Hypertension Research (2014) 37, 890–891

www.nature.com/hr

COMMENTARY

Carotid atherosclerosis progression: the importance of systolic blood pressure

Cesare Cuspidi, Marijana Tadic and Carla Sala

Hypertension Research (2014) **37,** 890–891; doi:10.1038/hr.2014.119; published online 17 July 2014

In this issue of the Journal, Xie *et al.*[1] report the findings of a longitudinal population-based study aimed at assessing the clinical value of several cardiovascular risk factors and their variations over time in predicting the development of carotid plaques in 1590 participants (38% men) selected from two Chinese communities without baseline alterations in carotid structure, as assessed by high-resolution B-mode ultrasonography. Before addressing the results of the study, the available evidence on this issue may deserve some consideration.

Numerous cross-sectional studies conducted in different clinical settings and ethnic groups reported a robust association between subclinical carotid structural alterations, such as intima-media (IM) thickening and/or plaque extension and traditional risk factors, as well as organ damage markers, including left ventricular hypertrophy, cerebral white matter lesions, peripheral arterial disease, micro-albuminuria and coronary calcifications.[2,3] In particular, high blood pressure (BP) has been reported to be a major risk factor for carotid IM thickening and plaque development, due to the combined effects of mechanical stress and growth/inflammatory factors on the arterial wall. In the population-based Rotterdam study, participants with carotid wall thickening during the ultrasound examination underwent high-resolution magnetic resonance imaging for carotid plaque characterization, and hypertension and active smoking were the main risk factors associated with unstable plaques (that is, intraplaque hemorrhage and large lipid core).

Since the mid-1990s, a number of prospective, observational and interventional trials were performed in population-based samples, and selected cohorts of individuals at high risk have shown that carotid IM thickness (IMT) and/or plaques predict incident heart disease and stroke after adjusting for major risk factors. These pioneering findings have been recently confirmed by prospective studies based on updated ultrasound technologies in a variety of clinical settings. In the Tromsø Study, a population-based survey including 6257 participants aged 25–84 years, the risk of myocardial infarction during a follow-up period of approximately 15 years markedly increased across the quartiles of mean carotid IMT ($P<0.001$) and total plaque area ($P<0.001$).[4] The results of the IMPROVE study, a multicenter observational trial designed to investigate the value of cross-sectional carotid IMT and overall IMT progression in predicting new vascular events in 4482 European individuals at high risk of cardiovascular disease, showed that carotid IMT progression over a median follow-up period of 21.5 months was a strong predictor of subsequent vascular events.[5]

Overall, a large body of evidence supports the view that carotid IMT is a valuable biomarker for refining the cardiovascular risk assessment in medium-high-risk subjects. Unfortunately, less consistent information is available on the effects of preventative strategies based on lifestyle interventions and/or drug treatment (that is, antihypertensive and lipid-lowering agents) on carotid atherosclerosis progression. Few studies have prospectively addressed the relationship between variations in cholesterol, blood glucose, body mass index, BP levels, metabolic syndrome status and IMT, and/or plaque progression at different sites of the carotid wall.

Investigators of the Amsterdam Growth and Health Longitudinal Study examined whether changes in metabolic syndrome status, which was categorized as never ($n=207$, reference group), incident ($n=31$), recovery ($n=23$) and persistent status ($n=32$) in young subjects without overt signs of atherosclerosis, was associated with changes in carotid structure and function;[6] all data were adjusted for sex, height, and changes in age, lifestyle variables, low-density lipoprotein cholesterol and use of antihypertensive medications. During a 6-year follow-up, individuals with persistent metabolic syndrome displayed a steeper increase in IMT compared with the reference group (11 *vs.* 5 μm per year). A concomitantly steeper increase in inter-adventitial (77 *vs.* 32 μm per year) and lumen diameter (55 *vs.* 23 μm per year) was also present. In the Healthy Women study, changes in cardiovascular risk factors during the perimenopausal and early post-menopausal years and their correlation with the carotid IMT and plaque index were assessed in a cohort of 375 women within 5–8 years after menopause.[7] Premenopausal levels of risk factors were strong determinants of carotid IMT and plaque after menopause; however, only pulse pressure changes during perimenopausal years were independently related to subsequent carotid disease beyond premenopausal pulse pressure levels, after adjustments for age and use of hormone replacement therapy.

Professor C Cuspidi is at Department of Health Science, University of Milano-Bicocca, Milano, Italy and Istituto Auxologico Italiano, Milano, Italy; M Tadic is at University Clinical Hospital Centre "Dragisa Misovic", Belgrade, Serbia; C Sala is at Department of Clinical Sciences and Community Health, University of Milano and Fondazione Policlinico di Milano, Milano, Italy
E-mail: cesare.cuspidi@unimib.it

The protective effect of antihypertensive treatment in reducing cardiovascular events and delaying organ damage may depend not only on the extent of BP reduction but also on its persistence over time (that is, stable on-treatment BP control over the long term). This aspect is supported by limited literature data. Mancia *et al.*[8] analyzed pooled data from the European Lacidipine Study on Atherosclerosis (ELSA) and investigated whether visit-to-visit BP variability and on-treatment systolic BP (SBP) obtained at 6- (clinic BP) and 12- (24 h BP) month intervals were related to IMT and cardiovascular events. In a multivariable linear regression model, the mean on-treatment clinic or 24-h SBP, but not on-treatment visit-to-visit clinic or 24-h BP variability, was associated with end-of-treatment carotid IMT. Of note, IMT progressively increased from the lowest to highest quartile of mean on-treatment clinic or 24-h SBP, but not along similar quartiles of the SBP variation coefficient. In a multivariable logistic regression model, mean BP, but not variability, was associated with cardiovascular outcomes. Both clinic and 24-h on-treatment mean SBP values were found to be independently and positively associated with carotid IMT and incidence of cardiovascular events. However, this was not the case for the baseline clinic or 24-h SBP. These findings suggest that the BP achieved during treatment plays a key role in preventing or delaying carotid damage and overt cardiovascular disease.

Xie *et al.*[1] adds a new piece of information on this topic by showing that the changes in clinic SBP at the end of a 5-year follow-up, in addition to several baseline variables including age, male gender, SBP, high-density lipoprotein cholesterol, triglycerides, active smoking and common carotid IMT, were significantly related to the occurrence of new carotid plaques and total plaque area in the general population free of carotid structural alterations at the initial observation. Such association was still significant after full adjustments for baseline risk factors. In contrast with SBP, the 5-year increase in pulse pressure exhibited an independent correlation with the total plaque area but not with the incidence of carotid plaques. Some further aspects and limitations of this study merit consideration. First, the incidence of carotid plaque was approximately 50% in the total population, ranging from 29% in women aged <50 years to 63% in elderly men. As expected, the atherosclerotic process occurred more in the carotid bifurcation than the common or internal carotid artery. These results show that the new-onset carotid structural alterations over a 5-year period may affect a large fraction of middle-aged subjects from a general population without history of cardiovascular disease and that this adverse process is highly frequent in individuals aged $\geqslant 50$ years. Second, only 5-year changes in SBP, but not in other risk factors, such as lipid and blood glucose levels or body mass index, showed an association with incident carotid plaques and total plaque area. When the strength of this correlation was assessed according to the baseline BP levels, statistical significance was maintained only among the 904 individuals without hypertension. Overall, this information indicates that the increase in SBP over time in the general population is a stronger determinant of carotid damage compared to the longitudinal variations of other risk factors.

Third, in the study by Xie *et al.*[1] SBP, but not diastolic BP, showed a prognostic importance. This finding further supports available evidence that SBP is a more important prognostic factor than diastolic BP, at least in middle-aged and elderly subjects. This observation is consistent with the results of a prospective investigation by Lakka *et al.*[9] in a European population, in which the relationship of SBP, diastolic BP and pulse pressure showed an increase in the parameters of early carotid atherosclerosis, that is, mean and maximal common carotid IMT. This study assessed in 1026 men aged 42 to 60 years over 4 years. The authors found that SBP had a strong, graded and direct association with the IMT increase regardless of diastolic BP levels; in contrast, diastolic BP had no relationship with the IMT increase when controlled for SBP.

Finally, some limitations of the paper by Xie *et al.*[1] need to be briefly discussed. Because all subjects with carotid plaques at the initial ultrasound examination were excluded from the study, data focusing on the evolution of carotid lesions over time and factors involved in this process are lacking. Furthermore, no information was provided on the impact of baseline IMT on subsequent changes in SBP. This intriguing issue was examined by Zureik *et al.*[10] in a population of 957 volunteers aged 59–71 years in a 4-year longitudinal study. The authors found that pulse pressure was associated with IMT changes over time and, vice versa, that IMT was associated with the pulse pressure changes over time. These associations were independent of other traditional cardiovascular risk factors and were observed in hypertensive and non-hypertensive subjects, as well as in antihypertensive-treated and untreated subjects.

In conclusion, the findings provided by Xie *et al.*[1] support the view that both baseline and gradual changes in SBP play a central role in the progression of carotid atherosclerosis and reinforce the notion that the prevention and adequate treatment of systolic hypertension is a key strategy in reducing vascular damage in the general population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Xie W, Liu J, Wang W, Wang M, Li Y, Sun J, Liu J, Qi Y, Zhao F, Zhao D. Five-year change in systolic blood pressure is independently associated with carotid atherosclerosis progression: a population-based cohort study. *Hypertens Res* 2014; **37**: 960–965.
2 Zanchetti A, Bond MG, Hennig M, Neiss A, Mancia G, Dal Palu' C, Hansson L, Magnani B, Rahn KH, Reid J, Rodicio J, Safar M, Eckes L, Ravinetto R. Risk factors associated with alterations in carotid intima-media thickness in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis. *J Hypertens* 1998; **16**: 949–961.
3 Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, Szklo M, Howard G, Evans GW. Risk factors for progression of common carotid atherosclerosis: The Atherosclerosis Risk in Communities Study, 1987–1998. *Am J Epidemiol* 2002; **155**: 38–47.
4 Hald EM, Lijfering WM, Mathiesen EB, Johnsen SH, Løchen ML, Njølstad I, Wilsgaard T, Rosendaal FR, Brækkan SK, Hansen JB. Carotid atherosclerosis predicts future myocardial infarction but not venous thromboembolism: the Tromso Study. *Arterioscler Thromb Vasc Biol* 2014; **34**: 226–230.
5 Baldassarre D, Veglia F, Hamsten A, Humphries SE, Rauramaa R, de Faire U, Mannarino E, Humphries SE, Giral P, Grossi E, Veglia F, Paoletti F, Tremoli E IMPROVE Study Group. Progression of carotid intima-media thickness as predictor of vascular events: results from the IMPROVE study. *Arterioscler Thromb Vasc Biol* 2013; **33**: 2273–2279.
6 Ferreira I, Beijers HJ, Schouten F, Smulders YM, Twisk JW, Stehouwer CD. Clustering of metabolic syndrome traits is associated with maladaptive carotid remodeling and stiffening: a 6-year longitudinal study. *Hypertension* 2012; **60**: 542–549.
7 Matthews KA, Kuller LH, Sutton-Tyrrell K, Chang YF. Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. *Stroke* 2001; **32**: 1104–1111.
8 Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation* 2012; **126**: 569–578.
9 Lakka TA, Salonen R, Kaplan GA, Salonen JT. Blood pressure and the progression of carotid atherosclerosis in middle-aged men. *Hypertension* 1999; **34**: 51–56.
10 Zureik M, Touboul PJ, Bonithon-Kopp C, Courbon D, Berr C, Leroux C, Ducimetière P. Cross-sectional and 4-year longitudinal association between brachial pulse pressure and common carotid intima media thickness in a general population: the EVA study. *Hypertension* 1999; **30**: 550–555.