (P=.01). Neither difference was considered clinically significant. Since we included patients with fatal stroke, no minimum follow-up period was required.

For analyses of zoster and stroke, we removed all patients with stroke before the index date which yielded 4,478 individuals with zoster and 16,800 individuals with no zoster. Stroke was associated with zoster in the first 3 months [odds ratio (OR) = 1.7, CI95 1.13–2.57], and

the first 6 months after zoster (OR=1.41, CI95 1.0–1.98) in univariate logistic regression that included only zoster and stroke. In stepwise multivariate logistic regression the association of zoster and stroke remained significant only at 3 months after zoster (OR 1.53, CI95 1.01–2.33). When considered individually, many factors in addition to zoster were significantly associated with stroke. However, in stepwise logistic regression which accounted for multiple risk factors and zoster simultaneously, most risk factors became non-significant, leaving only cardiac arrhythmias, a history of vasculopathy, age and zoster as significantly associated with stroke. (Table 2). The results were robust across different analysis methods, specifically conditional logistic regression and assessment of hazard ratios. (Supplementary Table e3).

While simple survival analysis demonstrated a difference in time to first stroke after zoster for case versus control patients over 20 years [HR = 1.11, CI 95 1.01–1.23, $P = .02$), the association was no longer significant when adjusting for comorbidities in a Cox proportional hazards model ($P = .14$). The top portion of the Figure shows the Kaplan Meier plot for 20 year follow- up with an insert highlighting the first 3 years after zoster.

Zoster and MI analyses included 4,454 individuals with zoster and 16,740 individuals with no zoster, all with no history of prior MI before their index date. The mean age was 68.2 (range 49.1–106 years) with an average of 7.0 years of follow-up (range 0–27.8 years). When considering zoster and each risk factor alone (univariate analyses), MI was associated with zoster at 3 months, 6 months and 1 and 3 years with a declining odds ratio over longer times after zoster from 1.88 (CI95 1.15–3.08) at 3 months to 1.29 (CI95 1.08–1.56) at 3 years (Table 3). However, when controlling for other risk and confounding factors in stepwise logistic regression, zoster remained significantly associated with MI at only 3 months with non-MI coronary artery disease diagnosed before their index date and age as the only other significant factors (Table 3). MI and zoster are not strongly associated at any point in time using any type of analyses and the association of MI and zoster identified at 3 month by logistic regression is not robust across differing analytic approaches.(See Supplemental Table) The associations between MI and zoster are non-significant at 6, 12 and 36 months time with all methods.

Simple survival analysis demonstrated a difference in time to first MI for patients with zoster compared to control patients (HR = 1.13, CI95 1.01–1.25, $P = .03$) but that association became non-significant after adjusting for co-morbidities ($P=.13$). The lower portion of the Figure shows both 20-year follow-up results as well as the insert for results from the first 3 years.

Discussion

In our geographically defined U.S. population of older adults, zoster was associated with an increased risk of stroke for three months after zoster even when controlling for multiple risk and confounding factors. The association was robust across multiple analytic strategies. The association between MI and zoster was less strong and not robust across different analytic methods suggesting that this association requires additional evaluation in larger data sets. No increased risk for either stroke or MI continued beyond 3 months including from survival

analysis for up to 20 years post zoster when adjusting for cardiovascular and cerebral vascular risk factors and confounding factors such as diabetes. Patients with zoster had significantly higher rates of other chronic diseases including the presence of multiple chronic conditions compared to those without zoster.

Table 4 summarizes the epidemiological studies assessing stroke, MI and TIA risk after zoster. All studies other than ours used administrative data to identify zoster which can result in 5–15% false-positive "cases".[25] Most studies focused only on stroke or stroke and TIA, accounting for multiple cardiovascular risk factors, but used differing study designs. Kang et al.[11] and Breuer et al.[12] compared zoster cases to age and sex matched control patients with no history of zoster before the date of zoster in the matched case. Langan et al.[13] used patients as their own controls comparing stroke rates in the year before zoster with stroke rates in the year after zoster. This may improve "matching" but limits the assessment period to one year. Lin et al.[15] included only cases with herpes zoster ophthalmicus (HZO) which we were unable to report over our entire period. Sreenivasan et al.[14] used prescribed antiviral medications to identify zoster, a proxy that may be problematic since antiviral agents are often used to treat other herpes virus infections.

Previous studies also differed in the time period of risk assessed. Both Langan et al.[13] and Sreenivasan et al.[14] reported results as early as two weeks after zoster which our sample size did not allow. However, our 53% increased risk for stroke at three months is similar to the 42% increase reported by Langan at 5–12 weeks.[14] Like Langan et al, we also found no increased risk of MI or stroke at 1 year after zoster in older adults[13], although both Kang et al.[11] and Sreenivasan et al.[14] reported increased risk of stroke at 1 year. Unfortunately, Kang et al.[11] did not stratify stroke risk by age group reporting only in all adults >18 years of age, making comparison to our results difficult. Although Sreenivasan et al.[14] reported a 17% increased risk of stroke in older adults at one year after zoster, the use of antiviral prescriptions as a proxy for zoster requires further confirmation.

Our results agreed with those from the only two other studies that assessed risk of stroke beyond 1 year, showing no long-term increased risk of stroke after zoster in adults older than 40 to 50 years of age when adjusted for multiple risk factors.[12,14] The other two studies do report increased risk for stroke in patients younger than 40 years for whom we have no data. We agree with the authors of those studies that results for younger patients must be interpreted with caution due to difficulty in controlling for risk factors which are often not assessed or reported.[12,14]

Our study is the first large U.S. epidemiological study to report on risk of MI in the immediate post zoster period. We found that the association between zoster and MI at 3 months is not strong and not robust across different analytic methods. However, our cohorts had very few MIs in that brief period suggesting that the results should be further evaluated using a larger dataset. Breuer et al.[12] reported a small 10% increased risk of MI in older adults in their long-term follow-up, similar to the unadjusted 13% increased risk we found long-term for MI. Considering the modestly increased risk and the large burden of co-morbid conditions in the zoster patients, these results deserve further scrutiny. Recent studies found that morbidity and multiple morbidities at younger ages strongly predict increasing

morbidities with aging.[36,37] In all reported studies, patients with zoster have greater numbers of chronic conditions at the time of zoster compared to age- and sex-matched controls. Thus, it is possible that an increased long-term risk of MI and stroke is due at least in part to the steeper multi-morbidity trajectory in zoster patients.

Mechanisms for Increased Short-term Risks Following Zoster

During the first 3 months after zoster, the increased risk of stroke is most likely due to productive VZV infection in intracerebral arteries after transaxonal spread of virus upon reactivation from cranial nerve ganglia. VZV has been found in intracerebral arteries as late as 10 months after zoster[38] with pathological changes that include loss of smooth muscle cells which may contribute to aneurysm formation and hemorrhagic stroke.[7] Similarly, any increased risk of MI within 3 months of zoster may be caused by virus infection of coronary arteries after transaxonal spread of VZV that reactivated from autonomic and dorsal root ganglia. A recent report described a patient on long-term steroids who developed thoracic zoster and died suddenly 5 months later; post-mortem examination revealed VZV in multiple coronary arteries, as well as in the posterior cerebral artery.[39]

Inflammatory cells that secrete soluble factors which contribute to vascular remodeling and can potentially disrupt pre-existing atherosclerotic plaques have also been detected in VZV-infected arteries[40] and are noted as potentially important in the increased risk of MI after respiratory and urinary tract infections and sepsis.[41,42]

Limitations and Strengths

The Olmsted County older adult population is primarily Caucasian prohibiting assessment of the impact of race or ethnicity on outcomes. Only the Taiwan studies report race or ethnicity.[11,15] Loss to follow up, primarily due to death in these elderly patients was almost 45% by year 5 but was less than 1% at 3 months (all due to non-stroke or MI related deaths) increasing to only 7% by 36 months. Therefore, it is unlikely that loss to follow up affected our 3 month to 3 year assessments and our long term assessment used Kaplan Meier calculations which account for death and other losses to follow up.

Although we included data from all hospital admissions and death records allowing us to capture patients who die from MI or stroke before hospital admission, we did not include “silent” strokes or MIs identified only by imaging. Timing of the initial “silent” event is difficult to ascertain and therefore not easily linked to a zoster or index date. We were unable to control for obesity or smoking status but know that the rate of current smokers in the Olmsted community population is less than one-third of the smoking rate reported in the largest UK study.[12] Therefore, it is possible that differences could be due to residual confounding from the smoking, obesity or factors which we were unable to assess.

Strengths of our study include medical record confirmation of all zoster cases, eliminating the 10–15% overestimate of zoster when only administrative data are used for diagnosis.[25] Moreover, risk factors for stroke and MI were identified using a broad set of diagnostic codes developed by an expert panel to facilitate assessing many important chronic conditions such as hypertension, depression and dyslipidemia.[32] Codes included those used by other studies that provided their list of ICD-9 codes for risk factor identification as well as

additional codes that may represent less commonly diagnosed but important representations of those chronic conditions. Finally, this is the first study to combine analytic strategies to assess both short term risk of stroke and MI at 3 months, 6 months, 1 year and 3 years. Our study also has the longest post zoster follow up period ever reported.

Conclusions

In adults aged 50 years and older, zoster is associated with an increased risk of stroke and possibly MI in the first 90 days, but not thereafter. Use of zoster vaccine may prevent zoster and therefore, the associated acute increased risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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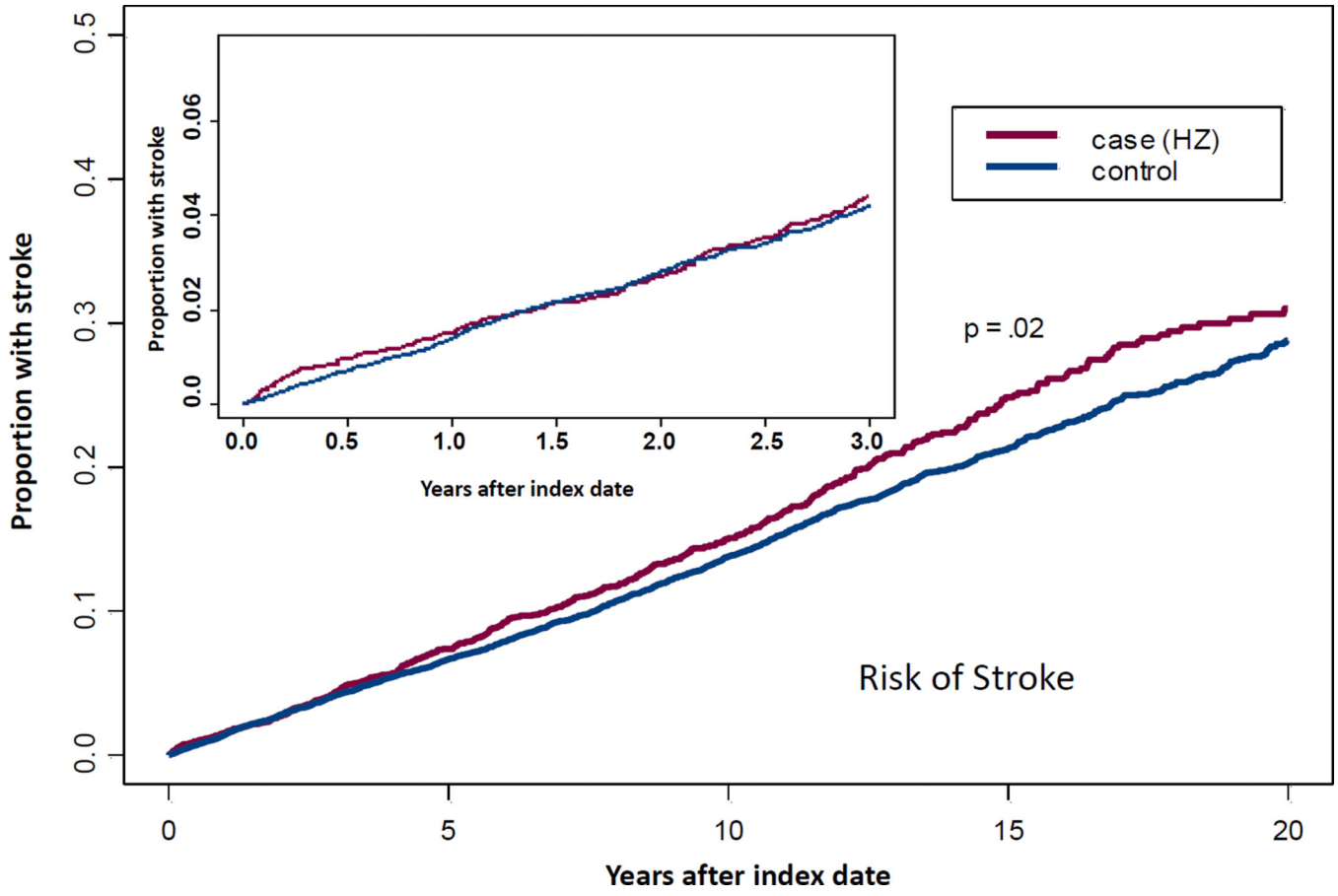

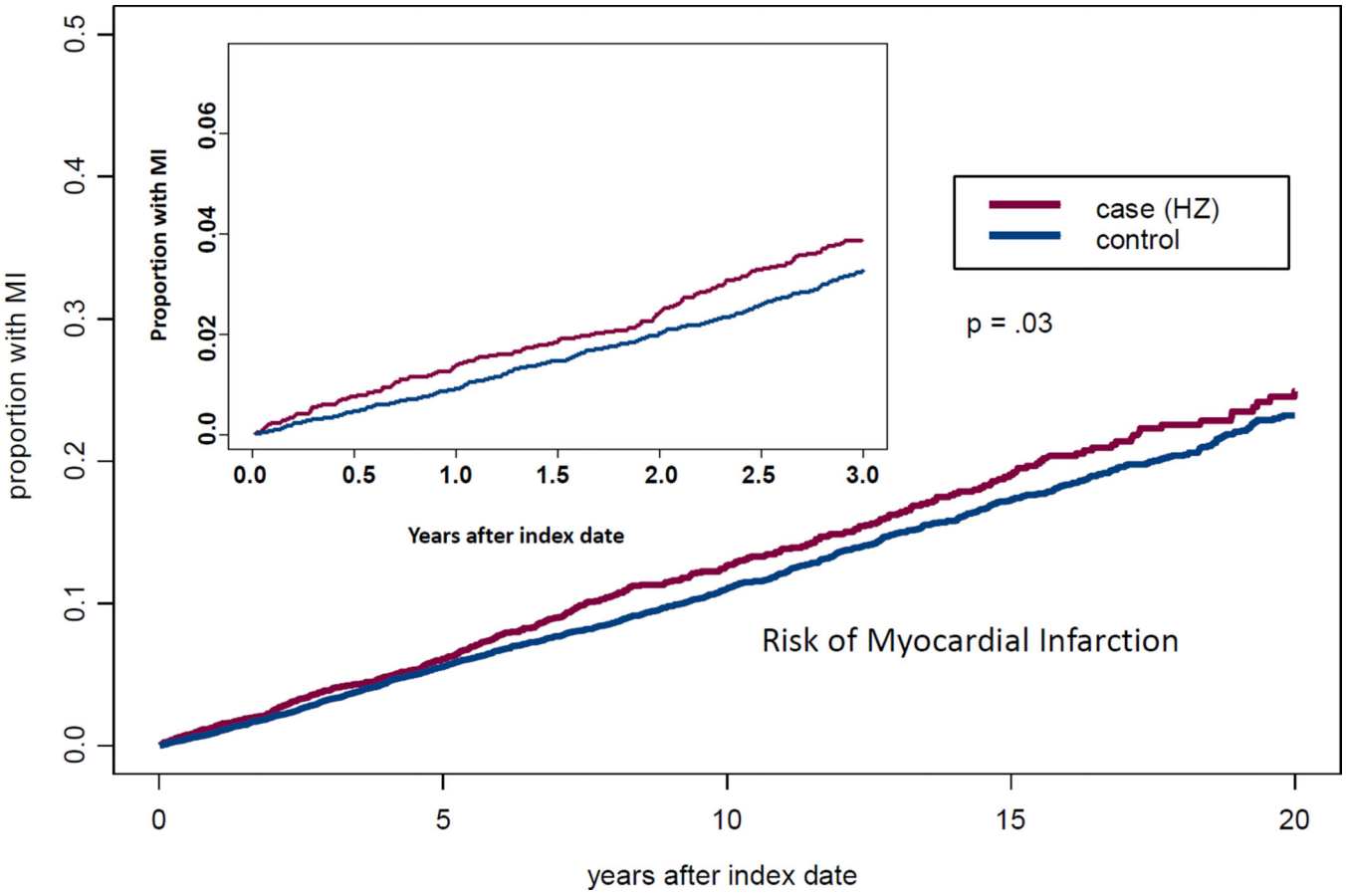

Figure.

Stroke: Time to First Stroke Over 20 Years after Zoster Compared with Time to First Stroke in Control Subjects Having No Zoster.

All subjects had no stroke prior to index date of zoster using that date also as index date for age and sex matched controls with no history of zoster. Time to stroke was estimated with Kaplan-Meier curves with Cox proportional hazards models for the full follow-up period, with case status, age, sex, and other co-morbidities, as predictors. The sample included 4,478 cases and 16,800 controls. Using a Cox proportional hazards model, controlling for multiple co-morbidities zoster was not associated with long term risk of stroke ($P = .14$). The insert highlights the shorter term risk over 0 to 3 years. Using step wise logistic regression accounting for multiple co-morbidities, the association of zoster and stroke remained significant at only 3 months after zoster, OR 1.53 (CI 95 1.01, 2.33), $P = .044$.

Myocardial Infarction: Time to First Myocardial Infarction (MI) Over 20 Years after Zoster Compared with Time to First MI in Control Subjects Having No Zoster.

All subjects had no MI prior to index date of zoster using that date also as index date for age and sex matched controls with no history of zoster. Time to MI was estimated with Kaplan-Meier curves with Cox proportional hazards models for the full follow-up period, with case status, age, sex, and other co-morbidities, as predictors. The sample included 4,454 case and 16,740 control patients. Using a Cox proportional hazards model, controlling for multiple co-morbidities zoster was not associated with long term risk of stroke ($P = .13$). The insert

highlights the shorter term evaluations of MI and zoster. Using step wise logistic regression accounting for multiple co-morbidities, the association of zoster and MI remained significant at only 3 months after zoster 1.68 (CI 95 1.03, 2.75), $P = .04$.

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Table 1

Demographic and Risk Factor Data

Patients for Zoster and Stroke Analyses				**Patients for the Zoster and MI Analyses**					
	N (%) with zoster 4478 Total	**N (%) without zoster/ 16800 Total**	**Chi-square *P*-value**	**N (%) with zoster 4454 Total**	**N (%) without zoster 16740 Total**	**Chi-square *P*-value**			
Sex = female	2782 (62.1)	10513 (62.6)	.59	2826 (63.4)	10831 (64.7)	.12			
Age mean (range)	68.5 (50,106)	67.8 (49,106)	< .001	68.6 (50,106)	68.1 (49,106)	.01			
Age 50–64	1964 (43.9)	7717 (45.9)	.01	1944 (43.6)	7604 (45.4)	.04			
Age 65–79	1662 (37.1)	6163 (36.7)	.61	1647 (37.0)	6053 (36.2)	.32			
Age 80+	852 (19)	2920 (17.4)	.01	863 (19.4)	3083 (18.4)	.02			
Morbidities							2065 (46.4)	6526 (39.0)	< .001
Hypertension	2068 (46.2)	6473 (38.5)	< .001	2065 (46.4)	6526 (39.0)	< .001			
CAD	861 (19.2)	2380 (14.2)	< .001	668 (15.0)	1818 (10.9)	< .001			
MI before index	312 (7.0)	900 (5.4)	< .001	NA	NA	NA			
Arrhythmias	953 (21.3)	2589 (15.4)	< .001	917 (20.6)	2543 (15.2)	< .001			
Dyslipidemia	1941 (43.3)	5955 (35.4)	< .001	1873 (42.1)	5808 (34.7)	< .001			
Depression	850 (19)	2640 (15.7)	< .001	862 (19.4)	2718 (16.2)	< .001			
Diabetes	873 (19.5)	2769 (16.5)	< .001	866 (19.4)	2741 (16.4)	< .001			
Substance abuse	183 (4.1)	649 (3.9)	.52	188 (4.2)	621 (3.7)	.12			
Anxiety	662 (14.8)	2020 (12)	< .001	663 (14.9)	2053 (12.3)	< .001			
Vasculopathy	118 (2.6)	316 (1.9)	.002	174 (3.9)	509 (3.0)	< .001			
Number of events for each analysis (Strokes)				**Number of events for each analysis (MI)**			35 (0.8)	81 (0.5)	.02
within 3 months	33 (0.7)	73 (0.4)	.02	24 (0.5)	48 (0.3)	.02			
in 6 months	46 (1)	123 (0.7)	.06	35 (0.8)	81 (0.5)	.02			
in 1 year	71 (1.6)	235 (1.4)	.39	61 (1.4)	155 (0.9)	.01			
in 3 years	176 (3.9)	591 (3.5)	.20	154 (3.5)	450 (2.7)	.01			
ever	562 (12.6)	1844 (11)	.003	443 (9.9)	1430 (8.5)	< .001			
Follow-up Period							1272 (28.6)	4637 (27.7)	.26

Patients for Zoster and Stroke Analyses				Patients for the Zoster and MI Analyses						
	N (%) with zoster 4478 Total	N (%) without zoster/ 16800 Total	Chi-square *P*-value	N (%) with zoster 4454 Total	N (%) without zoster 16740 Total	Chi-square *P*-value				
90 daus	4425 (98.8)	16716 (99.5)	.03	4405 (98.9)	16673 (99.6)	.03				
3 years	4151 (92.7)	15758 (93.8)	.06	4102 (92.1)	15652 (93.5)	.05				
> 5 years	2508 (56)	9155 (54.5)	.07	2481 (55.7)	9034 (54.0)	.04				
> 10 years	1281 (28.6)	4659 (27.7)	.25	1272 (28.6)	4637 (27.7)	.26				
> 15 years	506 (11.3)	1904 (11.3)	.97	519 (11.7)	1915 (11.4)	.71				

Table 2

Univariate and Mulivariate Stepwise Logistic Regression for Stroke at All Time Periods after Zoster

Univariate analyses: Stroke and Zoster		
Time After Index	**OR (95% CI)**	***P*-value**
3 months	1.70 (1.13–2.57)	.01
6 months	1.41 (1–1.98)	.05
1 year	1.14 (0.87–1.48)	.35
3 years	1.12 (0.95–1.33)	.19
Multiviariate Stepwise Logistic Regression Models:		
Variable	**OR (95% CI)**	***P*-value**
Model at 3 months		
Zoster	1.53 (1.01–2.33)	.04
Age vs. age 50–64: age 65–79	3.32 (1.84–5.99)	<.001
age 80+	6.37 (3.49–11.62)	<.001
Arrhythmias	1.74 (1.15–2.65)	.009
Vasculopathy	2.52 (1.24–5.11)	0.01
Model at 6 months		
Zoster	1.28 (0.91–1.8)	.16
Age vs age 50–64: age 65–79	1.77 (1.41–2.23)	<.001
age 80+	1.47 (1.31–1.64)	<.001
Hypertension	1.81 (1.31–2.51)	<.001
Vasculopathy	2.58 (1.47–4.54)	.001
Model at 1 year		
Zoster	1.04 (0.79–1.36)	.79
Age vs age 50–64: age 65–79	1.53 (1.3–1.81)	<.001
age 80+	1.45 (1.33–1.57)	<.001
Hypertension	1.73 (1.34–2.23)	<.001
Coronary artery disease	1.44 (1.09–1.89)	.01
Dyslipidemia	0.66 (0.5– 0.86)	.002
Vasculopathy	3.07 (2–4.7)	<.001
Model at 3 years		
Zoster	1.02 (0.86–1.22)	.81
Age vs age 50–64: age 65–79	1.88 (1.68–2.11)	<.001
age 80+	1.56 (1.47–1.65)	<.001
Sex = Female	0.90 (0.83–0.93)	.008
Hypertension	1.67 (1.41–1.96)	<.001
Coronary artery disease	1.41 (1.17–1.68)	<.001
Dyslipidemia	0.74 (0.62–0.87)	<.001
Depression	1.29 (1.07–1.55)	.009
Vasculopathy	1.68 (1.20–2.36)	.002

Table 3

Univariate and Mutivairate Stepwise Logistic Regression for Myocardial Infarction at All Time Periods after Zoster

Univariate logistic regression: MI and Zoster		
Time after index:	**OR (95% CI)**	**p-value**
3 months	1.88 (1.15–3.08)	.01
6 months	1.63 (1.09–2.42)	.02
1 year	1.49 (1.10–2.00)	.009
3 years	1.29 (1.08–1.56)	.006
Multivariate Stepwise Logistic Regression Models		
Model for 3 months		
Variable	OR (95% CI)	P-value
Zoster	1.68 (1.03–2.75)	.04
Age vs age<65: age 65–79	2.31 (1.19–4.47)	.01
age 80+	3.51 (1.77–6.95)	<.001
Coronary artery disease	4.17 (2.56–6.78)	<.001
Model for 6 months		
Zoster	1.44 (0.97–2.15)	.07
Age vs age<65: age 65–79	2.3 (1.35–3.92)	.002
age 80+	4.02 (2.34–6.9)	<.001
Coronary artery disease	3.55 (2.4–5.25)	<.001
Diabetes	1.62 (1.08–2.43)	.02
Model for 1 year		
Zoster	1.33 (0.99–1.8)	.06
Age vs age<65: age 65–79	2.61 (1.77–3.85)	<.001
age 80+	4.93 (3.31–7.34)	<.001
Sex = Male	1.64 (1.24–2.17)	<.001
Coronary artery disease	2.14 (1.58–2.91)	<.001
Depression	1.43 (1.03–1.98)	.03
Diabetes	1.73 (1.29–2.33)	<.001
Model for 3 years		
Zoster	1.17 (0.97–1.41)	.11
Age vs age<65: age 65–79	2.26 (1.8–2.85)	<.001
age 80+	4.51 (3.56–5.73)	<.001
Sex = Female	1.49 (1.25–1.76)	<.001
Hypertension	1.35 (1.13–1.62)	.001
Coronary artery disease	2.01 (1.66–2.43)	<.001
Diabetes	1.47 (1.21–1.78)	<.001

Table 4

Summary of Studies Assessing risk of stroke or MI after zoster

Author, year, country	Design	Population	Sample size	Stroke/TIA—short-term results	Stroke/TIA—long-term results	MI—short-term results	MI—long-term results
Breuer et al., 2014, UK	Matched cohort—age, sex and practice site Zoster from administrative data Follow-up Mean, 6.8 years (range 1 – 24 years)	All ages, attending GP offices Zoster from administrative data 2002–2010	106,601 cases 213,202 controls Mean age, 57.8 years	NA	Cox proportional hazard ratios **Older (>40 years)** TIA---HR = 1.15 (1.09–1.21) Stroke—not significant **Younger (<40 years)** Stroke---HR 2.42 (1.34–4.36) TIA--- HR 1.49 (1.04–2.15)	NA	Cox proportional hazard ratios **Older (>40 years)** MI---HR = 1.10 (1.05–1.16) **Younger (≤40 years)** MI----HR 1.74 (1.13–2.66)
Kang et al., 2009, Taiwan	Case and control cohorts, age- and sex-matched Zoster from administrative data	Adults 18+ Zoster from administrative data 1997–2001	7,760 cases 23,800 controls Mean age, 46.7 years	Kaplan-Meier and log rank test Stroke and TIA combined **All ages**: Crude--I year HR 1.31 (1.07–1.61) Adjusted--1 year HR 1.31 (1.06–1.60)	NA	NA	NA
Langan et al., 2014, UK	Cohort comparing individual in year before zoster with year after. Zoster from adminis-trative data	Adults 18+ Zoster from administrative data 1987–2012	6,584 eligible cases who served as their own controls Mean age at stroke, 77 years	Conditional Poisson regression, incidence rate ratios (IRR) **All ages:** 1–4 weeks, IRR 1.63 (1.32–2.02) 5–12 weeks, IRR 1.42 (1.21–1.68) 13–26 weeks, IRR 1.23 (1.07–1.42) 27–52 weeks, not significant	NA	NA	NA
Lin et al, 2010, Taiwan	Case and control cohorts, age by decade and sex-matched HZO from medical record review	Adults 18+ Zoster from administrative data 2003–2004	658 cases with HZO 1,974 controls without zoster Mean age 56.9 years	Kaplan-Meier log rank test Stroke **All ages**: Crude HR 5.15 (3.31–8.33) Adjusted HR 4.52 (2.40–11.10)	NA	NA	NA
Sreenivasan et al, 2013, Denmark	Cohort “Exposed” presumed zoster—prescribed antiviral therapy	Adults 18+ Zoster from antiviral proxy 1995– 2008	4.6 million cohort 117, 926 zoster cases Mean age – not reported	Poisson regression incident rate ratios (IRR) **All ages**: 2 weeks IRR, 2.27 (1.83–2.82) [no difference in age groups] 1 year IRR, 1.17 (1.09–1.24) [risk in younger than 40 years—p .0002]	Poisson regression incident rate ratios (IRR): Stroke and TIA combined **All ages**: >1 year IRR, 1.05 (1.02–1.09) [not significant in >60 years]	NA	NA
Yawn et al., 2015, US	Case/control, age-and sex-matched in same geographic area Zoster confirmed by medical records Mean follow-up, 7.1 years (range 0 – 28 years)	Adults 50+ Zoster confirmed by medical records 1986–2010	4,862 zoster cases 19,433 control patients Mean age, 68.1 years	Multivariate logistic regression **≥ 50 years:** 3 months OR 1.53 (1.10–2.33) 6, 9, 12 and 36 months—not significant	Kaplan Meier **≥ 50 years**: HR 1.11 (1.10–1.22) Not significant when accounting for multiple risk factors	Multivariate logistic regression **≥ 50 years**: 3 months 1.68 (1.03–2.75) 6, 9, 12 and 36	Kaplan Meier **≥ 50 years**: HR 1.13 (1.01–1.27) Not significant when accounting for multiple risk factors

Author, year, country	Design	Population	Sample size	Stroke/TIA—short-term results	Stroke/TIA—long-term results	MI—short-term results	MI—long-term results
						months--not significant	