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Individual progression of carotid intima media thickness as a surrogate for vascular risk (PROG-IMT): Rationale and design of a meta-analysis project

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Disclosures

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Carotid intima media thickness (IMT) progression is increasingly used as a surrogate for vascular risk. This use is supported by data from a few clinical trials investigating statins, but established criteria of surrogacy are only partially fulfilled. To provide a valid basis for the use of IMT progression as a study end point, we are performing a 3-step meta-analysis project based on individual participant data.

Objectives of the 3 successive stages are to investigate (1) whether IMT progression prospectively predicts myocardial infarction, stroke, or death in population-based samples; (2) whether it does so in prevalent disease cohorts; and (3) whether interventions affecting IMT progression predict a therapeutic effect on clinical end points.

Recruitment strategies, inclusion criteria, and estimates of the expected numbers of eligible studies are presented along with a detailed analysis plan.

Carotid intima media thickness (IMT) is a continuous ultrasound measure of early atherosclerosis and vascular remodeling with the advantages of quick, cheap, and noninvasive assessment. Today, IMT is an important epidemiologic tool that is frequently used in pathophysiologic studies, where it is often regarded as an “intermediate marker” of atherosclerosis. Increasingly, IMT is also used as a surrogate for vascular clinical events, such as myocardial infarction (MI), coronary intervention, stroke, and vascular or total mortality. In this context where the studied exposure is long-standing, as it is typical for genetic or environmental studies, single-measurement IMT is frequently used as the surrogate. In clinical trials where a study drug is tested, the change of IMT over time is typically used as the surrogate parameter.

The criteria of surrogacy have been expressed in various terms, both statistically¹⁻³ and medically.⁴ Different definitions of surrogacy usually include that the surrogate is associated with the end point and that the associations between intervention and surrogate on the one hand and between intervention and end point on the other hand are linked. For single-measurement IMT, the association with future vascular clinical end points has been shown repeatedly in large population-based samples.⁵⁻¹⁵ In a recent meta-analysis, Lorenz et al¹⁶ have provided pooled estimates summarizing this association.

The surrogate IMT change or “individual IMT progression” is typically calculated with linear regression from 2 ultrasound visits. Statements to justify this surrogacy are mostly based on clinical trials of statins¹⁷⁻¹⁹ where a beneficial effect of the study drug on the individual IMT progression is paralleled by a lower risk of the end point event (usually a composite end point including MI, death, and sometimes stroke). Up to now, the confirmation of the links between the treatment effects (expressed as the Prentice¹ criterion of conditional independence) relies on the finding of one single study¹⁷ where the treatment effect on the clinical end point seems to be mediated by IMT change.¹⁸

The current evidence, however, is insufficient for a general recommendation to use IMT progression as a surrogate for vascular risk in pathophysiologic studies or clinical trials. Before this recommendation can be given, 2 issues have to be addressed. First, we need to have quantitative estimates of the association between IMT progression and event risk for different populations and interventions. Second, the link between the treatment effects on IMT change and those on clinical end points have to be shown in >1 trial and for >1 type of intervention. To the best of our knowledge, there are no publications yet that have managed to close these gaps of evidence.

It is very unlikely that any of the open questions can be answered in a single data set. One important reason is the very large variability of IMT progression compared with single-measurement IMT. A second reason has to do with predicting clinical events. In

observational prospective studies, only events that happen after the last measurement defining IMT change can be predicted by IMT change. Therefore, the number of clinical events that can be collected is restricted by the shorter follow-up after (at least) 2 ultrasound visits. The working groups representing 3 of the largest population-based IMT studies (ARIC, CHS, and CAPS) have independently attempted to address this problem (personal communication) and did not succeed with their given sample size. We need considerably larger samples than previously attainable and, moreover, want to synthesize all the evidence currently available. A meta-analysis based on pooled individual data from multiple large population cohorts is the method of choice to answer the open questions and provides the logical continuation of the studies available so far.

The PROG-IMT project

The PROG-IMT is a multinational, multicenter effort to combine individual data from large IMT prospective studies (and in a later stage, clinical trials) to answer a series of questions to investigate whether individual IMT progression can be used as a surrogate for vascular risk. In a meta-analytic approach, we intend to determine the quantitative association between individual progression of carotid IMT and vascular end points. Principal investigators of large IMT studies are cooperating to generate a database containing individual participant data of carotid ultrasound, risk factors, and vascular end points. As the number of relevant studies is constantly growing, the project aims to include additional data sources as time goes by.

Objectives

To investigate individual IMT progression as a surrogate for vascular clinical events, and for the interpretation of the results from IMT progression-based clinical trials or pathophysiologic studies, we want to answer the following questions:

- a. Does IMT progression (independently) predict clinical vascular events (MI, stroke, death) in population-based samples, and how can we translate IMT progression in predicted risk?
- b. Does IMT progression (independently) predict clinical vascular events in prevalent disease populations (eg, coronary heart disease, stroke, hypertension, diabetes), and are the risk estimates comparable between different risk groups and between these and the general population?
- c. Do interventions affecting IMT progression quantitatively predict a therapeutic effect on clinical end points?

Three stages of the project

To answer these questions, data from different types of populations are required. Question (a) will naturally be answered by studying population-based cohorts. Question (b) may be answered by studying at-risk populations or, alternatively, by drawing high-risk subsets out of population samples. Question (c) can only be assessed by investigating multiple clinical trials. Therefore, the project is logically divided into 3 successive stages, even when their time frames overlap. The approximate timeline of the project is shown in Figure 1. At the time of publication of this rationale paper, the project has been running for >1 year.

Search strategy

The search strategy to ensure completeness of the relevant studies includes an extensive PubMed search and hand search of the reference lists of all identified papers, a PubMed search of review articles on IMT and hand search of their reference lists, personal contacts

of all study group members, and communication with pharmaceutical companies that produce drugs for the prevention or treatment of conditions related to atherosclerosis. The keywords for the search and the filter algorithm are derived from the inclusion criteria listed below.

Selection bias

To avoid selection bias, the most important means is to devote great effort and energy in finding relevant studies and in persuading those responsible to cooperate. To find published and unpublished studies, we plan to apply all measures listed above (search strategy). One full position is planned for the whole project duration whose main task is to find and persuade new contacts. The second important factor to ensure cooperation of new contacts is the “critical mass” of study group members who are opinion leaders in the academic world of many countries. Other measures to account for selection bias are the use of appropriate statistical methods (see “Statistical calculations” section below).

Individual patient data

To enable a detailed analysis, we intend to collect individual patient or participant data from eligible studies. These data sets are harmonized to standardize the analyses as far as possible; and the differences in variable definitions, particularities, and restrictions are recorded in a separate file.

Inclusion of studies

The inclusion criteria of stages 1 to 3 are listed in Table I. Before inclusion of a new study data set in the database, the study team is invited to name up to 3 members for admission in the PROG-IMT study group. Stage 1 of the project is already in progress. So far, the PROG-IMT study group comprises 25 scientists from 10 study teams contributing their data sets (Table II); and new members are constantly recruited. A list of study group members and their affiliations can be found in the online Appendix. The decision about when the database is closed for a first analysis of each stage will be made to ensure analyses as complete as possible at the given point of time, with the intention to obtain large numbers and to avoid selection bias.

Expected number of eligible studies

For the calculation of studies eligible for stages 1 and 2, we performed a sensitive PubMed search and filtered the resulting references (automated filter algorithm for relevance and to eliminate multiple publications from one cohort). From the residual references, we manually assessed eligibility in a random subset and extrapolated the results. Next, we made a forward projection over the estimated duration of the project. We found that 25 (95% CI 13-55) studies may be eligible for stage 1 and 10 (3-34) for stage 2.

An alternative approach is selected for clinical trials eligible for stage 3, using trial lists in review papers on the one hand and screening publicly accessible trial databases on the other hand. Under the assumption of 70% sensitivity and 100% specificity of this search, we estimate that 31 studies may be eligible for stage 3 of the PROG-IMT project (about half identified from trial databases, and half from PubMed and review papers).

Analysis strategy for stage 1

As we intend to study the general population, all subjects with previous MI or stroke (ie, before the second ultrasound visit) will be excluded from our analyses for stage 1. End point events analyzed will be MI, stroke (excluding transient ischemic attack), vascular death, and a combined end point consisting of MI, stroke, or vascular death. The studies included used

different end point definitions. To reduce heterogeneity, we will attempt to select end point variables that are as uniform as possible. Redefinition and revalidation of end points at a raw-data level would involve a tremendous workload and will therefore not be attempted.

As future vascular events are intended to be predicted, only events after the second ultrasound visit will be counted. To include as many events as possible, the earliest 2 available visits will be selected. This will usually be the baseline visit and the first follow-up visit. Most studies include only 2 ultrasound visits, so this approach meets the need for uniform analyses. In a secondary analysis, studies with more ultrasound visits may be used for a more precise estimation of individual IMT progression to assess regression dilution bias²⁰ within these studies. The considerable measurement error of IMT as a prognostic variable introduces regression dilution bias, especially when only 2 IMT measurements are used. The data available allow 2 approaches to estimate this bias. Firstly, every IMT study includes reproducibility data based on a short-term follow-up that allow us to estimate the IMT measurement error. With methods like the ones recommended by Hughes,²¹ it is possible to estimate dilution bias and to correct for it. Another approach is the more exact estimation of individual IMT progression in data sets with >2 ultrasound visits using linear regression and to compare the resulting hazard ratio with the estimates from the principal analyses.

The definition of carotid segments will differ between the studies, as found in an earlier paper.¹⁶ For the 3 carotid segments, “common carotid artery” (CCA), “internal carotid artery” (ICA), and “carotid bifurcation,” a compromise will be made between strict selection of studies with consistent definitions and a more liberal inclusion. As the majority of studies—and most IMT end point trials—measured mean CCA-IMT and fewer studies also determined maximal IMT, the principal analyses will focus on mean CCA-IMT. Secondary analyses may focus on maximal CCA-IMT and “meanmax” IMT (the mean of maximal IMT in 6 segments: CCA, bifurcation, and ICA bilaterally).

Some studies measured both near and far wall IMT, whereas a few measured only far wall IMT. Unpublished data from Bots et al (personal communication) show that the mean of near and far wall IMT has lower variance with comparable pathologic significance. In studies with both measures, the IMT will be calculated as the mean of near and far wall measurements; in studies with only far wall IMT, the latter will be analyzed.

Statistical calculations

Given the complexity of the analyses necessary, it is impossible to specify the construction of all the statistical models in advance. The following guidelines refer to the principal analyses planned; modifications and secondary analyses are likely to arise during the project.

Using Cox regression models, the influence of “individual IMT progression per year” on the hazard of clinical events will be calculated for every study in a uniform way. The estimates of all studies will be combined in a random-effects meta-analysis²² using the method of moments approach from DerSimonian and Laird²³ where the weights of the studies depend on the variance of their estimates and the extent of between-study heterogeneity.

To account for the potential influence of the time interval between the visits, this time span will be included in the model as a covariate. In a sensitivity analysis, the mean of IMT measurements 1 and 2 will be included, too. If influential, this variable can be added to the final model. All models will be reported adjusted for age and sex, and adjusted for a larger predefined set of confounders (age, sex, body mass index, systolic and diastolic blood pressure, antihypertensive treatment, total or low-density lipoprotein cholesterol, lipid-

lowering treatment, diabetes, smoking status, creatinine, hemoglobin). The list of confounders adjusted for may be modified depending on the variables universally available. As most confounders will be available for both visits, we may calculate both the mean of and difference between the 2 measurements. Where variables are not available for both visits or include many missing values, practical decisions will have to be made to exclude either confounders or studies.

Where a number of studies with <20 events for an end point are included (Table I), a model adjusted for many confounders may be overfitted. In this case, these small studies may be pooled in one model stratified for study, rather than entered separately into the random-effects meta-analysis. The strategies to deal with missing values will depend on the data with respect to the number of missing values. Multiple imputation²⁴ will be used and compared with complete cases analysis. For every regression model, the assumptions will be assessed with appropriate methods. With meta-regression techniques, the influence of study-level variables on the risk estimates may be assessed.²⁵ With funnel plot techniques, we will search for evidence of publication bias.²⁶

Analysis strategy for stage 2

The analysis of stage 2 of the PROG-IMT project will work along the lines of stage 1 in many aspects, with the following additions. To investigate comparable populations, it may be attempted to harmonize cohort inclusion criteria, if the number of events is not severely reduced. As the ways of recruiting the participants differ between population-based cohorts and at-risk cohorts, subsets of population samples will be analyzed separately (Table I).

Analysis strategy for stage 3

Compared with most observational studies, clinical trials measuring IMT typically have more ultrasound visits at more frequent intervals, for example, 5 in 2 years, to determine IMT progression more precisely. To preserve this precision, the ultrasound visits will be used as intended by the study protocol, as far as this does not interfere with the practicability of the meta-analysis. This is facilitated by the fact that, for this analysis, all clinical end points after inclusion into the trial (even before the last ultrasound visit) can be used.² A secondary analysis will be restricted to include only those clinical events that occur after the measurement of IMT progression during the trial. This will be done to address any potential bias that arises from selective dropout or loss to follow-up that prevents IMT from being measured during the trial for certain individuals. The choice of using mean or maximal IMT, or a combination (like meanmax IMT) will be made depending on the available data and on the results of stages 1 and 2 of the project.

To assess whether the effect of an intervention on IMT progression predicts the effect of this intervention on the clinical end points, the approach described by Daniels and Hughes² will be used. Their approach models the association of the intervention effect on the surrogate marker (difference in mean IMT progression) with the intervention effect on the clinical end point (log hazard ratio of a Cox regression model) with a bivariate normal distribution across trials. They recommend fitting the model with a Bayesian approach because this can allow for the imprecision in both estimated intervention effects. Given sufficient heterogeneity of the intervention effect on IMT, a linear association between these 2 effects can be tested and quantified. One particular property of this model is that, although the covariance estimate of this bivariate distribution can only be exactly determined from patient-level data, the covariance estimate may often be very similar between trials.² This fact may allow the option to include additional data sets of trialists unable to provide patient-level data by using publication-level information.

The trials will be analyzed stratified by type of intervention (see inclusion criteria) and—if the number of trials allows—by population type. Interventions will be classified as of the same type when they share the biological basis of action. Rare intervention types may be included if at least 5 trials of this type are available.

Summary

The PROG-IMT project addresses important steps on the way to a thorough understanding of the association between the change of IMT over time and the incident risk of vascular events. The project requires extensive statistical analyses, given the complex nature of the data available. In a joint effort, the project necessitates the cooperation of many coworkers in the field of atherosclerosis research, which has so far been exemplarily granted. We wish to encourage our fellow researchers to cooperate and to participate in our project to achieve its goals and to create a sound basis for the use of IMT progression in future studies and trials.

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References

1. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Statist Med.* 1989; 8:431–40.
2. Daniels MJ, Hughes MD. Meta-analysis for the evaluation of potential surrogate markers. *Stat Med.* 1997; 16:1965–82. [PubMed: 9304767]
3. Molenberghs G, Burzykowski T, Alonso A, et al. A perspective on surrogate endpoints in controlled clinical trials. *Stat Methods Med Res.* 2004; 13:177–206. [PubMed: 15198486]
4. Boissel JP, Collet JP, Moleur P, et al. Surrogate endpoints: a basis for a rational approach. *Eur J Clin Pharm.* 1992; 43:235–44.
5. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation.* 1993; 87(suppl II):II-56-65.
6. Bots ML, Hoes AW, Koudstaal PJ, et al. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation.* 1997; 96:1432–7. [PubMed: 9315528]
7. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol.* 1997; 146:483–94. [PubMed: 9290509]
8. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med.* 1999; 340:14–22. [PubMed: 9878640]
9. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol.* 2000; 151:478–87. [PubMed: 10707916]
10. Iglesias del Sol A, Bots ML, Grobbee DE, et al. Carotid intima-media thickness at different sites: relation to incident myocardial infarction; the Rotterdam Study. *Eur Heart J.* 2002; 23:934–40. [PubMed: 12069447]
11. Hollander M, Hak AE, Koudstaal PJ, et al. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. *Stroke.* 2003; 34:2367–72. [PubMed: 12958327]
12. Kitamura A, Iso H, Imano H, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. *Stroke.* 2004; 35:2788–94. [PubMed: 15528460]
13. Rosvall M, Janzon L, Berglund G, et al. Incident coronary events and case fatality in relation to common carotid intima-media thickness. *J Intern Med.* 2005; 257:430–7. [PubMed: 15836659]
14. Rosvall M, Janzon L, Berglund G, et al. Incidence of stroke is related to carotid IMT even in the absence of plaque. *Atherosclerosis.* 2005; 179:325–31. [PubMed: 15777549]
15. Lorenz MW, von Kegler S, Steinmetz H, et al. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke.* 2006; 37:87–92. [PubMed: 16339465]

16. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007; 115:459–67. [PubMed: 17242284]
17. Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med*. 1996; 124:548–56. [PubMed: 8597317]
18. Espeland MA, O'leary DH, Terry JG, et al. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. *Curr Control Trials Cardiovasc Med*. 2005; 6:3. [PubMed: 15760471]
19. Orloff DG. Use of surrogate endpoints: a practical necessity in lipid-altering and antiatherosclerosis drug development. *Am J Cardiol*. 2001; 87(suppl):35A–41A.
20. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990; 335:765–74. [PubMed: 1969518]
21. Hughes MD. Regression dilution in the proportional hazards model. *Biometrics*. 1993; 49:1056–66. [PubMed: 8117900]
22. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J Roy Stat Soc A*. 2009; 172:137–59.
23. DerSimonian R, Laird N. Meta-analysis in clinical studies. *Control Clin Studies*. 1986; 7:177–88.
24. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009; 338:b2393. [PubMed: 19564179]
25. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med*. 2002; 21:1559–73. [PubMed: 12111920]
26. Rothstein, HR.; Sutton, AJ.; Borenstein, M., editors. *Publication bias in meta-analysis*. Wiley; 2005. p. 75-98.

Figure 1.

Table I

Inclusion criteria for stages 1 to 3 of the PROG-IMT project

Stage 1	Stage 2	Stage 3
Prospective longitudinal study design		
Observational study	Randomized controlled trial with interventional arm and placebo or standard treatment arm Investigation of one of the following interventions: ○ Lipid-lowering agents ○ Antihypertensive drugs ○ Any other type of intervention when at least five trials studying this intervention type are available with the necessary data	
General population-based sample or a sample similar to the general population	Investigation of one of the following at-risk populations: - Hypertensive subjects - Diabetic subjects - Subjects with coronary heart disease - Subjects with stroke or transient ischemic attack - Other defined at-risk populations if a sufficient number of studies/trials is found	
	Alternatively, population-based samples with a relevant subcohort (at least 20 events) in at least one of the above named at-risk categories	
Well-defined and disclosed inclusion criteria and recruitment strategy		
At least two ultrasound visits where carotid IMT was determined		
Clinical follow-up after the second ultrasound visit, recording MI, stroke, death, vascular death or a subset of these	All clinical events recorded in the trial	
A minimum of 20 events per endpoint [*]	No minimum rate of endpoint events	

^{*} If the number of events for one end point is <20, the study will usually be excluded from analyses regarding this end point. If many studies have <20 events for some end points, it may be decided to include them all the same; however, the analyses may be modified for these studies (see text).

Table II

List of data sets for stage 1 of the PROG-IMT project

Study name	Acronym or abbreviation	Country	n	Time between ultrasound visits 1 and 2	Clinical follow-up after visit 2	IMT values available	Cooperation	Data available
Atherosclerosis Risk in Communities	ARIC	United States	15000	3 y	8 y	Mean, max	No, public use data set used	Delivered
Cardiovascular Health Study	CHS	USA	4500	3 y	12 y	Mean, max	Yes	Delivered
Rotterdam Study	Rotterdam	Netherlands	8000	6 y	6 y	Mean, max	Yes	Delivered
Carotid Atherosclerosis Progression Study	CAPS	Germany	5000	3 y	7 y	Mean	Yes	Delivered
Bruneck Study	Bruneck	Austria	1000	5 y	5 y	Mean, max	Yes	Delivered
Tromsø Study	Tromsø	Norway	5000	6 y	4 y	Mean, max	Yes	Delivered
Northern Manhattan Study	NOMAS	USA	1500	3y	4y	Mean, max	Yes	Delivered
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	INVADE	Germany	3500	2 y	6 y	Mean	Yes	Delivered
Progression of Lesions in the Intima of the Carotid	PLIC	Italy	2000	2 y	4 y	Mean	Yes	11/2009
Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk	SAPHIR	Austria	1500	4.5 y	6 y	Mean, max	Yes	12/2009
Malmö Diet and Cancer Study	MDCS	Sweden	5000	2 y	6 y	Mean	Yes	2010