The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Herpes Zoster: Epidemiological Links With Stroke and Myocardial Infarction

Charlotte Warren-Gash

Faculty of Epidemiology and Population Health, London School of Hygiene Tropical Medicine, UK

Routine data from electronic health records (EHRs) provide insights into links between herpes zoster (HZ) and cardiovascular complications such as stroke or myocardial infarction (MI) in different populations worldwide. Evidence from large EHR studies using both self-controlled case series and traditional cohort designs suggests that there is a transient increase in the risk of stroke after HZ, which gradually resolves over 6–12 months. In these studies, herpes zoster ophthalmicus was associated with a higher risk of stroke than HZ at other sites. A larger effect size was seen in people aged under 40 years. Existing studies also suggest that HZ may have a triggering effect on MI, although fewer studies examined this outcome. Further evidence is needed on the effectiveness and cost-effectiveness of vaccine and antiviral drugs to reduce cardiovascular complications after HZ from studies that are designed to minimize selection biases and confounding by indication.

Keywords. herpes zoster; cardiovascular disease; acute myocardial infarction; stroke; meta-analysis; vaccination; antiviral treatment.

Acute infections, such as influenza, can trigger cardiovascular events including stroke and myocardial infarction (MI) [1, 2]. Interest is growing in the effect of persistent reactivating viruses such as varicella zoster virus (VZV) on the pathogenesis of cardiovascular diseases, which are the leading global cause of death. There are biologically plausible mechanisms through which VZV could trigger acute vascular events: inflammatory responses following reactivation of VZV from latency to cause herpes zoster (HZ) may lead to endothelial dysfunction and development of a hypercoagulable state [3]. Pathological vascular remodeling associated with arterial VZV infection (VZV vasculopathy) may also contribute to vascular risk [4]. As the population ages, the burden of disease due to stroke, including disability, illness, and premature death, is projected to double worldwide by 2030 [5]. Understanding the current evidence and its limitations is crucial to inform vaccination and treatment strategies to minimize vascular complications of VZV.

EVIDENCE FOR ASSOCIATION BETWEEN HZ AND VASCULAR COMPLICATIONS

Historically, the ability to investigate relatively rare complications of infections was hampered by lack of power due to small sample sizes. Now, in the era of "big data", with routinely collected electronic health records (EHRs) available for large numbers of patients with clinically diagnosed HZ infections, vascular complications can be investigated in different population subgroups with increasing precision. There remain, however, methodological difficulties with interpreting data robustly from studies with different designs, exposure and outcome definitions, populations, and settings. In the last year, several systematic reviews synthesized evidence of the relationship between HZ and stroke from cohort and self-controlled case series studies [6–11]. Although the pooled effect estimates presented in these reviews vary due to differing methods and inclusion criteria, suggestions from the combined evidence are as follows (Table 1).

HZ Can Trigger Stroke

There is a transient increase in the risk of stroke after HZ, which is highest in the earliest time period after HZ diagnosis – adjusted incidence ratio (IR) for stroke 2.37 (95% confidence interval (CI) 2.17–2.59) up to 1 week after HZ [12] – and gradually diminishes to baseline by around 6–12 months. At 4 weeks, data from 3 powerful self-controlled case series studies using primary care EHRs from the United States, United Kingdom, and Germany, show a pooled IR for stroke of 1.55 (95% CI, 1.46–1.65) [12–14]. These studies have the major benefit of implicitly controlling for fixed between-person confounding effects [15]. The findings are corroborated by several prospective cohort studies using data from Asian, European, and US populations, which show a similar gradient of stroke risk up to 1 year [16–21]. Evidence for any longer-term effect of HZ on vascular risk is mixed, with marked heterogeneity between studies. A meta-analysis of 4 cohort studies using random effects found no association between HZ and stroke after 1 year: pooled odds ratio (OR) 1.20 (95% CI, 0.82–1.75) [11].

Correspondence: C. Warren-Gash, PhD, Room 248c, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (charlotte.warren-gash1@lshtm.ac.uk).

The Journal of Infectious Diseases® 2018;218(S2):S102–6

DOI: 10.1093/infdis/jiy385

Table 1. Study Characteristics and Main Results

Author (y)	Setting	Study Design and Period	Population	Exposure(s)	Outcome(s)	Effect of HZ on Stroke, Adjusted Effect Measure (95% CI)	Effect of HZ on MI, Adjusted Effect Measure (95% CI)
Minassian (2015) [12]	United States, Medicare claims data	Self-controlled case series, 2006–2011	Patients (≥65 y) with HZ and stroke/TIA Excluded if had HZ or vascular events preentry or SAH ever or encephalitis in 12 mo poststroke	HZ episode: I CD-9 code with antiviral 7 d before or after HZ Exposed period to 12 mo after HZ (wk 1, wk 2–4, 5–12, 13–26, 27–52)	Primary: (1) ischaemic stroke, (2) MI Secondary: hemorrhagic stroke (ICD-9 codes)	wk 1: IR 2.37 (2.17–2.59) wk 2–4: IR 1.55 (1.46–1.66) wk 5–12: IR 1.17 (1.11–1.22) wk 13–26: IR 1.03 (0.99–1.07) wk 27–52: IR 1.00 (0.96–1.03)	wk 1: IR 1.68 (1.47–1.92) wk 2–4: IR 1.25 (1.14–1.37) wk 5–12: IR 1.07 (1.00–1.14) wk 13–26: IR 1.02 (0.96–1.07) wk 27–52: IR 1.02 (0.98–1.07)
Langan (2014) [13]	UK, primary care records from CPRD linked to secondary care records from HES	Self-controlled case series, 1987–2012	Adults (≥18 y) with 1st ever HZ and stroke Exclusions: incident TIA, SAH, encephalitis in 12 mo after stroke	First ever HZ: Read and ICD-10 codes Exposed period from day after HZ to 12 mo (wk 1–4, 5–12, 13–26, 27–52)	Primary: arterial stroke Secondary: cerebral infarction, hemorrhagic, or unspecified stroke (Read and ICD-10 codes)	wk 1–4: IR 1.63 (1.32–2.02) wk 5–12: IR 1.42 (1.21–1.68) wk 13–26: IR 1.23 (1.07–1.42) wk 27–52: IR 0.99 (0.88–1.12)	…
Schink (2016) [14]	Germany, health claims from 4 insurance providers, hospitalizations, and outpatients data	Self-controlled case series, 2004–2011	Patients (any age) with HZ and stroke, ≥12 mo follow-up, no history of HZ or stroke in 12 mo before cohort entry	First or recurrent HZ: ICD-10 code or antiviral with HZ outpatient diagnosis Exposed period to 12 mo after HZ (0–2 wk, 3–4 wk, 2–3 mo, 4–6 mo, 7–12 mo)	Primary: first stroke Secondary: ischaemic, hemorrhagic, unspecified type of stroke or TIA (ICD-10 codes for main discharge diagnosis in hospital record)	<2 wk: IRR 1.30 (1.00–1.68) wk 3–4: IRR 1.52 (1.20–1.91) mo2–3: IRR 1.24 (1.08–1.42) mo 4–6: IRR 1.09 (0.97–1.24) mo 7–12: IRR 0.96 (0.87–1.06)	…
Sreenivasan (2013) [16]	Denmark, routinely collected civil registration data and health registers	Cohort, 1995–2008	All Danish adults (≥18 y) alive during study period Persons with outcome before start of follow-up excluded	HZ treated with antivirals: acyclovir prescription (800 mg in packages of 35 tablets)	Stroke or TIA, composite outcome (ICD-8 and 10 codes from National Patient Registry)	<14 d since HZ: IRR 2.27 (1.83–2.82) 14 d–1 y: IRR 1.17 (1.09–1.24) >1 y: IRR 1.05 (1.02–1.09)	…
Sundström (2015) [17]	Sweden, routinely collected health data from 1 county	Cohort, 2008–2010	All incident cases of HZ occurring within the study period in this region No age restriction	HZ from ICD-10 diagnosis codes with no history of HZ in the previous year	Stroke (ICD-10 diagnosis within 1 y of HZ)	IRR 1.34 (1.12–1.62)	…

Table 1. *Continued*

Author (y)	Setting	Study Design and Period	Population	Exposure(s)	Outcome(s)	Effect of HZ on Stroke, Adjusted Effect Measure (95% CI)	Effect of HZ on MI, Adjusted Effect Measure (95% CI)
Yawn (2016) [18]	United States, medical records from Olmsted County	Cohort, 1986–2011	All adults (≥50 y) with HZ matched by sex and age ± 1 y to adults without HZ Patients with history of stroke excluded	First or recurrent HZ: ICD-9 code and HZ clinical symptoms in medical records	(1) Stroke, (2) MI (diagnostic codes from hospital admissions or death records, <30 days before cohort entry or until cohort exit)	3 mo: OR 1.53 (1.01–2.33) 6 mo: OR 1.28 (0.91–1.80) 1 y: OR 1.04 (0.79–1.36) 3 y: OR 1.02 (0.86–1.22)	3 mo: OR 1.68 (1.03–2.75) 6 mo: OR 1.44 (0.97–2.15) 1 y: OR 1.33 (0.99–1.80) 3 y: OR 1.17 (0.97–1.41)
Calabrese (2017) [19]	United States, Medicare claims data	Cohort, 2006–2013	Adults (≥65 y) with HZ, ≥12 mo follow-up at entry, inflammatory disease (AS/ IBD/ psoriasis/ psoriatic arthritis/ RA), no prior stroke or antiviral therapy	Inpatient or outpatient diagnosis of HZ: ICD-9 diagnosis code and no same day code for zoster vaccine	Primary: any stroke (ICD-9 diagnosis code in any position on hospital claim) Secondary: ischaemic stroke	0–90 days: IRR 1.36 (1.10–1.68) 91–365 days: IRR 1.18 (1.00–1.40) Baseline: 366–730 days	…
Kang (2009) [20]	Taiwan, National Health Research Institute claims database	Cohort, 1997–2001	Adults (≥18 y) with HZ and no history of stroke matched by age/sex to 3 patients with no history of HZ or stroke before 2001	Treatment for HZ in ambulatory care: ICD-9 codes	Primary: stroke, any Secondary: ischaemic or hemorrhagic stroke (ICD-9 codes)	Risk of stroke during the 1-y follow-up period: HR 1.31 (1.06–1.60)	…
Lin (2010) [21]	Taiwan, National Health Research Institute claims database	Cohort, 2003–2005	Immunocompetent adults (≥18 y) with HZO, matched by age/sex to 3 patients without HZO Those with stroke prior to entry excluded	Ambulatory care for HZO: ICD-9 code (Patients with HZO in previous year excluded)	Stroke, definition unspecified (likely ICD-9 codes)	HR 4.52 (2.45–8.33)	…
Breuer (2014) [22]	UK, primary care records from THIN	Cohort, 2002–2010	Adults (≥18 y) with HZ; age (±2 y), sex and practice matched adults with no HZ	Nonrecurrent HZ: Read codes	Primary: (1) first incident stroke or TIA, (2) MI Secondary: stroke type (Read codes)	Stroke: HR 1.02 (0.98–1.07) TIA: HR 1.15 (1.09–1.21)	MI: HR 1.10 (1.05–1.16)
Kwon (2016) [23]	Korea, 1 million sample of national health insurance database	Cohort, 2003–2013	All patients (>18 y) in database: those with HZ or stroke during 1st year of observation period excluded	First HZ in observation period: ICD-10 codes	First stroke or TIA (ICD-10 codes)	18–30 y: HR 1.52 (1.26–1.83) 30–40 y: HR 1.34 (1.19–1.51) 40–50 y: HR 1.19 (1.12–1.29) 50–60 y: HR 1.12 (1.06–1.19) 60–70 y: HR 1.14 (1.08–1.20) >70 y: HR 1.14 (1.06–1.23)	…
Wang (2014) [24]	Taiwan, National Health Research Institute claims database	Cohort, 1999–2010	Patients (age not stated) with HZ and no history of acute coronary syndrome matched by age, sex, and year to 4 patients without HZ	Incident HZ: ICD-9 code	Incident ACS (ICD-9 codes)	…	HR 1.15 (1.07–1.24)

Abbreviations: ACS, acute coronary syndrome; AS, ankylosing spondylitis; CI, confidence interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HR, hazard ratio; HZ, herpes zoster; HZO, herpes zoster ophthalmicus; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; IR, incidence ratio; IRR, incidence rate ratio; MI, myocardial infarction; OR, odds ratio; RA, rheumatoid arthritis; SAH, subarachnoid hemorrhage; THIN, The Health Improvement Network; TIA, transient ischaemic attack.

Herpes Zoster Ophthalmicus Leads to a Higher Risk of Stroke Than HZ at Other Sites

Point estimates for the effect of herpes zoster ophthalmicus (HZO) on stroke are generally higher than those for HZ at other or unspecified sites. HZO refers to reactivation of VZV in the first division of the trigeminal nerve, and it has been proposed that the proximity of the trigeminal ganglion to cerebral arteries may increase these patients' susceptibility to large-vessel stroke [11]. However, many EHR studies do not specify zoster site, which is likely to lead to underestimation of effect because some HZ at unclassified sites could actually be HZO. The stronger effect for HZO was noted in 2 self-controlled case series studies that stratified by HZ site [12, 13] as well as 2 Asian cohort studies [20, 21]. A further study found no effect of HZ site on long-term stroke risk, although few participants had HZO records [22].

Stroke Risk May Be Highest for Younger People With HZ

Intriguing evidence suggests a more marked effect in younger people. Point estimates for the effect of HZ on stroke are highest for younger people, aged less than 40 years, although the relatively small numbers of strokes in this age group mean that confidence intervals tend to overlap with those for older ages. Of 5 cohort studies that stratified by age, 4 found a greater effect in younger age groups [16, 17, 22, 23] and 1 study showed no difference in effect size by age [20].

HZ Can Trigger Myocardial Infarction

One self-controlled case series study using US Medicare data [12] showed a similar though smaller transient triggering effect of HZ on MI for week 1 after HZ: IR 1.68 (95% CI, 1.47–1.92). An elevated risk of acute coronary syndrome (ACS) or MI up to 3 months after HZ was also suggested by combined results from 2 prospective population cohort studies from the United States [18] and Taiwan [24]: pooled OR 1.34 (95% CI, 0.98–1.82) [11], although this just failed to reach statistical significance in a random effects model. The Taiwanese study also showed a small increase in ACS risk associated with HZ in follow-up to 12 years (HR 1.10; 95% CI, 1.02 to 1.19) [24], which was mirrored in a cohort using UK primary care data with follow-up to 24 years [22].

EFFECT OF HZ PREVENTION ON VASCULAR COMPLICATIONS

It seems plausible that reducing HZ incidence and severity through vaccination is likely to result in fewer vascular complications. A single dose of the live attenuated zoster vaccine (Zostavax) reduces herpes zoster incidence by around 50% [25]. However, at present, evidence of direct cardiovascular benefit from the live attenuated zoster vaccine is lacking; in the Shingles Prevention Study, rates of serious adverse events, including MI and stroke, were the same in recipients of vaccine and placebo but follow-up was short (to 42 days) and the trial was not powered for these endpoints [25]. Observational safety studies have also shown no effect of Zostavax on stroke risk in follow-up to 5–6 weeks [26, 27], although longer-term follow-up is needed to assess fully the vaccine's effectiveness against vascular outcomes. The recent development of the highly efficacious subunit vaccine HZ/su (Shingrix), which reduces HZ incidence by 90% after 2 doses in older adults [28], has potential for major impact on VZV disease burden, including vascular complications, in settings achieving good vaccine uptake. A recent modeling study based on RCT data showed that Shingrix, at a price of $280 for 2 doses, was more cost-effective than Zostavax (current price $213 per dose) [29].

EFFECT OF HZ TREATMENT ON VASCULAR COMPLICATIONS

It remains uncertain whether antiviral agents used to treat HZ alter the risk of vascular events; results from 1 cohort study [19] and 1 self-controlled case series study [13] suggest that patients receiving antivirals may have a lower stroke risk than patients not taking antivirals, especially earlier after HZ diagnosis. Another cohort study, however, found no difference in stroke risk at 1 year between those who did and did not receive antivirals for HZO [21], although data on timing and duration of treatment were unavailable in that study and it was difficult to exclude confounding by indication – the situation in which patients who were more unwell and had a higher risk of vascular complications preferentially received antiviral treatment.

CONCLUSIONS

In future, our ability to prevent HZ-induced vascular events will depend upon improving the understanding of the nature of risk, including any effects of subclinical VZV reactivation or long-term effects. Large-scale population-based studies to identify the characteristics of affected patients will help to guide intervention targeting. Adequately powered studies of HZ prevention and treatment strategies against specific vascular endpoints are needed, which are carefully designed to avoid selection biases and confounding by indication. As the evidence base develops, it will be important to (re)assess the cost-effectiveness of policy options such as introducing universal varicella vaccination in countries where it is not routine, for example in Northern Europe, or expanding recommendations for zoster vaccination to include younger age groups at high cardiovascular risk.

Notes

Financial support. This work was supported by a Wellcome Intermediate Clinical Fellowship (grant number 201440/Z/16/Z).

Potential conflicts of interest. Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Supplement sponsorship. This work is part of a supplement sponsored by the Royal Society of Medicine (Royal Charter number RC000525)

funded through unrestricted educational grants from Merck, Sanofi Pasteur MSD, The Research Foundation for Microbial Diseases of Osaka University, Seqirus and GlaxoSmithKline.

References

1. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. Lancet Infect Dis **2009**; 9:601–10.
2. Kwok CS, Aslam S, Kontopantelis E, et al. Influenza, influenza-like symptoms and their association with cardiovascular risks: a systematic review and meta-analysis of observational studies. Int J Clin Pract **2015**; 69:928–37.
3. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. Lancet Infect Dis **2010**; 10:83–92.
4. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol **2009**; 8:731–40.
5. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. **2016**; 15:913–24.
6. Yang SY, Li HX, Yi XH, et al. Risk of stroke in patients with herpes zoster: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis **2017**; 26:301–7.
7. Liu X, Guan Y, Hou L, et al. The short- and long-term risk of stroke after herpes zoster: a meta-analysis. PLoS One **2016**; 11:e0165203.
8. Zhang Y, Luo G, Huang Y, Yu Q, Wang L, Li K. Risk of stroke/transient ischemic attack or myocardial infarction with herpes zoster: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis **2017**; 26:1807–16.
9. Marra F, Ruckenstein J, Richardson K. A meta-analysis of stroke risk following herpes zoster infection. BMC Infect Dis **2017**; 17:198.
10. Lian Y, Zhu Y, Tang F, Yang B, Duan R. Herpes zoster and the risk of ischemic and hemorrhagic stroke: a systematic review and meta-analysis. PLoS One **2017**; 12:e0171182.
11. Erskine N, Tran H, Levin L, et al. A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. PLoS One **2017**; 12:e0181565.
12. Minassian C, Thomas SL, Smeeth L, Douglas I, Brauer R, Langan SM. Acute Cardiovascular events after herpes zoster: a self-controlled case series analysis in vaccinated and unvaccinated older residents of the United States. PLoS Med **2015**; 12:e1001919.
13. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. Clin Infect Dis **2014**; 58:1497–503.
14. Schink T, Behr S, Thöne K, Bricout H, Garbe E. Risk of stroke after herpes zoster - evidence from a German self-controlled case-series study. PLoS One **2016**; 11:e0166554.
15. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res **2009**; 18:7–26.
16. Sreenivasan N, Basit S, Wohlfahrt J, et al. The short- and long-term risk of stroke after herpes zoster - a nationwide population-based cohort study. PLoS One **2013**; 8:e69156.
17. Sundström K, Weibull CE, Söderberg-Löfdal K, Bergström T, Sparén P, Arnheim-Dahlström L. Incidence of herpes zoster and associated events including stroke–a population-based cohort study. BMC Infect Dis **2015**; 15:488.
18. Yawn BP, Wollan PC, Nagel MA, Gilden D. Risk of stroke and myocardial infarction after herpes zoster in older adults in a US community population. Mayo Clin Proc **2016**; 91:33–44.
19. Calabrese LH, Xie F, Yun H, et al. Herpes zoster and the risk of stroke in patients with autoimmune diseases. Arthritis Rheumatol **2017**; 69:439–46.
20. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. Stroke **2009**; 40:3443–8.
21. Lin HC, Chien CW, Ho JD. Herpes zoster ophthalmicus and the risk of stroke: a population-based follow-up study. Neurology **2010**; 74:792–7.
22. Breuer J, Pacou M, Gauthier A, Brown MM. Herpes zoster as a risk factor for stroke and TIA: a retrospective cohort study in the UK. Neurology **2014**; 82:206–12.
23. Kwon SU, Yun SC, Kim MC, et al. Risk of stroke and transient ischaemic attack after herpes zoster. Clin Microbiol Infect **2016**; 22:542–8.
24. Wang CC, Lin CL, Chang YJ, Wang GJ, Sung FC, Kao CH. Herpes zoster infection associated with acute coronary syndrome: a population-based retrospective cohort study. Br J Dermatol **2014**; 170:1122–9.
25. Oxman MN, Levin MJ, Johnson GR, et al.; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med **2005**; 352:2271–84.
26. Baxter R, Tran TN, Hansen J, et al. Safety of Zostavax™–a cohort study in a managed care organization. Vaccine **2012**; 30:6636–41.
27. Tseng HF, Liu A, Sy L, et al.; Vaccine Safety Datalink (VSD) Team. Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. J Intern Med **2012**; 271:510–20.
28. Cunningham AL, Lal H, Kovac M, et al.; ZOE-70 Study Group. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med **2016**; 375:1019–32.
29. Le P, Rothberg MB. Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine in older adults. JAMA Intern Med **2018**; 178:248–58.