5-1-2022

Reliability, Reproducibility, and Advantages of Measuring Carotid Total Plaque Area

M. Reza Azarpazhooh
Robarts Research Institute, Reza.Azarpazhooh@lhsc.on.ca

Ellisiv Mathiesen
UiT Norges Arktiske Universitet

Tatjana Rundek
University of Miami Leonard M. Miller School of Medicine

Michel Romanens
Vascular Risk Foundation

Ansgar Adams
B·A·D Health Care and Safety Technology Centre GmbH

See next page for additional authors

Reliability, Reproducibility, and Advantages of Measuring Carotid Total Plaque Area

To the Editor:

Measuring carotid total plaque area (TPA) is useful for risk stratification, treating patients, and research into the epidemiology, genetics, and biology of atherosclerosis.[1] Total plaque area is strongly correlated with coronary calcium scores[2] and is predictive of risk[3]; intima-media thickness is neither.[2,3] Total plaque area is far superior to measuring carotid intima-media thickness in many respects,[1] but it is very much underutilized.

In 2020, a guideline from the American Society for Echocardiography recommended quantification of carotid arterial plaque volume using three-dimensional (3D) ultrasound and measurement of plaque thickness, which the authors called "plaque height," for cardiovascular risk stratification.[4] However, the authors failed to recommend measurement of TPA, due to concerns regarding measurement variability and other issues.[4] They were entirely mistaken; measurement of TPA is very reliable and reproducible, as is plaque thickness (see the Online Supplement). In response to that statement, we performed a systematic review and meta-analysis of this issue. Measurement of TPA had almost perfect interobserver reliability (0.95; 95% CI, 0.83-0.99) and intraobserver reliability (0.96; 95% CI, 0.94-0.97). Supporting data are in the Online Supplement.

A second objection of the guideline committee was that measuring TPA is time-consuming. Although plaque thickness predicts risk and can be measured reliably and quickly, measuring 3D plaque burden is even more time-consuming than TPA if done by manual segmentation, and the automated 3D methods available to date require so many adjustments of the contours that are segmented automatically that it is also very time-consuming. Newer automated methods based on artificial intelligence will soon be available for both 3D plaque burden and TPA. Pending those developments, TPA can be measured with any good duplex ultrasound machine; 3D ultrasound is not available at all sites. There are important advantages to measuring TPA, which is easy to teach and learn. Most experienced and skillful vascular ultrasound technologists can learn to measure TPA reliably in a day. Unlike intima-media thickness and plaque thickness, the quantities measured (TPA, plaque volume, and vessel wall volume) are so much larger than the spatial resolution of ultrasound that errors in measurement represent a very small fraction of the quantity, that is, the coefficient of variation (SD/mean) is very small. The interobserver coefficient of variation of TPA is thus very low.

Although plaque thickness is predictive of risk, and can be measured reliably, it has a very small dynamic range (~1.5-3 cm) compared with TPA (~0-12.00 mm^2); this is important with regard to statistical power and study sample size. Furthermore, plaques progress along the carotid, in the axis of flow, 2.4 times faster than they thicken.[5] As shown in Figure 1, TPA and plaque composition change rapidly, over several months, and can therefore be used to treat arteries instead of merely treating risk factors. The objective of treating arteries is not only to achieve consensus target levels of risk factors such as blood pressure or low-density lipoprotein cholesterol; it is to achieve plaque regression or at least stop progression. Doing so has markedly improved outcomes in vascular prevention clinics in Canada,[7] Argentina[8] (Figure 2), and Germany.[9]

The process of treating arteries begins with showing patients images of their plaque and explaining the severity of their atherosclerosis compared with healthy people of the same age; this markedly improves compliance.[1] Among high-risk patients with asymptomatic stenosis, this approach was associated with a >80% reduction of stroke and myocardial infarction over 2 years.[7] In prevention clinics across Argentina, treatment of arteries was implemented in 2010. As shown in Figure 2, the annual risk of cardiovascular events among patients ages >65 years declined from 5.85% in 2011 to 2.35% in 2015.[8] In a study in Germany, patients with a high TPA who were treated with statins on the basis of TPA rather than serum cholesterol levels had a markedly lower risk of cardiovascular events over a mean follow-up of 3.9 years, 5.4% versus 23%.[9]

In summary, carotid plaque measurement is a reliable and reproducible way to assess the burden of atherosclerosis. Measurement is learned easily and has almost perfect intra- and interobserver reliability; new automated methods will eliminate issues about the time required to perform measurements. Total plaque area should be used much more widely in preventive medicine and in atherosclerosis research.

M. Reza Azarpazhooh, MD
Stroke Prevention and Atherosclerosis Research Centre
Robarts Research Institute
University of Western Ontario
London, Ontario, Canada

Ellisiv Mathiesen, MD
Department of Clinical Medicine
University of Tromsø
Arctic University of Norway
Tromsø, Norway

Tatjana Rundek, MD
Department of Neurology and Evelyn F. McKnight Brain Institute
University of Miami Miller School of Medicine
Miami, Florida

Michel Romanens, MD
Vascular Risk Foundation
Olten, Switzerland

Ansgar Adams, MD
B·A·D Health Care and Safety Technology Centre GmbH
Koblenz, Germany

Luis Armando, MD
Blossom DMO
Córdoba, Argentina

Conflicts of Interest: J.D.S., L.A., and H.V. are unpaid officers of a dormant corporation, Vascularis Inc. J.D.S. receives modest royalties from Enable Technologies on a small share, with Professor Aaron Fenster, of a patent on measurement of three-dimensional plaque volume. T.R. is funded by the grants from the National Institutes of Health, United States (R01 MD012467, R01 NS029993, R01 NS040807, 1U24 NS107267), the National Center for Advancing Translational Sciences, United States (UL1 TR002736 and KL2 TR002737), and the Florida Department of Health, United States. None of the other authors has a relevant conflict of interest to declare.

Reprint requests: J. David Spence, CM, MD, FRCPC, FAHA, Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute, University of Western Ontario, 1400 Western Road, London, ON, Canada N6G 2V4. (E-mail: dspence@robarts.ca).

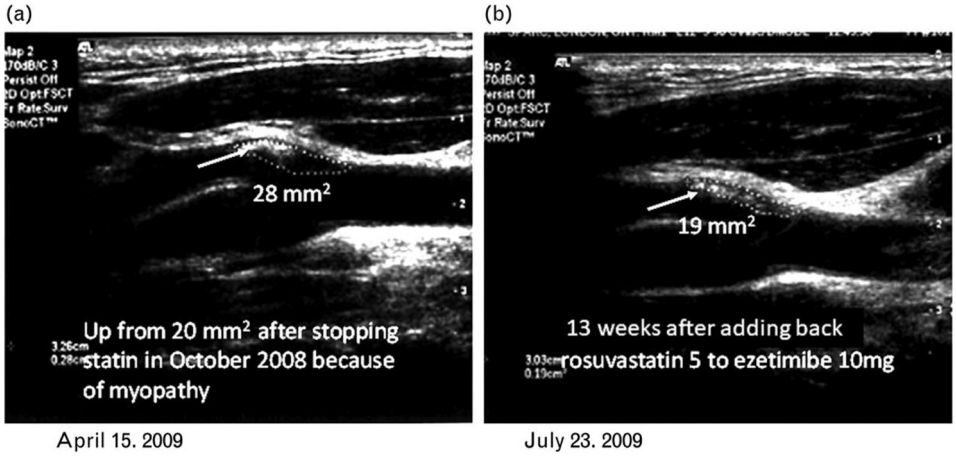

Figure 1 Plaque regression and change in plaque composition occur much faster than most practitioners would expect. **(A)** Soft plaque at the origin of the left external carotid in a 64-year-old man using ezetimibe alone because of myalgia and cramps with statins. His plaque (*white arrow*) had progressed from 20 mm^2 6 months earlier to 28 mm^2 after stopping rosuvastatin and taking ezetimibe alone. After restarting rosuvastatin 5 mg daily with ezetimibe 10 mg daily, the plaque area regressed to 19 mm^2 over 13 weeks **(B)**. The plaque had also become denser, with regression of the echolucent portion of the plaque. The echolucent portion of the plaque in panel A was outlined using Doppler color flow around it, as is done with juxtaluminal black plaque. Reproduced with permission from Elsevier from reference 6. The subject granted permission for use of these images and their identifying data, including all dates.

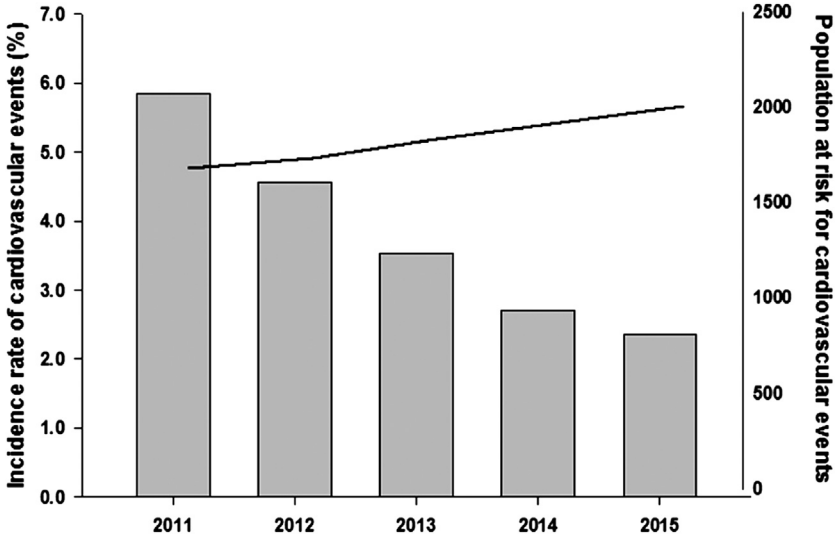

Figure 2 Effect of treating arteries in prevention clinics in Argentina. The process of treating arteries was implemented in seven vascular prevention clinics in health maintenance organizations across Argentina in 2010 by Blossom DMO. *Bars* represent the annual rate of cardiovascular events in patients > 65 years or older, while the *upper line* represents the number of patients at risk for the development of a cardiovascular event. Reproduced with permission from Elsevier from reference 7.

Hernan Perez, MD, PhD
Research, Department of Diagnostic Radiology and Nuclear Medicine
Center for Advanced Imaging
Maryland University
Baltimore
Maryland

Hugo Villafañe, MD
Blossom DMO
Córdoba, Argentina

Nestor H. Garcia, MD
Instituto de Investigaciones en Ciencias de la Salud
Córdoba, Argentina

Borja Ibañez, MD, PhD
Centro Nacional de Investigaciones Cardiovasculares Carlos III
Madrid, Spain

Chrysi Bogiatzi, MD
Division of Neurology
University of Calgary
Calgary, Alberta, Canada

Reza Tabrizi, PhD
Noncommunicable Disease Research Center
Fasa University of Medical Sciences
Fasa, Iran

Valentín Fuster, MD
Zena and Michael A. Wiener Cardiovascular Institute
Icahn School of Medicine at Mount Sinai
New York, New York

J. David Spence, MD
Stroke Prevention and Atherosclerosis Research Centre
Robarts Research Institute
University of Western Ontario
London, Ontario, Canada

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2021.12.016.

REFERENCES

1. Spence JD. Measurement of carotid plaque burden. Curr Opin Lipidol 2020;30:291-8.
2. Sillesen H, Muntendam P, Adourian A, Entrekin R, Garcia M, Falk E, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the high risk plaque bioimage study. JACC Cardiovasc Imaging 2012;5:681-9.
3. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol 2015;65:1065-74.
4. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. J Am Soc Echocardiogr 2020;33:917-33.
5. Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress and the progression of carotid atherosclerosis. J Hypertension 1997;15:49-55.
6. Spence JD. Coronary calcium is not all we need: carotid plaque burden measured by ultrasound is better. Atherosclerosis 2019;287:179-80.
7. Spence JD, Coates V, Li H, Tamayo A, Munoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Arch Neurol 2010;67:180-6.
8. Perez HA, Adeoye AO, Aballay L, Armando LA, Garcia NH. An intensive follow-up in subjects with cardiometabolic high-risk. Nutr Metab Cardiovasc Dis 2021;31:2860-9.
9. Adams A, Bojara W, Romanens M. Effect of statin treatment in patients with advanced carotid atherosclerosis: an observational outcome study. Cardiol Res 2021;12:335-9.

https://doi.org/10.1016/j.echo.2021.12.016

Response to Azarpazhooh et al., *Reliability, Reproducibility and Advantages of Measuring Carotid Total Plaque Area*

To the Editor:

In response to Azarpazhooh *et al.*'s concerns related to our American Society of Echocardiography statement on plaque measurements, we would like to clarify and emphasize that there is no recommendation against evaluating total plaque area (TPA). We agree that in the hands of highly skilled experts at leading research centers, high reliability can be obtained no matter the complexity of measurement, especially for *single measures*. This is shown by the perfect reliability achieved by these experts for even total plaque volume (TPV), which is a complex measurement currently conducted by only a few centers. However, our statement was meant for all clinical users, and hence we recommended and stand by our recommendation of using plaque height as it is relatively simpler to use and standardize.[1]

Other two-dimensional techniques including TPA and TPV are well expounded upon in our statement. There is no recommendation against any technique. Furthermore, one of the greatest challenges in follow-up imaging is achieving the same plane of imaging, that is, *acquisition variability* (as apparent in the figure included by Azarpazhooh *et al.* in their letter) which can lead to exponentially compounded measurement error. Recognition of such *acquisition variability* continues to drive future advances and improvements in technology.

As the authors note, "Newer automated methods based on artificial intelligence will be available soon for both 3D plaque burden and TPA." Indeed, if these newer automated methods help with reliability and reproducibility as the authors suggest by this statement, we believe that TPA and TPV could then be incorporated by any lab and may very well become the gold standard measure in the future. We look forward to reviewing findings from artificial intelligence and automation for TPA in our future updates.

Amer M. Johri, MD, MSc, FRCPC, FASE
Queen's University
Kingston, Ontario, Canada

Vijay Nambi, MD, FASE
Baylor College of Medicine
Houston, Texas

Henrik Sillesen, MD, DMSc
Rigshospitalet
University of Copenhagen
Copenhagen, Denmark

REFERENCE

1. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. J Am Soc Echocardiogr 2020;33:917-33.

https://doi.org/10.1016/j.echo.2022.01.015

Conflicts of Interest: None.

Reprint requests: Amer M. Johri, MD, MSc, FRCPC, FASE, Queen's University, Kingston, ON, Canada. (E-mail: *amerschedule@gmail.com*).