Editorial

Risk of Ischemic Stroke and Decreased Serum Bilirubin Levels
Is There a Causal Link?

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Bilirubin, often thought to be a toxic end product of heme, is a potent antioxidant compound in vivo.¹²

As shown in the schematic Figure, degraded red blood cells release heme, which is broken down by heme oxygenase to biliverdin, which is reduced by biliverdin reductase into the hydrophobic compound bilirubin. Unconjugated bilirubin is a lipid-soluble molecule that must be made water soluble to be excreted. Unconjugated bilirubin is carried by albumin to the liver, where it is conjugated into a water-soluble form by hepatic glucuronyl transferase. The hepatic enzyme UDP-glucuronyl transferase 1A1 (UGT1A1) converts bilirubin to a soluble (conjugated) form suitable for renal and biliary elimination.¹² Importantly, in healthy European populations, common genetic variation of the UGT1A1 promoter region explains ≈50% of the variability in serum total (TB) and conjugated bilirubin levels.³ UGT1A1 is also responsible for the glucuronidation of many other small lipophilic molecules, such as steroid hormones and drugs that affect the vasculature.¹²

Currently, there is sparse and less convincing evidence for an inverse association between TB levels and risk of ischemic stroke. Perlstein et al¹¹ examined the association of TB levels with the prevalence of stroke among 13,214 US adults. After multivariable adjustment, a 0.1 mg/dL increment in TB levels was associated with a 9% reduced odds of stroke among all participants and with a 10% reduced odds of an adverse stroke outcome among participants with a history of stroke. Similar findings were reported by Oda and Kawai¹² in a health screening cohort of 5,444 Japanese people. Interestingly and most importantly, in the only published prospective study that involved 78,724 Korean healthy individuals (41,054 men, aged 30–89 years), Kimm et al¹³ reported that, compared with those with lower TB levels, male individuals with mildly higher TB levels showed a ≈30% decreased risk of incident ischemic stroke (as ascertained by hospital admission discharge records), independently of multiple risk factors, during a median follow-up period of 9.4 years. However, these associations were not observed in hemorrhagic stroke or in women.¹³

Few recent studies that have explored the association of TB levels with the severity and subtypes of stroke among hospitalized patients with a first-ever acute ischemic stroke have shown that patients with mildly higher TB levels had a significantly greater admission severity of stroke (as assessed by the National Institutes of Health Stroke score), but not short-term clinical outcomes (ie, in-hospital death or National Institutes of Health Stroke score ≥10), than those with lower TB levels.¹⁴–¹⁶ In a retrospective study of 626 patients with acute ischemic stroke, Zhang et al¹⁷ reported that mildly higher TB levels at admission were associated with an increased odds for nonlacunar ischemic stroke. It is possible to assume that higher TB levels after acute ischemic stroke reflect the intensity of the initial oxidative stress induced by the neurological damage.

In this scenario, the study published by Li et al¹⁸ in this issue of the journal adds to the body of evidence showing, for the first time, a graded, inverse relationship between serum levels of TB (conjugated and unconjugated bilirubin) and increased prevalence of silent cerebral infarctions in middle-aged Chinese individuals. Notably, this relationship remained significant after adjusting for established stroke risk factors and potential confounders. No association was observed between TB levels and the dimensions of brain infarcts on MRI. Although the cross-sectional design of the study does not allow to draw causal inferences, these findings are clinically important because they identify lower TB levels as a possible novel marker for silent cerebral infarctions. Despite not causing identifiable symptoms, silent cerebral infarctions are common in healthy elderly people and place...
the patient at increased risk for major stroke, dementia, cognitive decline, and depression in the future.\textsuperscript{19,20} Collectively, the evidence from this\textsuperscript{18} and other studies\textsuperscript{11–17} supports the possibility that the early measurement of TB levels might be useful to assess the risk of silent cerebral infarction(s) and major stroke and that mildly elevated TB levels might protect from stroke events and from neurological damage in stroke.

In general, from a pathophysiological perspective, there are some key questions that should be addressed. First, is decreased serum TB associated with increased risk of stroke as a consequence of the coexisting cardiovascular risk factors, or does decreased serum TB contribute to the development of stroke, independently of these risk factors? Second, is it biologically plausible that increased serum TB could confer specific vascular protection? Third, could novel therapeutic approaches (eg, pharmacological, nonpharmacological, or genetic interventions) that increase TB levels provide more direct evidence on the protective role of bilirubin in stroke prevention?

To date, it is uncertain whether decreased TB levels pose an independent risk above and beyond known risk factors. There is a suggestion in that direction, but studies are too few and methodologically not rigorous. Additional large-scale prospective studies of a more extensive panel of known risk factors are needed to draw firm conclusions about an independent prognostic role of decreased TB levels for the development of stroke and other CVD complications.

Little information is also currently available on the potentially vasoprotective effects of mildly elevated TB levels. It is uncertain whether genetic variation in the UGT1A1 is associated with variable risk of coronary heart disease (CHD). The

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**Figure.** Schematic representation of the bilirubin metabolism and the putative biological mechanisms by which higher levels of serum bilirubin might exert vasoprotective effects on the development of silent brain infarcts and other cardiovascular complications. HO-1 indicates heme oxygenase-1.
Framingham Heart Study investigators found that UGT1A1 polymorphism, resulting in higher TB levels, was associated with lower risk of CHD. However, other smaller studies have failed to show the same association. Conversely, it has been shown that patients with Gilbert syndrome have a lower risk of CHD than normobilirubinemic control subjects, thus supporting the concept that mildly elevated (unconjugated) bilirubin levels might help protect against CHD.

The underlying mechanisms by which increased TB may exert vasoprotective effects are still incompletely understood, and further research is required to uncover other specific mechanisms by which bilirubin may protect from stroke and CHD events. The putative mechanisms of benefit that have been experimentally described are bilirubin-mediated inhibition of lipid oxidation, bilirubin-mediated inhibition of immune reactions and inflammatory processes, bilirubin-mediated inhibition of cell migration and proliferation, bilirubin-mediated inhibition of apoptosis, and bilirubin as a marker reflecting enhanced heme oxygenase-1 activity (Figure). However, it is important to remember that markedly elevated TB levels may exert neurotoxic effects in some circumstances. Thus, in the absence of definitive evidence, being bilirubin a Janus Bifrons, I think that prudence is still required. Additional large and long-term observational studies in different ethnic groups are warranted to establish the role of serum TB firmly as a causal risk factor for CHD and, especially, for ischemic stroke. This is also important particularly if one considers that novel therapeutic strategies aimed to achieve mild-to-moderate elevations of serum bilirubin (eg, use of heme oxygenase-1 inducers or drugs that reduce hepatic glucuronidation activity or inhibit hepatocyte uptake) might be used, in the future, as tools for preventing and treating CHD/stroke and other diseases in which oxidants play a prominent pathogenic role.

Disclosures
None.

References

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