Is the weight of hypertension heavier than dyslipidemia and diabetes mellitus on carotid atherosclerosis?

Wen-Ling Lee[a,b,c], Fa-Kung Lee[d,e], Peng-Hui Wang[b,e,f,g,*]

[a]Department of Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan, ROC; [b]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan, ROC; [d]Department of Obstetrics and Gynecology, Cathay General Hospital, Taipei, Taiwan, ROC; [e]Female Cancer Foundation, Taipei, Taiwan, ROC; [f]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [g]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

Cardiovascular disease (CVD) remains one of the most common causes of impairment of human well-being and is also the main cause of death in the world.[1] CVD is apparently the biggest health problem in Taiwan since it is secondary to malignant diseases and ranks as the second leading cause of mortality in Taiwan.[2] Any strategy to screen and/or identify the risk factors and/or precursors of CVD providing a better chance to prevent or delay adverse health outcomes by early detection and prompt intervention and subsequently to improve global health is always encouraged.[1,3,4] CVD is a noncommunicable disease, partly because of the presence of high debates about risk scoring system, part of the uncertainty of the value of using screening for asymptomatic CVD, particularly for asymptomatic carotid atherosclerosis, and partly because of the argument of appropriate time to intervention or management.[5–9] We are happy to introduce a manuscript entitled "Combined effects of hypertension, hyperlipidemia, and diabetes mellitus (DM) on the presence and severity of carotid atherosclerosis in community-dwelling elders: A community-based study" published in the February issue of the *Journal of the Chinese Medical Association* to focus on the topic.[10] Lu et al investigate the effect of comorbidities, such as hypertension, DM, and hyperlipidemia on carotid atherosclerosis in community-dwelling elders and found that many well-known risk factors, such as age at enrollment (per 1 year), male gender, cigarette smoking, and number of common CVD comorbidities are associated with carotid atherosclerosis, and also involved in the severity of carotid atherosclerosis.[10]

Additionally, the authors attempted to investigate the effects of each comorbidity item or combined comorbidity items of hypertension, DM, and hyperlipidemia on carotid atherosclerosis and found that hypertension was the most critical factor associated with moderate or severe carotid atherosclerosis with an odds ratio (OR) of 1.56 (95% CI, 1.01-2.41).[10] Furthermore, hypertension also plays an important role for the development of carotid atherosclerosis with an OR of 1.43 (95% CI, 0.97-2.11), although it does not reach a statistical significance.[10] Moreover, hypertension adding any one or two CVD comorbidities seemed to further deteriorate the carotid vessel health (moderate [≥50%] or severe [≥70%] atherosclerosis), including an OR of 2.71 on adding hyperlipidemia, an OR of 5.29 on adding DM, and an OR of 4.07 on adding both hyperlipidemia and DM.[10] Finally, the effects of deterioration of the carotid vessel health (all forms of carotid atherosclerosis) are also noted with an OR of 2.08 on adding hyperlipidemia, an OR of 3.56 on adding DM, and an OR of 3.78 on adding both hyperlipidemia and DM.[10] The current article is interesting and worthy of further discussion.

First, the clinical significance of carotid atherosclerosis should be discussed, particularly for asymptomatic carotid atherosclerosis, since the argument about wide-screening of asymptomatic carotid atherosclerosis for the general population existed consistently.[1] Screening for carotid atherosclerosis in unselective community population may face the following uncertainties raised by Dr. Poorthuis and colleagues,[1] including (1) who should be screening?; (2) what imaging tools should be used to qualify and quantify the presence and/or severity of carotid atherosclerosis to minimize the risk of the false positivity or the low sensitivity?; and (3) what are clinical implications if asymptomatic carotid atherosclerosis is detected since the cost-effectiveness benefits should be always considered? The data in the current study were based on an "unselective" community population,[10] resulting in the adding little value for clinical routine practice. Although the authors identified independent predictive factors for carotid atherosclerosis, all of them are well-known.

Second, whether carotid atherosclerosis is a unique form of atherosclerosis or the results of a similar metabolic process that may be associated with all forms of atherosclerosis remains uncertain, there is no doubt that metabolic disorders[11,12] and mechanical vascular abnormalities[13] should be approached simultaneously because both probably causing an increased carotid atherosclerosis predisposition.[13] Evidence shows major risk factors for carotid atherosclerosis, including elevated low-density lipoprotein cholesterol (LDL-C), DM, cigarette smoking, hypertension, and increased chronic inflammation process,[13,14] resulting in a various kinds of diagnostic risk models produced by combination of different risk factors (age, sex, cigarette smoking, DM and existed CVD, and measured blood pressure [BP] and cholesterol levels) which have been already implemented in clinical practice, such as atherosclerotic CVD in the US or SCORE in Europe, to detect asymptomatic

** Address correspondence. Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail addresses: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).*

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carotid atherosclerosis specifically and to provide a better discrimination reliable prediction of the prevalence of asymptomatic carotid atherosclerosis.[1] These risk scores consist of modifiable and non-modifiable components, contributing to the creation of cardiovascular health scores as Life's Simple 7 (the four life-modification styles, such as body mass index, cigarette smoking, physical activity, and diet; as well as the three biological factors, containing fasting blood glucose concentrations, BP, and blood total cholesterol levels) by the American Heart Association, in an attempt to reduce CVD-related death.[9,14] Adherence to the Life's Simple 7 has been shown associated with lower CVD risk in elderly in the western countries (American and European populations).[9] Therefore, it is not surprising to find the number of comorbidity, such as hypertension, DM, and hyperlipidemia are positively associated with the prevalence and severity of carotid atherosclerosis, just like the authors' mention,[10] since all three have already been enrolled into one of the essential predictive factors to establish diagnostic risk models, and are well-known critical factors in reducing prevalence and severity of carotid atherosclerosis in elderly.[9]

Third, the pathophysiology of atherosclerosis is initiated by hemodynamic forces and/or reduction of nitric oxide-inducing endothelial dysfunction accompanied by LDL retention and its modification (oxidation and more), followed by a cascade of events (accumulation of lipids, fibrous elements, and calcification), endothelial activation, monocyte recruitment, and foam cell formation; triggers the vessel narrowing (from fatty streak to fibrous plaque development) and activation of inflammatory pathway, and finally results in atheroma plaque (plaque rupture and healing), along with these processes, contributing to cardiovascular complications.[15] Simply, mechanical stress (elongation [tensile] and wall shear stress) and changes of metabolites affecting endothelial cells of vessels with subsequently involvement in homeostasis and atherogenic hemodynamics contribute to both the onset and progression of atherosclerosis.[15] It is reasonable to show the importance of hypertension on the development and/or exacerbation of carotid atherosclerosis as shown by authors.[10] Hypertension-involved hemodynamic forces and subsequent association with low wall shear stress or highly oscillatory wall shear stress plays a key step and an initial role for the development and/or exacerbation of carotid atherosclerosis. Dr. Lu in the current article also emphasized the critical role of BP controls to reduce the impact of atherosclerotic diseases, and they concluded that BP controls precede the control of blood lipid and glucose in the community-dwelling elders.[10]

Fourth, the negative impact of lipids on the development and progression of carotid atherosclerosis may be underestimated by Dr. Lu's group. As shown above, besides hypertension-induced mechanic force for the initiation and progression of carotid atherosclerosis, LDL-C is an essential and key component for the development and deterioration of carotid atherosclerosis, contributing to enough evidence-based medical results to demand intensive preventive and therapeutic measures by using a lipid-lowering agent (statins-use associated with marked reduction of the LDL-C) and BP-lowering agents for both prevention and management of carotid atherosclerosis.[13] We believe that the authors never neglect the critical role of dyslipidemia on carotid atherosclerosis, although the data showed that hyperlipidemia alone was not associated with increasing risk of presence and severity of carotid atherosclerosis by authors. We totally agree the audience' comments that there are many confounding factors contributing to Dr. Lu's finding and subsequent conclusion.[16] At the end, just like our concerns about the statistical significance in the research works, any conclusion and/or recommendation made should be based on the clinical relevance and not just relegate the patients with statistical significance to decision-making only involving the experts' interest.[17,18]

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