Netherlands
The Journal of Medicine

EDITORIAL

Use of intermediate cardiovascular endpoints in intervention studies: not as easy as it seems?

M.L. Bots

Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Heidelberglaan 100, Internal post number D.01.335, 3584 CX Utrecht, the Netherlands, tel: +31 (0)30-2509352, fax: +31 (0)30-2505485, e-mail: m.l.bots@jc.azu.nl

In the current issue of the Journal, Van den Berkmortel and coworkers[1] report on the effect of smoking cessation on cardiovascular risk reduction, as estimated by assessment of progression of carotid intima-media thickness (CIMT) and arterial stiffness. Much to the authors' surprise, their nonrandomised study among 33 subjects who stopped smoking for at least two years, 55 persistent smokers and 50 never-smokers showed no difference in rate of change in CIMT or arterial stiffness across the groups after two years of intervention. The intriguing question of the paper is whether the finding is true or may be attributed to potential flaws of the study, focussing on design and analytical procedures, the choice of the endpoint and the power of the study.

The most desirable study design to evaluate the efficacy of interventions on cardiovascular risk is a randomised controlled trial (RCT). However, in the case of smoking this is ethically not possible. Therefore, an approach should be sought that at least tries to resemble an RCT in design and data analytic approach as closely as possible. Ideally, subjects should be analysed in a 'intention to treat' fashion, i.e. final analyses are based on the groups as these were at the start of the study. In the paper by Van den Berkmortel and coworkers, a considerable number of 'dropouts' occurred, in particular in the intervention group: from 127 smokers at baseline to 33 completers. The study should be designed in a way that the number of evaluable patients is the same at the end of the study. In studies using intermediate endpoints this may be achieved by having end of study measurements performed in those who dropped out during the study.[2] The extent to which this approach was taken is unclear from the paper. Finally, in order to compare non-randomised groups of patients with respect to outcome in a valid manner, multivariate regression models may be applied to adjust for differences at baseline that may lead to different progression rates.[3] Apart from baseline CIMT and alcohol consumption, the authors reported the absence of significant differences across groups at baseline. However, a multivariate analysis would have been appreciated in the paper in addition to the current data presented.

Ideally, one would tend to study smoking effects using cardiovascular events as primary outcome. Yet, using established intermediate endpoints, such as CIMT and arterial stiffness,[4] the sample size of the study and possibly the duration of the study may be considerably reduced. The pros and cons of the final choice of the primary endpoint in a study like the one by Van den Berkmortel has recently been discussed in detail for CIMT measurements.[2] Rather than providing estimates of CIMT progression for all carotid segments separately, there is strong view towards using the mean maximum CIMT as primary outcome. There is considerable variation in the CIMT measurement, which has been attributed to variability due to individuals, sonographers and readers. Obtaining CIMT measurements from various carotid segments, i.e. common and internal carotid artery and carotid bifurcation, near and far wall, left and right carotid artery, and averaging those estimates will likely reduce measurement variability and increase precision of the associations.[5] Recent unpublished analyses from a large multicentre trial[2] indeed showed that reproducibility of CIMT measurements improved considerably when the estimate was based on several measurements as compared with one measurement. Furthermore, rather than subtracting the follow-up measurement from the baseline measurement to obtain a progression estimate, an approach

might be considered in which all in-between measurements are taken into account.[6] The information was collected by Van den Berkmortel, yet not analysed in this manner. In a study where the main focus is on change over time in the outcome parameter, information on reproducibility is essential. The cornerstone of reproducibility is the data based on repeat scans, i.e. where subjects are being examined twice with some time interval (weeks) in between the examinations. Such data reflect variability due to subjects, sonographers, readers and equipment. It is also important to have these repeat scans performed, not only at baseline, not only at the end of the study, but also during the study. In a trial as reported, it should be shown that the reproducibility between readers and that within a reader is good. However, we know that there are 'thick' and 'thin' readers.[7] This means that using the same B-mode images, the reading by reader 1 leads to a higher CIMT estimate compared with the reading by reader 2. What is important for estimates of change over time is that the proportion thick/thin readers remains constant over time.[8] Otherwise, progression estimates tend to become artificially large or small. When, however, the mix thick/thin readers changes over time but equally across the intervention groups it will unlikely affect the comparison across groups. As pointed out by Van den Berkmortel and coworkers, their reproducibility seems good although the data indicating reproducibility over time were not reported. Yet, in almost all of their progression estimates of CIMT, the direction is towards 'regression', which might be indicative of either drift within readers or change in the thick/thin readers mix over time.

When embarking on an intervention study, the assumed effect of the intervention on the primary outcome of the study and the variability of the progression rate, apart from the alpha and power, are the driving forces of the sample size. Van den Berkmortel and coworkers unfortunately did not provide information on sample size assumptions. Based on the start of the study with 127 subjects to intervene upon and the 50 nonsmoking control subjects, one may come up with an effect size of ~100% (no progression in the intervention group compared with controls), assuming a two-sided alpha of 0.05, a 80% power, a two-year CIMT progression of 0.02 mm, and a standard deviation (SD) of the progression rate of 0.05.[5] If we assume an SD of 0.02 (*table 2* in Van den Berkmortel's paper), the effect of quitting smoking should be around a 60% reduction in progression. However, based on the literature,[9] the annual difference in CIMT progression between quitters and those continuing to smoke is around -0.0035 for white middle-aged women and -0.0014 mm for white middle-aged men, constituting much smaller differences in effect than assumed above. In fact, the study by Van den Berkmortel and coworkers was based on the comparison of 33 quitters (instead of 127) with ~50 controls. The posterior power calculation, assuming a 100% reduction, indicated a power of 47%. This may indicate that there is a large probability of falsely saying that 'it is true that quitting smoking has no effect on progression of CIMT or arterial stiffness'.

In conclusion, the authors are to be complimented on their efforts to conduct a study on the effects of quitting smoking on progression of CIMT and arterial stiffness. There may be some possibilities to perform further analyses on the data in order to reduce measurement variability. Yet, the study is likely underpowered to conclude that quitting smoking has no effects on progression of CIMT or arterial stiffness. In light of the adverse effects of smoking on cardiovascular and cancer risk, the authors are correct to conclude that 'Despite the study results, cessation of smoking should be recommended'.

REFERENCES

1. Berkmortel FWPJ van den.Two years of smoking cessation does not reduce arterial wall thickness and stiffness. Neth J Med 2004;62(7/8):235-41.
2. Bots ML, Evans GW, Riley W, et al. The Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) study: design and baseline characteristics. Control Clin Trials 2003;24:752-75.
3. Hoes AW, Grobbee DE, Lubsen J. Primary prevention in hypertension. Valid conclusions from observational studies. Circulation 1991;84:VI78-83.
4. Bots ML, Dijk JM, Oren A, Grobbee DE. Carotid intima-media thickness, arterial stiffness and risk of cardiovascular disease: current evidence. J Hypertens 2002;20:2317-25.
5. Bots ML, Evans GW, Riley W, Grobbee DE. Carotid intima-media thickness measurements in intervention studies. Designs options, progression rates and sample size considerations: a point of view. Stroke 2003;34:2985-94.
6. Espeland MA, Byington RP, Hire D, Davis VG, Hartwell T, Probstfield J. Analysis strategies for serial multivariate ultrasonographic data that are incomplete. Stat Med 1992;11:1041-56.
7. Furberg CD, Byington RP, Craven TE. Lessons learned from clinical trials with ultrasound end-points. J Intern Med 1994;236:575-80.
8. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. JAMA 1996 Sep;276:785-91.
9. Chambless LE, Folsom AR, Davis V, et al. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987-1998. Am J Epidemiol 2002;155:38-47.