Atherosclerosis 275 (2018) 450

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Correspondence

Strokes, cholesterol and statins: When mortality is an endpoint

Keywords:
Cholesterol
Mortality
All-cause mortality
Statin
Population study

To the Editor,

The Yi et al. stroke mortality study, with 5.2 million person-years of observation in a representative Korean population cohort with a single baseline total cholesterol (TC) measurement, highlights several important issues [1]. First, the authors note the fact that cholesterol lowering "particularly by statins" does not lower stroke mortality in randomized trials. Second, the fact that 53% of stroke deaths were from hemorrhagic strokes, far surpassing its incidence of about 10–20% in all strokes in many countries [1], and that are mainly nonfatal ischemic strokes. The relative lethality of hemorrhagic strokes is not surprising and its significant association with low TC (</~170 mg/dL, as found) is worrying in regard to statin users, of whom there was an unknown number in this cohort.

The authors correctly suggest that statins, however, reduce nonfatal ischemic strokes and transient ischemic attacks (in placebo-controlled trials), a phenomenon that may simply be explained either by the nitroglycerin mimicking effect of statins, promoting the NO/eNOS pathways that affect vasculature and blood cell behavior [2], or by some sort of anti-inflammatory effect increasingly mentioned as an alternative explanation. In other words, the benefit in nonfatal ischemic events may have nothing to do with lowered cholesterol while lowered cholesterol may well be causally linked to hemorrhagic strokes [3].

However, this benefit is too small in absolute risk reduction to make statin prescribing clinically relevant for patients who expect to live longer, especially so since there are no placebo-controlled statin trials that reduced mortality in, for example, women of any risk, prior stroke victims and older men. Furthermore, cardiovascular mortality is not demonstrably reduced by the two most powerful statins, rosuvastatin and atorvastatin.

An earlier 3 million person-year follow-up study in Korean men (only) found lowest mortality at TC 231 ± 20 mg/dL [4], incidentally near the nadir for hemorrhagic stroke mortality in the current study. Should statins still be contemplated in East Asian populations, if not others, if mortality is an endpoint, and where (statin-caused) low levels may have their own problems? The available data suggest that they should not, or with extreme caution and with a clear reality check for patients hoping for a longevity benefit.

Interestingly, a massive observational study using simvastatin in hypercholesterolemic Japanese found lowest end-of-study mortality at cholesterol levels ~220–260 mg/dL, with significantly highest mortality in the group with TC < 160 mg/dL, and its authors issued a caveat about "hyper-responders" to statin.[5] Therefore, the "borderline" high cholesterol group in the current study (mean TC 219.1 mg/dL) appears to be in fact at the more "desirable" cholesterol level. The caveats in this, and in almost all population studies, are the early mortality risks associated with low cholesterol.

Considering that the authors have full mortality data regarding this representative group of Koreans, could they comment about TC and all-cause mortality?

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

[1] S.W. Yi, D.H. Shin, H. Kim, J.J. Yi, H. Ohrr, Total cholesterol and stroke mortality in middle-aged and elderly adults: a prospective cohort study, Atherosclerosis 270 (2018 Mar) 211–217, https://doi.org/10.1016/j.atherosclerosis.2017.12.003. PMID: 29241770.

[2] E. Vos, C.P. Rose, P. Biron, Point: why statins have failed to reduce mortality in just about anybody, J Clin Lipidol 7 (3) (2013 May-Jun) 222–224, https://doi.org/10.1016/j.jacl.2013.01.007. PMID 28838741.

[3] E. Vos, P. de Groot, Re: low LDL cholesterol, statins, and brain hemorrhage: should we worry? Neurology 69 (14) (2007 Oct 2) 1469, https://doi.org/10.1212/01.wnl.0000286556.98846.6d. PMID: 17909161.

[4] Y.M. Song, J. Sung, J.S. Kim, Which cholesterol level is related to the lowest mortality in a population with low mean cholesterol level: a 6.4-year follow-up study of 482,472 Korean men, Am. J. Epidemiol. 151 (8) (2000 Apr 15) 739–747. PMID: 10965970.

[5] M. Matsuzaki, T. Kita, H. Mabuchi, et al., J-LIT Study Group. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia, Circ. J. 66 (12) (2002 Dec) 1087–1095. PMID: 12499611.

Eddie Vos*
127 Courser Road, Sutton, QC, J0E 2K0, Canada

Pierre Biron
Université de Montréal, 205-800, rue Muir, Montreal, QC, H4L 5N5, Canada

* Corresponding author.
E-mail address: vos@health-heart.org (E. Vos).

18 April 2018
Available online 3 May 2018

DOI of original article: https://doi.org/10.1016/j.atherosclerosis.2017.12.003.

https://doi.org/10.1016/j.atherosclerosis.2018.04.035

Reply to: “Strokes, cholesterol and statins: When mortality is an endpoint”

Keywords:
Blood cholesterol
Stroke mortality
All-cause mortality

To the Editor,

The authors generally concur with Dr. Vos and Dr. Biron [1] that long-term low cholesterol levels caused by long-term statin use might be a concern, when overall mortality or survival, is an endpoint, since many prospective cohort studies have shown that a low cholesterol levels was associated with higher mortality [2–4], and the effects of the long-term cholesterol lowering treatment have not been sufficiently investigated [5]. Clinical trials, mainly performed in men with a high risk of heart disease, have shown that statin therapy reduces all-cause mortality, almost entirely by reducing heart disease mortality, during the follow-up period of clinical trials. However, a long term prospective cohort study showed that Japanese-American populations who maintained low cholesterol levels over a 20-year period had the highest all-cause mortality [4]. A recent research of statins users concluded that the cholesterol hypothesis of “the lower, the better” should not be indiscriminately applied to long-term patients with ischemic heart disease in the community setting [5].

We agree that the protective effects of statins against non-fatal stroke may be explained, at least partly, by pleiotropic effects of statins [6], such as effect of statins on eNOS, anti-inflammatory effect, and anti-oxidant effect, rather than cholesterol lowering effects. Paucity of evidence of protective effects against stroke mortality from any cholesterol lowering interventions including statins and against heart disease mortality from any interventions other than statins has been a major source of debates about the cholesterol hypothesis [7]. We hope the exact mechanism will be clearer in the forthcoming years.

All-cause mortality is perhaps the most important health outcome for patients or the general population, when assessing the effectiveness of interventions both in the individual and population settings [8,9]. In our study populations, the total cholesterol levels of 200–219 mg/dL were associated with the lowest risk of all-cause mortality, and the ranges of 180–199, 220–239, and 240–259 mg/dL were not associated with statistically higher risk of mortality, compared to 200–219 mg/dL. However, the analyses of disease-specific mortality, such as stroke mortality, also have their own merits. Assuming causality, our study suggests that lowering TC level down to around 200 mg/dL reduces the risk of fatal stroke, without increasing the risk of fatal hemorrhagic stroke [10]. These results will help inform decision makings about interventions, such as target cholesterol levels, among populations with a high risk of stroke in the clinical and public health settings, especially, when definitive evidence of benefits on stroke mortality from clinical trials is lacking as in now.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

[1] E. Vos, P. Biron, Strokes, cholesterol and statins: when mortality is an endpoint, Atherosclerosis (2018).
[2] D. Jacobs, H. Blackburn, M. Higgins, et al., Report of the conference on low blood cholesterol: mortality associations, Circulation 86 (1992) 1046–1060.
[3] Y. Kirihara, T. Hamazaki, Y. Ogushi, et al., The relationship between total blood cholesterol levels and all-cause mortality in fukui city, and meta-analysis of this relationship in Japan, J.Lipid Nutr. 17 (2008) 67–78.
[4] I.J. Schatz, K. Masaki, K. Yano, et al., Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study, Lancet 358 (2001) 351–355.
[5] M. Leibowitz, T. Karpati, C.J. Cohen-Stavi, et al., Association between achieved low-density lipoprotein levels and major adverse cardiac events in patients with stable ischemic heart disease taking statin treatment, J. Am. Acad. Intern. Med. 176 (2016) 1105–1113.
[6] A. Oesterle, U. Laufs, J.K. Liao, Pleiotropic effects of statins on the cardiovascular system, Circ. Res. 120 (2017) 229–243.
[7] C.E. Ramsden, D. Zamora, S. Majchrzak-Hong, et al., Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73), BMJ 353 (2016) i1246.
[8] S.W. Yi, H. Ohrr, S.A. Shin, et al., Sex-age-specific association of body mass index with all-cause mortality among 12.8 million Korean adults: a prospective cohort study, Int. J. Epidemiol. 44 (2015) 1696–1705.
[9] S.W. Yi, S. Park, Y.H. Lee, et al., Fasting glucose and all-cause mortality by age in diabetes: a prospective cohort study, Diabetes Care 41 (2018) 623–626.
[10] S.W. Yi, D.H. Shin, H. Kim, et al., Total cholesterol and stroke mortality in middle-aged and elderly adults: a prospective cohort study, Atherosclerosis 270 (2018) 211–217.

DOIs of original article: https://doi.org/10.1016/j.atherosclerosis.2018.04.035, https://doi.org/10.1016/j.atherosclerosis.2017.12.003.

https://doi.org/10.1016/j.atherosclerosis.2018.06.861

Sang-Wook Yi*
Department of Preventive Medicine and Public Health, Catholic Kwandong University College of Medicine, Gangneung, 25601, Republic of Korea

Heechoul Ohrr
Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, 03722, Republic of Korea

* Corresponding author. Department of Preventive Medicine and Public Health, College of Medicine, Catholic Kwandong University, Bumil-ro 579, Gangneung, Gangwon-do, 25601, Republic of Korea.
E-mail address: flyhigh@cku.ac.kr (S.-W. Yi).

1 June 2018
Available online 18 June 2018