Risk of, and risk factors for, vasculopathy associated with acute herpes zoster

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Objectives: We aimed to summarize the known risk of vasculopathy (stroke, myocardial infarction [MI], and transient ischemic attack [TIA]) after herpes zoster (HZ) and the impact of antiviral treatment and vaccination against HZ on the risk of vasculopathy. *Materials and methods:* A narrative literature review was conducted in PubMed to identify evidence published in the past 15 years that was relevant to the scope of this article. *Results:* Ten studies reported that HZ was associated with an increased risk of stroke and one UK study reported no association. Four studies reported that HZ was associated with an increased risk of MI, and four reported that HZ was associated with an increased risk of TIA. Two studies reported that antiviral treatment was associated with a reduced risk of stroke and an additional two studies reported no association between antiviral treatment and the risk of stroke. In addition, two studies reported that vaccination against HZ using the live zoster vaccine (ZVL) was associated with a reduced risk of stroke, and an additional two studies reported that the risk of stroke or MI after HZ was similar between ZVL vaccinated and unvaccinated individuals. *Conclusions:* HZ is associated with an increased risk of stroke, MI, or TIA (strongest association is between HZ and stroke). Further studies are needed to determine whether antiviral treatment or ZVL vaccination influence the risk of HZ-associated vasculopathy. In addition, the effect of the recombinant zoster vaccine on the risk of HZ-associated vasculopathy should be studied.

Keywords: Herpes zoster—Shingles—Vasculopathy—Myocardial infarction—Transient ischemic attack—Stroke—Antiviral treatment—Vaccination

Pathophysiology of herpes zoster-associated vasculopathy

Primary infection with varicella zoster virus (VZV) results in chickenpox, which is typically self-limiting.[1] After the primary infection resolves, VZV enters a lifelong latent phase during which it resides in sensory ganglia.[1] Subsequent reactivation of latent VZV can occur during a decline in cell-mediated immunity; major risk factors for reactivation are older age and immunosuppression.[1,2] Peripheral propagation of reactivated VZV results in herpes zoster (HZ), a painful unilateral vesicular eruption with a typical dermatomal distribution.[1,3]

HZ is associated with a range of vasculopathies such as ischemic stroke, aneurysm, cerebral and subarachnoid hemorrhage, monocular loss of vision, arterial dissection, peripheral arterial disease, myocardial infarction (MI), and transient ischemic attack (TIA).[2-6] The biological

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mechanisms that give rise to these diverse phenomena are likely multifactorial. VZV in the sensory ganglia may travel transaxonally to cerebral arteries, where nerves terminate in the adventitia, and to coronary arteries.[7,8] These mechanisms may result in inflammation and pathological vascular remodeling, leading to the development of vasculopathies. Other factors that may contribute to an elevated risk of vasculopathy include increased sympathetic tone and blood pressure, and altered immunological status.[9]

A post-mortem analysis of a patient who experienced fatal vasculitis involving the central nervous system found that his cerebral arteries contained VZV DNA and VZV-specific antigen, supporting the hypothesis that his vasculitis was caused by VZV.[10] The question whether VZV triggers giant cell arteritis is controversial, with some biopsy studies suggesting that reactivated VZV is associated with the condition[11] and others suggesting that it is not.[12,13]

Humans are the only natural host for VZV, which has hampered attempts to understand the pathophysiology of VZV-associated vasculopathy.[3] Based on studies conducted in animals, it is presumed that afferent fibers connected to intracranial and extracranial blood vessels provide an anatomical pathway for the spread of VZV after reactivation in the ganglia.[2,14-16]

We conducted a narrative literature review in PubMed to identify evidence published in the past 15 years on the risk of vasculopathy (stroke, MI, and TIA) after HZ and the impact on the risk of vasculopathy of antiviral treatment and vaccination against HZ.

Association between herpes zoster and the risk of vasculopathy

Population-based studies suggest that HZ-associated vasculopathy is associated with a broad spectrum of clinical events, such as TIA, ischemic and hemorrhagic stroke, and MI.[9,17-24] Moreover, the results of these studies suggest a strong temporal association between the onset of HZ and the occurrence of HZ-associated vasculopathy. The strength and significance of these relationships vary with the size of the study and the population studied. The designs of the studies, including matching of controls, outcomes of interest, and follow-up period after onset of HZ, were heterogenous [**Table S1; Table S2**].

A community cohort study (January 1, 1986−October 1, 2011) of 4862 adults aged ≥50 years with HZ in Olmsted County, Minnesota, USA, matched with 19,433 adults with no history of HZ, used detailed medical record review and demonstrated that HZ was associated with an increased risk of stroke 3 months after HZ when controlling for multiple risk factors (odds ratio 1.53 [95% confidence interval (CI), 1.01−2.33; p=0.04]).[8] This study also assessed the risk of MI after HZ, but the association at 3 months was not robust across analytic methods.[8] HZ was not associated with an increased risk of stroke or MI at any time after 3 months.[8]

A nationwide, retrospective cohort study in Taiwan used administrative data and showed a significant increase in the incidence of stroke up to 1 year after the onset of acute HZ (adjusted hazard ratio [HR] 1.31 [95% CI, 1.06−1.60]), with an even greater increase after HZ ophthalmicus (adjusted HR 4.28 [95% CI, 2.01−9.03]) [**Fig. 1; Table S1**].[17] The study cohort comprised 7760 adult patients aged ≥18 years who visited an ambulatory care center in Taiwan for treatment of HZ over a 5-year period (1997−2001) and the control cohort comprised 23,280 control subjects with no history of HZ treatment or stroke.

Subsequently, an analysis of administrative data collected between 2002 and 2013 in Korea showed that patients with HZ (N=23,213) had a significantly higher risk of a composite cardiovascular endpoint (stroke and acute MI; HR 1.41 [95% CI, 1.25−1.59]), individual risk of stroke (HR 1.35 [95% CI, 1.18−1.54]), and risk of acute MI (HR 1.59 [95% CI, 1.27−2.01]) compared with a group that did not have HZ [**Fig. 1; Table S1**].[9] The relative risk (RR) of stroke, but not MI, was highest in patients aged <40 years who had experienced HZ (HR 3.74 [95% CI, 1.51−9.25; p=0.004] compared with a control group) and decreased with age.[9] Risk factors for stroke and MI (i.e., older age, hypertension, diabetes, dyslipidemia, angina pectoris, peripheral vascular disease, rheumatoid disease, and malignancy) were more common in patients with HZ; however, propensity score matching was used to control for differences between cases and controls.

Other retrospective cohort studies have also reported an increased RR of vasculopathy after HZ in patients aged ≤40 years. A retrospective cohort study of 319,803 patients recorded in the UK general practice database showed that the risk of TIA and MI, but not stroke, was significantly increased in adult patients with HZ [**Fig. 1; Table S1**].[18] Among patients aged ≤40 years the RR of TIA, stroke, and MI after onset of HZ was higher than in the overall population despite much lower event rates.[18] Similarly, a Swedish cohort study showed that the risk of stroke was elevated in patients with HZ (N=13,269), especially in the first year after onset, and that the RR of stroke was highest in patients aged ≤40 years.[21] Another Korean analysis showed that HZ was associated with an increased risk of TIA or stroke and that the RR was highest in those aged 18−30 years and decreased with age.[22] Finally, an analysis of a US insurance claims database showed that HZ was associated with an increased risk of TIA in adults, which was most marked in those aged 18−49 years.[25] Overall, the reduced presence, recording, and monitoring of other vascular risk factors in patients aged <50 years might confound the reported associations. Nevertheless, these data highlight that HZ might be linked with vasculopathy in adults of all ages and,

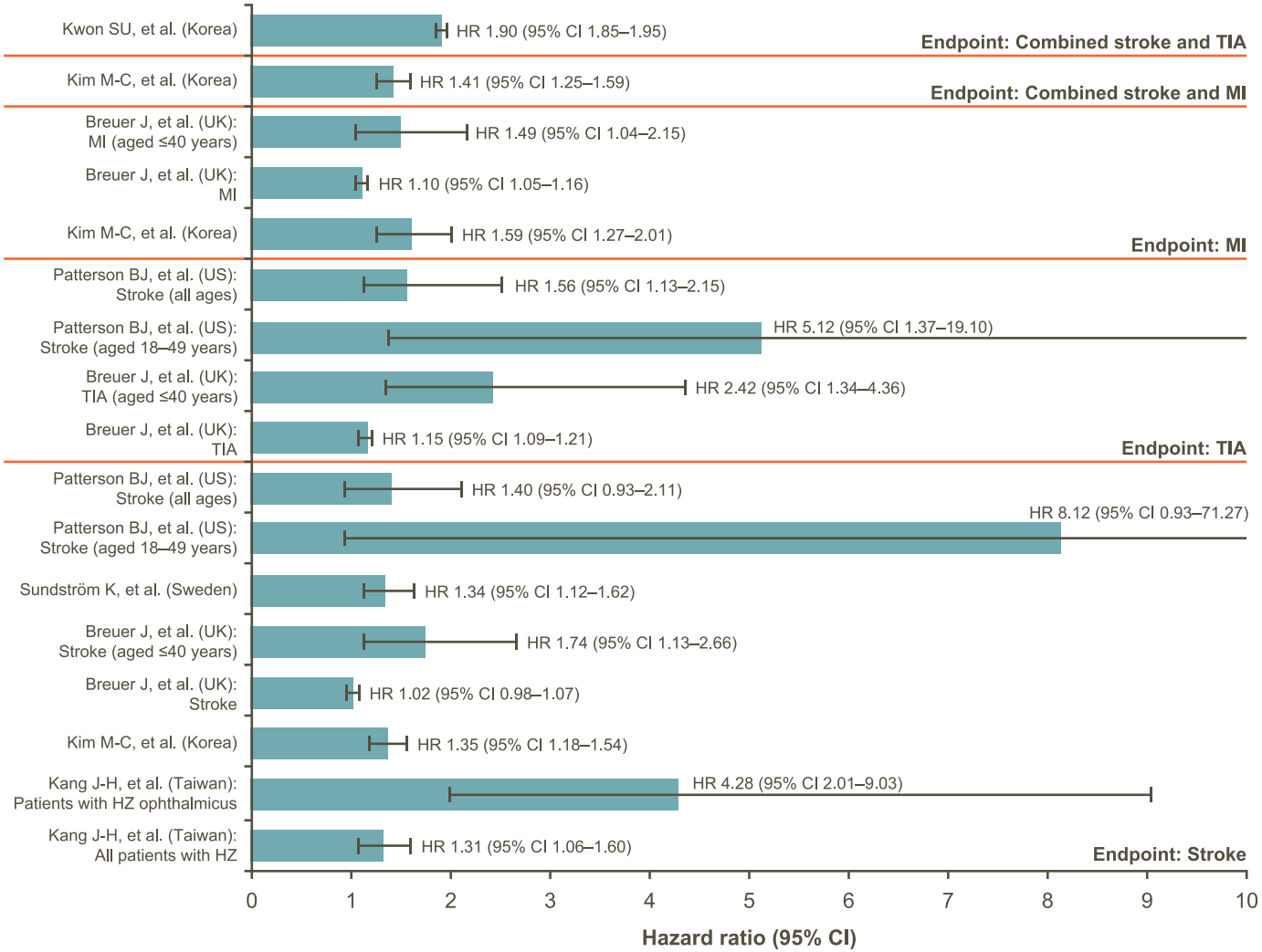

Fig. 1. *Retrospective cohort studies that have investigated associations between herpes zoster and vasculopathies*
CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; MI, myocardial infarction; TIA, transient ischemic attack.

therefore, the potential risk should not be disregarded in younger populations.

Associations between HZ and vasculopathy have been explored in several self-controlled case series [**Fig. 2; Table S2**].[19,20,23,24] With this method, the risk of an event of interest, for example stroke, is compared during different time periods for an individual.[26] This method has the advantage of controlling for fixed confounders, because patients act as their own controls, and can provide estimates of event rates during different periods and show how the risk of an event evolves over time.[26]

A self-controlled case series that included data from the Clinical Practice Research Datalink in the UK showed a higher risk of stroke after HZ, with an even greater risk in patients who experienced HZ ophthalmicus.[19] The risk was greatest in the first 4 weeks following the onset of HZ (age-adjusted incidence rate 1.63 [95% CI, 1.32−2.02] vs baseline), after which the risk of stroke diminished over a 6-month follow-up period.[19] For patients with HZ ophthalmicus, the greatest risk of developing vasculopathy was observed 5−12 weeks after onset of HZ (incidence rate ratio (IRR) 3.38 [95% CI, 2.18−5.24]).[19] This analysis included 6584 adults aged ≥18 years with HZ and stroke and excluded patients with TIA or subarachnoid hemorrhage.[19] Most strokes (60%) were coded as unspecified and only a small proportion (6%) were hemorrhagic, so it was not possible to provide precise estimates by stroke type.

A large, German, self-controlled case series that included data from 6035 patients from the German

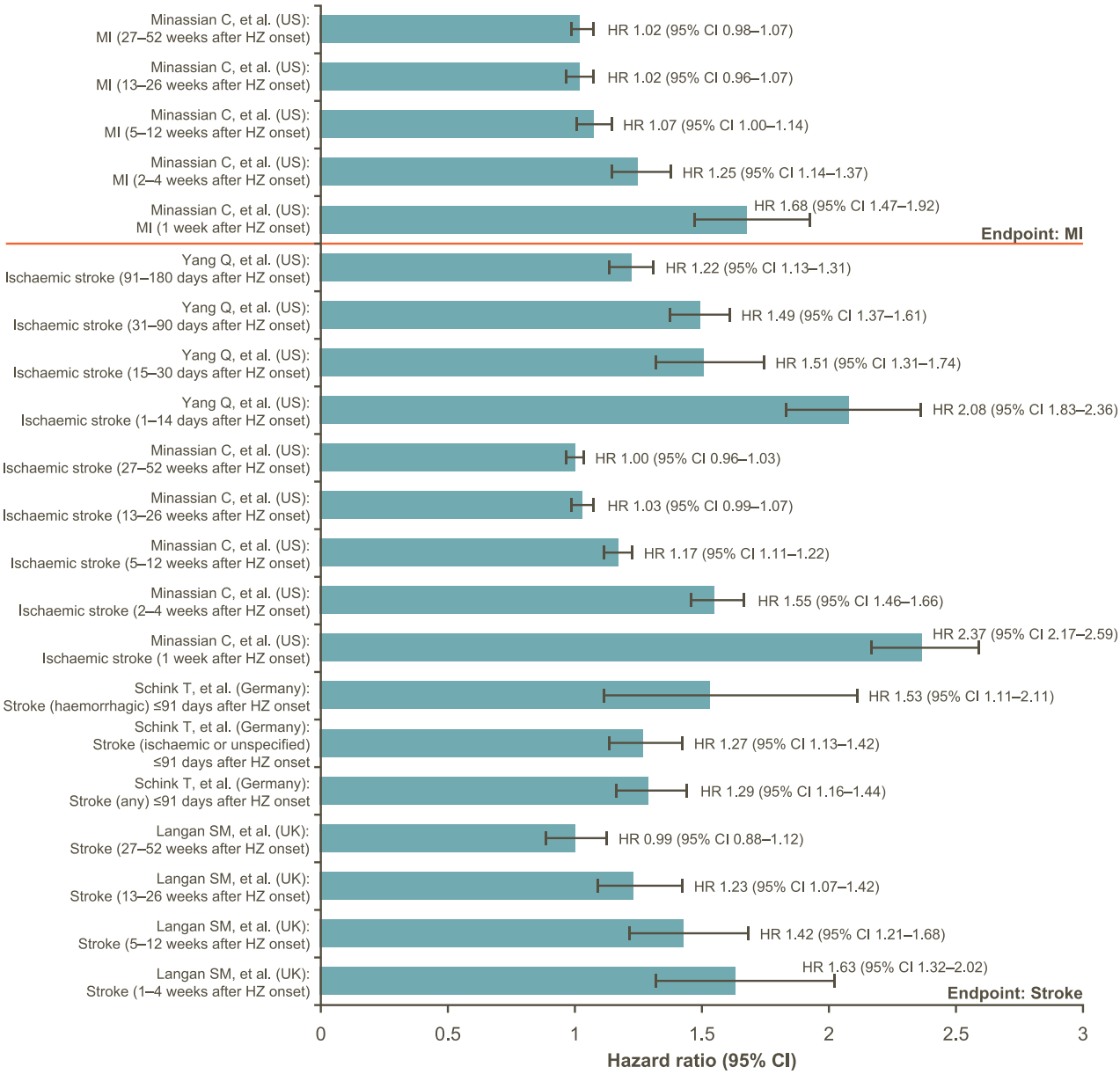

Fig. 2. *Self-controlled case series that have evaluated associations between herpes zoster and vasculopathies*
CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; MI, myocardial infarction; TIA, transient ischemic attack.

Pharmacoepidemiological Research Database who had been hospitalized for stroke and diagnosed with HZ showed that the risk of stroke (hemorrhagic, ischemic, or unspecified) was significantly increased 3 months after the occurrence of HZ when compared with control periods (IRR 1.29 [95% CI, 1.16−1.44]).[23] The risk of hemorrhagic stroke (IRR 1.53 [95% CI, 1.11−2.11]) was higher than the risk of ischemic stroke (IRR 1.27 [95% CI, 1.13−1.42]), although there were considerably fewer hemorrhagic strokes (n=42) than ischemic strokes (n=310).[23] A similar trend was observed in patients who experienced HZ ophthalmicus, although the overall number of patients in this subgroup was low (n=31).[23] The analysis, which was restricted to a 91-day period after the onset of HZ, showed that the risk of stroke was highest in the first 3 to 4 weeks after the onset of HZ and decreased thereafter.

Two self-controlled case series have been conducted using data from Medicare beneficiaries in the USA.[20,24] These analyses were restricted to patients aged ≥65 years. The first of these used data collected between 2006 and 2011 and showed a significant increase in the risk of TIA/ischemic stroke and MI in the 3 months after the onset of HZ.[20] The risk was greatest during the first week after HZ onset (IRR for ischemic stroke during week 1: 2.37 [95% CI, 2.17−2.59]; IRR for MI during week 1: 1.68 [95% CI, 1.47−1.92]).[20] A more recent analysis that included data collected from 87,405 Medicare beneficiaries between 2008 and 2017 showed that the risk of acute ischemic stroke was significantly increased over the 6 months following the onset of HZ.[24] The risk of acute ischemic stroke was highest in the 2 weeks following the onset of HZ (IRR 1.89 [95% CI, 1.77−2.02]), and diminished thereafter but remained elevated between 91 and 180 days after the onset of HZ (IRR 1.19 [95% CI, 1.15−1.23]).[24]

A meta-analysis of 11 studies that included data from more than four million participants with follow-up periods of 1−12.5 years after the onset of HZ showed that the risk of stroke or TIA was elevated after onset of HZ (pooled RR 1.3 [95% CI, 1.17−1.46]) or HZ ophthalmicus (pooled RR 1.91 [95% CI, 1.32−2.76]),[27] and that the risk of MI was elevated after onset of HZ (pooled RR 1.18 [95% CI, 1.07−1.30]).[27] The risk of vasculopathy was highest in the first month (RR 1.92 [95% CI, 1.47−2.51]) and remained elevated 1−3 months after onset of HZ (RR 1.27 [95% CI, 1.05−1.53]).[27] The RR of stroke was highest in patients aged <40 years (pooled RR 2.03 [95% CI, 1.64−2.51]).[27]

Vasculopathy after HZ has also been demonstrated in a pharmacoepidemiological study. A nationwide analysis of data collected between 1995 and 2008 showed that 117,926 Danish patients who were prescribed the HZ-specific dosage of acyclovir (800 mg five times a day for 7 days) had a higher incidence of stroke than those who had not received antiviral treatment.[28] Moreover, the association between antiviral treatment and stroke was strongest during the first 14 days after the onset of HZ.[28] However, this study was limited by the use of acyclovir as a marker for HZ, which might have resulted in false positives as some patients might have received acyclovir for the treatment of herpes simplex virus.[28] To minimize this potential bias, only patients who received the recommended acyclovir regimen for HZ (800 mg five times a day for 7 days; 35 tablets) were included.

Effect of antiviral treatment on vasculopathy after herpes zoster

The impact of antiviral treatment on vasculopathy after HZ has not been examined in large, randomized studies. However, timely antiviral treatment (<72 hours after onset of rash) has been shown to decrease the duration of rash and the severity of pain associated with rash.[29]

In a self-controlled case series that included data from 6584 patients in a UK database, absence of antiviral treatment was associated with a higher incidence of stroke in patients with HZ.[19] This effect was magnified in patients with HZ ophthalmicus who had not received antiviral treatment, among whom there was a greater than fivefold increase in the rate of stroke during weeks 5 to 12 after the onset of HZ.[19] The study did not specify why some patients did not receive antiviral treatment for HZ, but did note that the antiviral prescription rate in this study was consistent with previous studies.[19] In addition, the authors noted that antiviral treatment would be expected to have an even greater effect on the risk of stroke after HZ than demonstrated in this study, as patients who received antiviral treatment were likely to have had more severe disease compared with patients who did not receive antiviral treatment.[19] Further, the authors noted that antiviral treatment is associated with reduced acute pain and HZ severity, accelerated healing, and may reduce post-herpetic neuralgia.[19] Therefore, antiviral treatment may reduce the risk of vasculopathies after HZ by reducing inflammation.[19] In a retrospective cohort study of 43,527 patients (mean age of 71 years) with autoimmune diseases and HZ in the Medicare claims database, antiviral treatment was associated with a reduced incidence of stroke (IRR 0.83 [95% CI, 0.70−0.98]).[30]

In contrast, a population-based study in Taiwan showed that antiviral therapy had no impact on the incidence of stroke in patients with HZ ophthalmicus.[31] The study used data from the 2003−2005 National Health Insurance Research Database and analyzed the effect of antiviral therapy in 658 patients. In the study, it was not specified why some patients did not receive antiviral treatment for HZ.[31] In addition, a self-controlled case series of 87,405 Medicare beneficiaries aged ≥66 years with HZ demonstrated that antiviral treatment had no impact on the risk of acute ischemic stroke.[24]

A meta-analysis that included six studies of the impact of antiviral treatment on the risk of vasculopathy after HZ

showed that the risk of stroke was marginally higher after HZ in patients who had not received antiviral treatment (RR 1.38 [95% CI, 1.06−1.80]) compared with those who had received antiviral treatment (RR 1.17 [95% CI, 1.08−1.27]).[27] However, the authors noted that patients who received antiviral treatment were more likely to have severe disease, which may have confounded the outcome and reduced the apparent benefit of antiviral treatment.[27]

Further studies are needed to fully elucidate the effect of antiviral treatment on the risk of developing HZ-associated vasculopathy.

Effect of vaccination on herpes zoster-associated vasculopathy

The limited available literature points towards an association between HZ vaccination and lower risk of vasculopathy.

In two studies of US Medicare beneficiaries who had HZ, the risk of acute ischemic stroke or MI after HZ seemed to be similar between individuals with HZ regardless of whether they received live zoster vaccine (ZVL),[20,24] indicating that the protective effect of ZVL against stroke may be a consequence of the reduced incidence of HZ in ZVL-vaccinated individuals.

In a cross-sectional study, the prevalence of stroke was significantly higher in US citizens aged 50−79 years who had not received ZVL compared with vaccinated individuals (HR 1.73 [95% CI, 1.71−1.76]).[32] The impact of vaccination on stroke was strongest in individuals who were white and aged 65−69 years. The authors interpreted a diminished impact of vaccination on stroke with increasing age as potential evidence of diminishing protection conferred by ZVL.[32] However, the protective effect from ZVL was not observed in the African American or Hispanic populations (the study did not control for stroke risk factors that are more common in these populations), and, due to the cross-sectional design, the study was unable to determine the temporal order of ZVL vaccination and stroke. In addition, the study was limited by the use of self-reported ZVL vaccination status and history of stroke and by not assessing the rate of HZ after ZVL vaccination.

In a large population-based cohort study of US Medicare beneficiaries aged ≥66 years without a history of stroke, the risk of fatal or nonfatal stroke was significantly lower in individuals who had received ZVL compared with non-vaccinated individuals.[33] The incidence of stroke (HR 0.84 [95% CI, 0.83−0.85]), ischemic stroke (HR 0.83 [95% CI, 0.82−0.84]), and hemorrhagic stroke (HR 0.88 [95% CI, 0.85−0.91]) was consistently lower in individuals vaccinated against HZ compared with non-vaccinated individuals over a median of 5.1 years of follow-up.[33] This translated into a 16%, 17%, and 12% reduction in the risk of all-cause, ischemic, and hemorrhagic stroke, respectively. The benefit of vaccination appeared to be greater in individuals aged 66−74 years than individuals aged 75−84 years and ≥85 years and among those who did not take antihypertensive medications or statins compared with those who did take antihypertensive medications or statins.[33]

Discussion

Epidemiological studies with varied study designs and heterogenous populations have shown that HZ is associated with an increased risk of stroke, MI, and TIA and that the association appears to be stronger between HZ and stroke than between HZ and MI or TIA. The RR is greatest in the first few weeks after the onset of HZ and in younger patients. However, assessing the increased risk of TIA after HZ is difficult as there is currently no reliable method of diagnosing TIA. In addition, stroke, MI, and TIA are multifactorial, which makes them difficult to specifically attribute to HZ.

Moreover, it should be noted that most of the epidemiological studies assessing the association of HZ with the risk of stroke, MI, and TIA were conducted using data from administrative databases. Available evidence on the effects of antiviral treatment or ZVL vaccination on HZ-associated vasculopathy also mostly derives from such studies. Therefore, inherent limitations of these databases should be considered when interpreting the results. Routine data captured during clinical care is not intended to answer specific research questions, therefore there is a risk of misclassification and underreporting of exposures (HZ, antiviral treatment, ZVL vaccination) and outcomes (vasculopathy). The outcomes of interest were usually identified using the International Classification of Diseases codes, and the specificity and sensitivity of these codes were not evaluated, while the definition of HZ varied across studies with different diagnostic algorithms. In addition, information might be missing on adherence to, or duration of, antiviral treatment, vaccination data, and risk factors that confound the associations of interest. Finally, in these databases, patient age varies and younger populations are often excluded, such as in the case of Medicare beneficiaries (usual age of eligibility ≥65 years).[24]

On the other hand, self-controlled case series are effective at controlling stable risk factors, but they are susceptible to time-dependent factors (e.g., age or time since vaccination), which are highly related to the development of vasculopathy. Furthermore, the increased mortality rate of stroke/MI and other severe outcomes in survivors make it challenging to identify a suitable control period. Therefore, quantifying the effect of HZ on the risk of vasculopathy is challenging. The mechanisms of association seem to be most relevant for vasculopathies of the head and neck, such as stroke and TIA.

Currently, the available limited evidence suggests that vaccination with ZVL could reduce the risk of stroke in

adults. There have been two US studies that investigated the protective effect of ZVL against stroke.[32,33] One of these studies was limited by its cross-sectional design, self-reporting of stroke and ZVL vaccination, and its inability to determine the temporal order of ZVL vaccination and stroke.[32] Further studies are warranted to confirm the relationship between ZVL vaccination and vasculopathy after HZ. These should include outcomes such as MI or TIA in addition to stroke. Large, randomized studies with sufficient statistical power to detect a difference between vaccinated and non-vaccinated individuals would be preferred but may be impractical given the overall incidence of stroke in the target population. In addition, the protection from ZVL varies substantially across age groups and decreases over the first few years after vaccination. The studies will be informative to concurrently assess variations in ZVL effectiveness and protection against vasculopathy by age and time since vaccination so that the trends in ZVL effectiveness against HZ and vasculopathy can be evaluated together.

Moreover, owing to the licensure and increasing uptake of recombinant zoster vaccine (RZV), which confers much higher and longer-lasting protection against HZ than ZVL,[34,35] studies are needed to evaluate the effect of RZV on vasculopathy after HZ, including vasculopathies other than stroke. The differential efficacy and duration of protection associated with each HZ vaccine provide a unique opportunity to evaluate the protection conferred by each vaccine against HZ, vasculopathy after HZ, and verify the association between HZ and the development of vasculopathy. Although prospective studies with comparable designs (e.g., self-controlled case series or cohort studies) to assess the impact of ZVL or RZV vaccination status on the risk of vasculopathy after HZ would be ideal, they would require large sample sizes and at least 12 months of follow-up, which may be unrealistic. A more realistic approach may be to include studies of large databases from multiple countries to represent a broad cross-section of a country's population and background risk factor rates, and use careful definitions of events, patient demographics, and vaccine status and type. Although comparisons with studies conducted prior to the introduction of vaccines against HZ are informative, owing to the diversity of the study designs it is difficult to draw conclusions. In addition, caution should be exercised when comparing data with previous studies due to the continuous advances in medical care regarding the identification and management of risk factors for vasculopathies.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106891.

References

1. Cohen JI. Clinical practice: herpes zoster. N Engl J Med 2013;369:255-263.
2. Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol 2009;8:731-740.
3. Bahouth MN, Venkatesan A. Acute viral illnesses and ischemic stroke: pathophysiological considerations in the era of the COVID-19 pandemic. Stroke 2021;52:1885-1894.
4. Warren-Gash C. Herpes zoster: epidemiological links with stroke and myocardial infarction. J Infect Dis 2018;218:S102-S106.
5. Hartney T, Birari R, Venkataraman S, et al. Xanthine oxidase-derived ROS upregulate Egr-1 via ERK1/2 in PA smooth muscle cells; model to test impact of extracellular ROS in chronic hypoxia. PLoS One 2011;6:e27531.
6. Nagel MA, Jones D, Wyborny A. Varicella zoster virus vasculopathy: the expanding clinical spectrum and pathogenesis. J Neuroimmunol 2017;308:112-117.
7. Nagel MA, Bubak AN. Varicella zoster virus vasculopathy. J Infect Dis 2018;218:S107-S112.
8. Yawn BP, Wollan PC, Nagel MA, et al. Risk of stroke and myocardial infarction after herpes zoster in older adults in a US community population. Mayo Clin Proc 2016;91:33-44.
9. Kim MC, Yun SC, Lee HB, et al. Herpes zoster increases the risk of stroke and myocardial infarction. J Am Coll Cardiol 2017;70:295-296.
10. Gilden DH, Kleinschmidt-DeMasters BK, Wellish M, et al. Varicella zoster virus, a cause of waxing and waning vasculitis: the New England Journal of Medicine case 5-1995 revisited. Neurology 1996;47:1441-1446.
11. Gilden D, White T, Khmeleva N, et al. VZV in biopsy-positive and -negative giant cell arteritis: analysis of 100+ temporal arteries. Neurol Neuroimmunol Neuroinflamm 2016;3:e216.
12. Sammel AM, Smith S, Nguyen K, et al. Assessment for varicella zoster virus in patients newly suspected of having giant cell arteritis. Rheumatology (Oxford) 2020;59:1992-1996.
13. Solomon IH, Docken WP, Padera Jr RF. Investigating the association of giant cell arteritis with varicella zoster virus in temporal artery biopsies or ascending aortic resections. J Rheumatol 2019;46:1614-1618.
14. Nagel MA, Traktinskiy I, Azarkh Y, et al. Varicella zoster virus vasculopathy: analysis of virus-infected arteries. Neurology 2011;77:364-370.
15. Mayberg M, Langer RS, Zervas NT, et al. Perivascular meningeal projections from cat trigeminal ganglia: possible pathway for vascular headaches in man. Science 1981;213:228-230.
16. Mayberg MR, Zervas NT, Moskowitz MA. Trigeminal projections to supratentorial pial and dural blood vessels in cats demonstrated by horseradish peroxidase histochemistry. J Comp Neurol 1984;223:46-56.
17. Kang JH, Ho JD, Chen YH, et al. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. Stroke 2009;40:3443-3448.
18. Breuer J, Pacou M, Gauthier A, et al. Herpes zoster as a risk factor for stroke and TIA: a retrospective cohort study in the UK. Neurology 2014;82:206-212.

19. Langan SM, Minassian C, Smeeth L, et al. Risk of stroke following herpes zoster: a self-controlled case-series study. Clin Infect Dis 2014;58:1497-1503.
20. Minassian C, Thomas SL, Smeeth L, et al. 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.
21. Sundstrom K, Weibull CE, Soderberg-Lofdal K, et al. Incidence of herpes zoster and associated events including stroke—a population-based cohort study. BMC Infect Dis 2015;15:488.
22. Kwon SU, Yun SC, Kim MC, et al. Risk of stroke and transient ischaemic attack after herpes zoster. Clin Microbiol Infect 2016;22:542-548.
23. Schink T, Behr S, Thone K, et al. Risk of stroke after herpes zoster - Evidence from a German self-controlled case-series study. PLoS One 2016;11:e0166554.
24. Yang Q, George MG, Chang A, et al. Effect of herpes zoster vaccine and antiviral treatment on risk of ischemic stroke. Neurology 2020;95:e708-e717.
25. Patterson BJ, Rausch DA, Irwin DE, et al. Analysis of vascular event risk after herpes zoster from 2007 to 2014 US insurance claims data. Mayo Clin Proc 2019;94:763-775.
26. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res 2009;18:7-26.
27. Zhang Y, Luo G, Huang Y, et al. Risk of stroke/transient ischemic attack or myocardial infarction with herpes zoster: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2017;26:1807-1816.
28. 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.
29. Schmader K. Management of herpes zoster in elderly patients. Infect Dis Clinic Pract 1995;4:293-299.
30. Calabrese LH, Xie F, Yun H, et al. Herpes zoster and the risk of stroke in patients with autoimmune diseases. Arthritis Rheumatol 2017;69:439-446.
31. Lin HC, Chien CW, Ho JD. Herpes zoster ophthalmicus and the risk of stroke: a population-based follow-up study. Neurology 2010;74:792-797.
32. Klaric JS, Beltran TA, McClenathan BM. An association between herpes zoster vaccination and stroke reduction among elderly individuals. Mil Med 2019;184:126-132.
33. Yang Q, Chang A, Tong X, et al. Herpes zoster vaccine live and risk of stroke among Medicare beneficiaries: a population-based cohort study. Stroke 2021;52:1712-1721.
34. EMA. SHINGRIX (herpes zoster vaccine [recombinant, adjuvanted]) summary of product characteristics. URL https://www.ema.europa.eu/en/documents/product-information/shingrix-epar-product-information_en.pdf (accessed November 2022).
35. FDA. SHINGRIX (zoster vaccine recombinant, adjuvanted) prescribing information. URL https://www.fda.gov/media/108597/download (accessed November 2022).