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Prediction of Clinical Cardiovascular Events With Carotid Intima-Media Thickness

A Systematic Review and Meta-Analysis

Matthias W. Lorenz, MD; Hugh S. Markus, MD, PhD, FRCP; Michiel L. Bots, MD, PhD; Maria Rosvall, MD, PhD; Matthias Sitzer, MD, PhD

Background—Carotid intima-media thickness (IMT) is increasingly used as a surrogate marker for atherosclerosis. Its use relies on its ability to predict future clinical cardiovascular end points. We performed a systematic review and meta-analysis of data to examine this association.

Methods and Results—Using a prespecified search strategy, we identified 8 relevant studies and compared study design, measurement protocols, and reported data. We identified sources of heterogeneity between studies. The assumption of a linear relationship between IMT and risk was challenged by use of a graphical technique. To obtain a pooled estimate of the relative risk per IMT difference, we performed a meta-analysis based on random effects models. The age- and sex-adjusted overall estimates of the relative risk of myocardial infarction were 1.26 (95% CI, 1.21 to 1.30) per 1–standard deviation common carotid artery IMT difference and 1.15 (95% CI, 1.12 to 1.17) per 0.10-mm common carotid artery IMT difference. The age- and sex-adjusted relative risks of stroke were 1.32 (95% CI, 1.27 to 1.38) per 1–standard deviation common carotid artery IMT difference and 1.18 (95% CI, 1.16 to 1.21) per 0.10-mm common carotid artery IMT difference. Major sources of heterogeneity were age distribution, carotid segment definition, and IMT measurement protocol. The relationship between IMT and risk was nonlinear, but the linear models fitted relatively well for moderate to high IMT values.

Conclusions—Carotid IMT is a strong predictor of future vascular events. The relative risk per IMT difference is slightly higher for the end point stroke than for myocardial infarction. In future IMT studies, ultrasound protocols should be aligned with published studies. Data for younger individuals are limited and more studies are required. **(*Circulation*. 2007;115:459-467.)**

Key Words: atherosclerosis ■ carotid arteries ■ meta-analysis ■ myocardial infarction ■ stroke

Carotid intima-media thickness (IMT) is an intermediate phenotype for early atherosclerosis. Because it can be measured relatively simply and noninvasively, it is well suited for use in large-scale population studies. Ultrasonic measurements correlate well with histology,[1] and increased IMT is associated with vascular risk factors[2–12] and the presence of more advanced atherosclerosis, which includes coronary artery disease.[2–5,7,10,12] IMT is being increasingly used for risk stratification in individuals and as an end point in intervention studies. An important precondition for this application of IMT is that it can predict future risk of clinical vascular events. A number of longitudinal studies have examined the relationship between IMT and future events, most frequently the incidence of cardiac events (myocardial infarction [MI], angina pectoris, coronary intervention) and cerebrovascular events (stroke or transient ischemic attack [TIA]).[2–12]

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Different longitudinal studies have used different measurement methods and studied different populations. Furthermore, some studies have investigated relatively small populations, which resulted in large confidence intervals (CIs) for the risk estimates. We carried out a systematic review of the literature to provide an overview of the relevant studies, critically appraise the methods used, and where possible perform a meta-analysis to gain more robust estimates of the predictive value of increased IMT for clinical cardiovascular end points.

Methods

Study Selection and Data Collection

Data sources were identified with a Medline search and a manual search of the citation lists of the relevant publications. Key words for

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TABLE 1. Overview of Studies on the Association of Carotid IMT and Clinical End Points, Sorted by Date of First Publication

Study	Publication	Design	End Points	Population	Sample Size at Risk/Events	Follow-Up	Segments*	IMT Definition	Adjusted for	IMT Modelled as
KIHD (Kuopio Ischemic Heart Disease Risk Factor Study)	Salonen 1993[2]	Longitudinal	Definite or possible MI	Men 42 to 60 y	1275/36	1 mo to 3 y	CCA	Maximal IMT, near+far wall	Unadjusted (effect size for adjusted model not published)	Continuous
ARIC (Atherosclerosis Risk in Communities Study)	Chambless 1997[4] or unpublished data†	Longitudinal	MI	45 to 64 y without previous event	10 841/290 or 13 204/626†	5.2 y or 10.6 y †	CCA, Bif, ICA, combined‡	Mean IMT, far wall	Age, race, community, stratified for sex	Continuous, tertiles, 95th percentile, fixed cut-off points
	Chambless 2000[6] or unpublished data†	Longitudinal	Stroke		14 214/199 or 14 165/371†	7.2 y or 10.7 y †	CCA, Bif, ICA, combined‡	Mean IMT, far wall	Age, race, community, stratified for sex	Continuous, tertiles, 95th percentile, fixed cut-off points
Rotterdam Study	Bots 1997[3]	Nested case-control	MI, stroke	≥55 y	Cases: 98 (MI), 95 (strokes); Controls: 1373	2.7 y	CCA	Mean IMT, near+far wall	Age, sex, BMI, smoking, diabetes, hypertension, systolic and diastolic blood pressure, total and HDL cholesterol, previous stroke and MI	Continuous, quartiles
	Iglesias del Sol 2002[7]	Case-cohort	MI		Cases: 194; Controls: 2073	4.6 y	CCA, Bif, ICA, combined	Maximal IMT, near+far wall, far wall	Age, sex, BMI, systolic and diastolic blood pressure, total and HDL cholesterol, smoking, diabetes	Continuous, quartiles
	Hollander 2003[8]	Longitudinal	Stroke		5479/378	6.1 y	CCA	Mean IMT, near+far wall	Age, sex, diabetes, smoking history, systolic and diastolic blood pressure, total and HDL cholesterol, history of cardiovascular disease	Continuous, tertiles
CHS (Cardiovascular Health Study)	O'Leary 1999[5]	Longitudinal	MI, stroke	≥65 y without cardiovascular disease	4476/267 (MI), 284 (strokes)	6.2 y	CCA, ICA, combined	Maximal IMT, near+far wall	Age, sex, systolic and diastolic blood pressure, atrial fibrillation, diabetes, nicotine consumption	Continuous, quintiles
(No acronym)	Kitamura 2004[9]	Longitudinal	Stroke	Men 60 to 74 y without previous stroke or CHD	1289/34	4.5 y	CCA, ICA, combined	Maximal IMT, near+far wall	Age, systolic blood pressure, antihypertensive medication, ST-T abnormalities, BMI, community	Quartiles
MDCS (Malmö Diet and Cancer Study)	Rosvall 2005 (a)[10]	Longitudinal	MI or cardiac death	46 to 68 y without previous stroke or cardiovascular disease	5163/113	7 y	CCA	Mean IMT, far wall, right side only	Age, sex, low physical activity, smoking habits, systolic blood pressure, treatment for hypertension, presence of diabetes, LDL-cholesterol, HDL-cholesterol, triglycerides, waist circumference	Continuous, tertiles, fixed cut-off points
	Rosvall 2005 (b)[11]	Longitudinal	Stroke		5163/86	7 y	CCA	Mean IMT, far wall, right side only	Age, sex, low physical activity, smoking habits, systolic blood pressure, treatment for hypertension, presence of diabetes, LDL-cholesterol, HDL-cholesterol, triglycerides, waist circumference	Continuous, tertiles, fixed cut-off points
LILAC (Longitudinal Investigation for the Longevity and Aging in Hokkaido County)	Murakami 2005[19]	Longitudinal	All-cause and vascular mortality	>75 y	298/30 (death), 9 (cardiovascular death)	3.2 y	CCA	Near+far wall§	Age, Mini-Mental State Examination Score	Continuous
CAPS (Carotid Atherosclerosis Progression Study)	Lorenz 2006[12]	Longitudinal	MI, stroke	19 to 90 y	5052/228 (myocardial event), 107 (stroke or TIA), 50 (death)	4.2 y	CCA, Bif, ICA	Mean IMT, far wall	Age, sex, BMI, systolic and diastolic blood pressure, antihypertensive and lipid-lowering medication, LDL cholesterol, nicotine consumption, diabetes	Continuous, quartiles

*CCA indicates common carotid artery; Bif, carotid bifurcation; ICA, internal carotid artery.
†Authors' own calculations with the ARIC limited access data set (see Methods).
‡Missing values if IMT sites were imputed.
§No clear description of IMT measurement protocol.

the Medline search were *carotid intima media thickness* or *carotid intima media thickening* and *stroke* or *myocardial infarction* or *death*. In a second Medline search, we identified reviews on IMT and checked them for relevant citations. Key words included *review* and *carotid intima media thickness* or *carotid intima media thickening*. Studies were considered to be relevant if the sample was general-population based (and not a specific risk population), if carotid IMT had been measured, and if subjects had been followed up for vascular clinical end points. If the desired results, ie, relationship between IMT and prospective risk of vascular events, were not reported in the publications identified, we searched for additional publications by study/author name. The search was carried out on January 31, 2006.

If the publications did not contain the full information necessary for meta-analysis, we obtained the missing information directly from the authors (see Acknowledgments). The National Heart, Lung, and Blood Institute in the United States provided the original data (limited-access dataset) of the Atherosclerosis Risk in Communities (ARIC) study, from which the hazard ratios (HRs) were newly calculated for uniformity of the estimates. Exclusion criteria and end point definitions were applied exactly as stated in the publications, but because the available dataset contained a later follow-up, the number of events is higher than in the publications (Table 1).

Statistical Analyses

The HRs and CIs of comparable studies were illustrated with forest plots. Pooled estimates were calculated with a random effects model as recommended by Blettner et al,[13] with the method of moments approach from DerSimonian and Laird.[14] Different standard deviations (SDs) of IMT distributions can be caused by population properties (eg, different age distributions[12]) or properties of the ultrasound technique (eg, reproducibility), or a combination of both aspects. If one assumes that the populations in the different studies share the same underlying IMT distribution and the same hazard function, then different SDs of IMT measurements are likely to be

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the result of measurement error, and the risk per IMT difference of 1 SD can be compared without conversion. On the other hand, if we compare populations with different baseline hazards that are influenced by a common IMT hazard function, we have to compare HRs per absolute IMT difference. We decided to implement both strategies: to compare HRs per 1 SD and those expressed as HRs per (absolute) 0.10-mm difference.

To ensure uniformity of estimates, we compared HRs that were adjusted by age and sex. Because the publications from the ARIC study[4,6] were stratified by sex, we recalculated age- and sex-adjusted HRs from the original dataset (see Study Selection and Data Collection). To compare fully adjusted models, we tried to gain uniformly adjusted HRs by recalculation of our own datasets (M.R. for the Malmo Diet and Cancer Study [MDCS], M.B. for the Rotterdam Study, and M.W.L. for the Carotid Atherosclerosis Progression Study [CAPS]) and the ARIC data, and by personal communication with the other authors.

From every study, the HRs per IMT difference were log-transformed to obtain symmetric CIs. The standard error of this point estimator was recalculated for every study by log-transformation of the 95% CI limits. The difference between the log(lower limit) and log(upper limit) was divided by 2×1.96 (the 97.5% normal percentile) to obtain the standard error. The point estimator from every study was weighted with the inverse of the square of its standard error to calculate compound estimators. To investigate heterogeneity, we used the I^2 statistics provided by Higgins et al.[15] To identify study variables that contributed particularly to heterogeneity, we performed a meta-regression analysis with restricted maximum likelihood estimates that accounted for residual heterogeneity, as recommended by Thompson and Sharp.[16] To assess possible publication bias, we used a nonparametric iterative trim-and-fill procedure suggested by Duval and Tweedy.[17,18]

The reporting of HRs per IMT difference is based on the assumption that there is a linear relationship between IMT and hazard (in the strict sense, a relationship implied by a linear model is log-linear but is mostly referred to as linear[4,6]). To reassess this assumption with reference to the publications of interest, we used a graphical technique introduced by Chambless et al.[4,6] The relative hazards for vascular events are plotted against baseline IMT for a set of 3 to 6 IMT categories and compared with the assumed linear relationship. Because the IMT cut points must define large proportions of the samples, they depend on the distribution and cannot use the same reference category. The relative hazards for the IMT categories were recalculated or taken from the publications, and the mean IMT values for every IMT category were acquired from the corresponding author directly.

The recalculation of the ARIC, MDCS, and CAPS HRs and the meta-regression were performed with SAS (The SAS Institute, Cary, NC). Forest plots were produced by a Microsoft Excel macro program provided by Peter Rothwell and Enrico Flossmann and modified by M.W.L. Intraclass correlation coefficients were recalculated with SPSS 11.5 (SPSS Inc., Chicago, Ill). The trim-and-fill procedure was calculated manually with assistance of an Excel spreadsheet. M.W.L. had full access to and takes responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

We identified 8 observational studies with general population-based samples for which carotid IMT was measured and follow-up for clinical end points was provided. For the analysis, we focused on the data given in 12 publications on these 8 studies,[2–12,19] which represent 37 197 subjects.

Table 1 provides an overview of the studies in terms of the study design, definition of clinical end points, observed population, sample size, follow-up period, carotid segments studied, definition of IMT, model construction (which accounts for potential bias factors), and report of results. The studies exhibited considerable variation in all of these aspects. In particular, there are marked differences in age distribution, with a lower limit that ranges from 19[12] to 75 years.[19] Furthermore, the publications can be divided into 2 categories: those that use mean carotid IMT, determined from a number of IMT measurements at specific positions or by automated software over a segment of the artery, and those that use maximal carotid IMT. The Rotterdam Study is the only one in which IMT was determined by both methods in the same population.[7,8]

For further analyses, the Kuopio Ischemic Heart Disease Risk Factor Study,[2] the study reported by Kitamura et al,[9] and the Longitudinal Investigation for the Longevity and Aging in Hokkaido County[19] were excluded because they did not provide estimates that were comparable to the other studies.

Assessment of Potential Sources of Heterogeneity and Confounding

To determine the comparability of the populations, we calculated event rates (events per 1000 person-years) and absolute common carotid artery (CCA) IMT values for all the studies (Table 2). The event rates show distinct differences that may be largely attributable to the definition of end points. Maximal IMT was more or less comparable in terms of mean values, but the SDs were different. Mean IMT values were similar, but values from different studies exhibited different distributions.

The study design was longitudinal in all publications apart from those by Bots et al and Iglesias del Sol et al,[3,7] who used a nested case-control design and a case-cohort design, respectively. The work by Iglesias del Sol et al[7] was analyzed with the longitudinal studies, as the Cox regression model estimators of a case-cohort design are comparable with those of a longitudinal design.[23] The publication by Bots et al[3] was omitted because it refers to the same population as the other 2 publications on the Rotterdam Study and has a study design that provides results that are somewhat difficult to compare with those from longitudinal studies.

Figure 1 illustrates the definitions of the carotid segments for each study. This is obviously a major source of heterogeneity, because, between some studies, the "same" segments do not even overlap. Furthermore, the publications differed in terms of how the results were reported (Table 1). The majority of studies reported calculations from age- and sex-adjusted models. The most commonly reported estimator was the relative risk (provided as HR) per (linear) IMT difference of 1 SD. Another source of heterogeneity is the reproducibility of the IMT measurement procedures, as shown in Table 2. The reproducibility has clearly improved over time.

By means of a meta-regression analysis (see Methods), we determined the influence of sample properties (mean age, duration of follow-up, mean deviation, and SD of IMT) and measurement properties (maximal or mean IMT, near and far wall versus far wall IMT, 1 side versus both sides, position and length of the examined carotid segment, and reproducibility) on the hazard estimate between studies. The duration of follow-up was the strongest (and the only significant) predictor of the magnitude of the log-HR for stroke per IMT difference ($P=0.0424$). However, this result withstood neither multivariate modeling nor adjustment for multiple testing.

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TABLE 2. Comparison of Age Range, Event Rates, CCA IMT, and Reproducibility in Different Populations

Population	Mean Age, y	Event Rate for MI (per 1000 Person-Years)	Event Rate for Stroke (per 1000 Person-Years)	Mean IMT, mm	Maximal IMT, mm	Intersonographer Reproducibility: Intraclass Correlation Coefficient of CCA IMT	Intersonographer Reproducibility: Average Absolute Difference of Replicate Measures, mm
ARIC*	54	4.4	2.4	0.63±0.16	. . .	0.48	0.17±0.17
Rotterdam Study[3,7,8]	70	. . .	11.3	0.80±0.16	1.03±0.22	0.78–0.84[20]	0.06±0.09†
CHS[5]	73	9.6	10.2	. . .	1.03±0.20	ICC not given, r^2=0.52	0.20±0.26[21]
Kitamura 2004[9]	66	. . .	5.9	. . .	1.03±0.43	Not given§	Not given§
MDCS[10,11]	57	3.2	2.4	0.77±0.15†‡	. . .	ICC not given, r^2=0.85[22]	0.10±0.10[22]
CAPS[12]	50	10.7	5.0	0.73±0.16	. . .	0.97	0.11±0.08

*Missing values if IMT sites were imputed; IMT values were adjusted according to reader differences. All statistics are the authors' own calculations on the ARIC data set (see Methods).

†Ascertained by contacting the corresponding author directly.

‡Only right side was examined.

§Only 1 observer.

Assessment of the Relationship Between IMT and Hazard

To challenge the assumption of a linear IMT–hazard relationship, we used the graphical method described above (Figure 2). The confidence bands cross the dashed lines, which indicate that the linear model violates the assumption of linearity in the 2 largest studies[4–6] (data not shown). For the majority of populations, the slope of the relationship between IMT and hazard is steeper for low to average IMT values (as can be seen in Figure 2), with the slope for the highest IMT categories being relatively moderate. In most of the studies, however, the linear model corresponds well to the categorized analysis for higher IMT values.

HR per IMT Difference Meta-Analysis

As stated in the Methods, different assumptions of the underlying distributions lead to different reference units of IMT. In Figure 3 we display the risk of MI and stroke in the 5 remaining studies, expressed as HR per CCA IMT difference of 1 SD of baseline IMT. Figure 4 shows the plots that correspond to HR per absolute CCA IMT difference of 0.1 mm. Figures 5 and 6 display the same calculations for the HRs of fully adjusted models. In comparison of the plots, we observed that HRs decrease when adjusted for a complete set of cardiovascular risk factors as compared with age- and sex-adjusted estimates. Furthermore, we can see that the HR per IMT difference is slightly higher for stroke than for MI. The heterogeneity is larger for the estimates of MI risk. In an attempt to reduce heterogeneity by strict selection of studies that used identical, or at least comparable, definitions of the carotid segments (Figure 1), we calculated the overall estimates shown in Table 3. The estimates or relative risk for stroke still remained higher than for MI, and the studies are more heterogeneous for MI.

The trim-and-fill procedure found no evidence of publication bias.

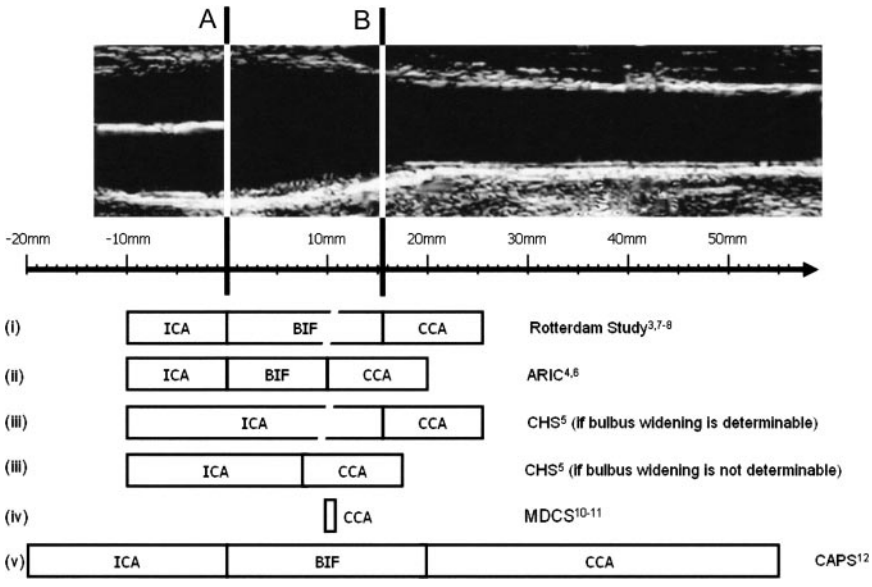

Figure 1. Definitions of the carotid segments in each clinical study, illustrated with an example scan. Anatomic landmarks used as reference points were (A) the tip of the flow divider and (B) the beginning of the bulb widening. Definition of CCA: (i) 10-0 mm before the bulb widening; (ii) 20-0 mm proximal to the tip of the flow divider; (iii) 10-0 mm before bulb widening or (if widening is not determinable) 18-8 mm proximal to the tip of the flow divider; (iv) 10-0 mm before the bulb widening; (v) 60-20 mm proximal to the tip of the flow divider. Definition of bifurcation (BIF): (i) between the beginning of the bulb widening and the tip of the flow divider; (ii) 10-0 mm proximal to the tip of the flow divider; (iii) none; (iv) none; (v) 20-0 mm proximal to the tip of the flow divider. Definition of internal carotid artery (ICA): (i) 0-10 mm distal from the tip of the flow divider; (ii) 0-10 mm distal to the tip of flow divider; (iii) carotid bulb up to 10 mm distal to the tip of the flow divider; (iv) none; 0-20 mm distal to the tip of the flow divider. CHS indicates Cardiovascular Health Study.

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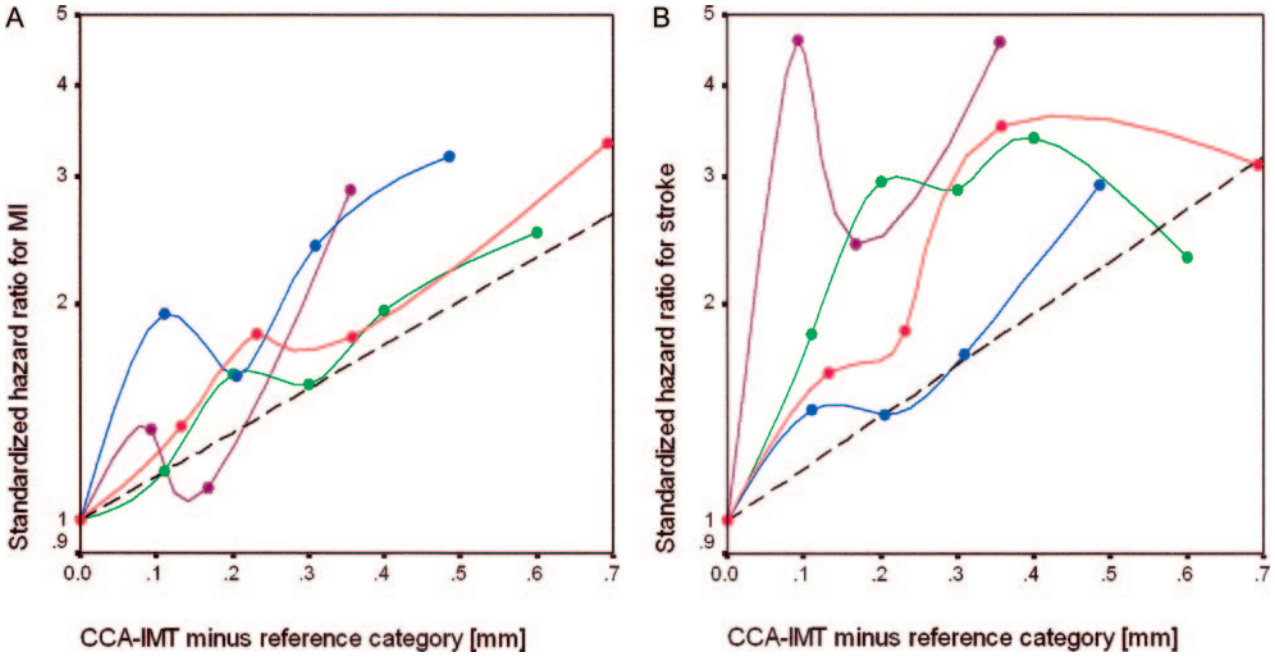

Figure 2. Plots of HRs for vascular events against CCA-IMT (adjusted for age and sex). A, the HRs for MI; B, the HRs for stroke. The HRs were standardized with a constant exponent per study to refer to common linear relationship, which is indicated by the dashed black line. Red line, ARIC study (our own calculations with the ARIC limited access dataset; see Methods); blue line, CHS[5]; green line, MDCS[10,11]; purple line, CAPS.[12]

Discussion

In this systematic review and meta-analysis, we reviewed data from 37 197 subjects who were followed up for a mean of 5.5 years. Our analysis provides data on the use of carotid IMT to predict MI and stroke in the general population. By means of meta-analysis techniques we obtained robust age- and sex-adjusted risk estimates. For an absolute carotid IMT difference of 0.1 mm, the future risk of MI increases by 10% to 15%, and the stroke risk increases by 13% to 18%. The risk for both end points decreased with the number of adjustments for risk factors. The present review also highlights potential difficulties that result from the different methodologies used.

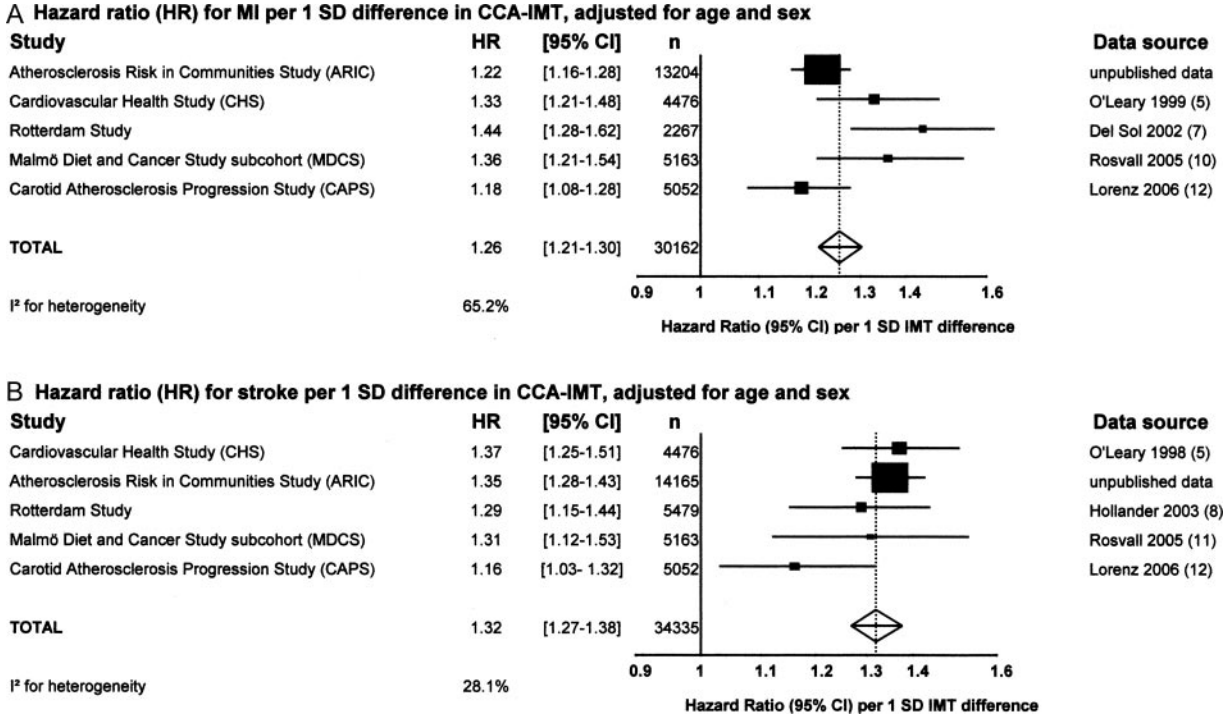

Figure 3. Forest plots of the HRs per 1 SD difference in the CCA-IMT, adjusted for age and sex.

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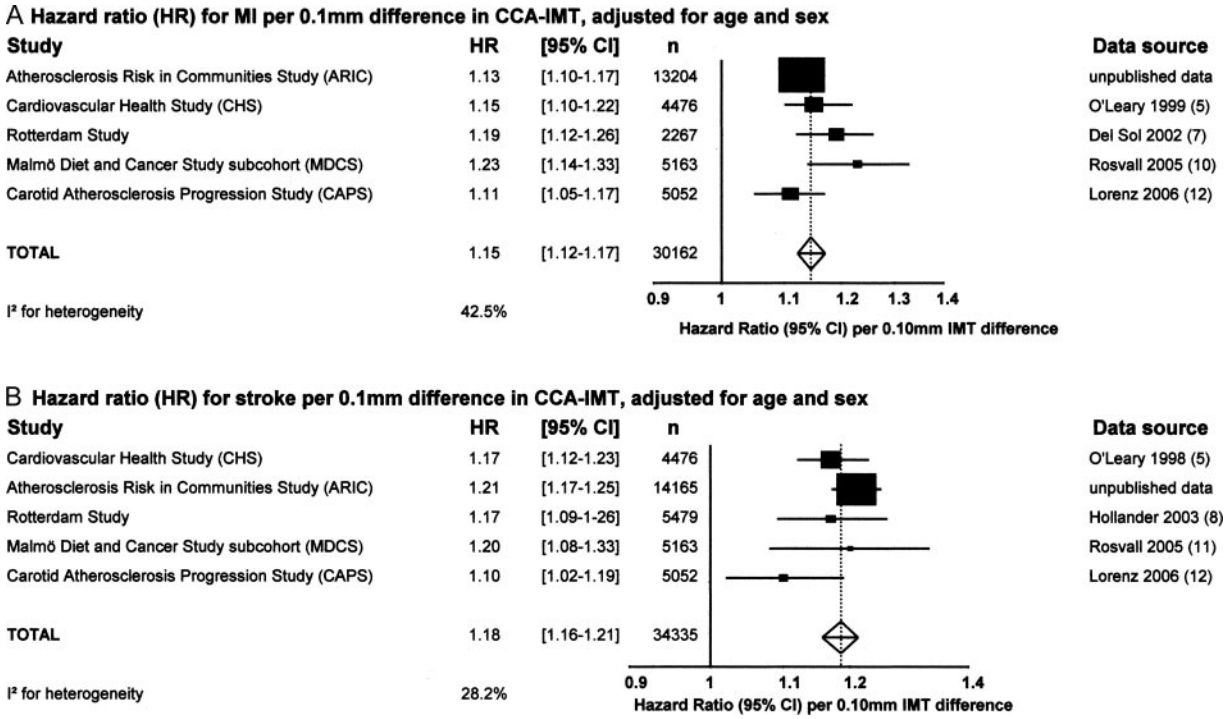

Figure 4. Forest plots of the HRs per 0.10-mm difference in the CCA-IMT, adjusted for age and sex.

Low Specificity of IMT Location for a Clinical End Point

Most studies that investigated the risk of both myocardial and cerebrovascular end points resulted in similar HRs for both end points. The ARIC study[4,6] revealed the largest differences (eg, MI versus stroke risk, 1.13 versus 1.21, translated into risk ratio per 0.10-mm CCA IMT difference, adjusted for age and sex). The Cardiovascular Health Study[5] shows a higher relative risk for stroke, too. The other 3 large studies[7,8,10–12] resulted in an insignificantly higher relative risk of MI. The difference found in this meta-analysis is just statistically significant, as the CIs do not overlap for the models of HR per SD IMT difference. However, the difference is small. This lack of specificity for the target organ has been described by other authors,[5–6] who drew the conclusion that early atherosclerotic changes are noncausal and nonspecific markers of atherosclerotic complications.[6]

Heterogeneity of Ultrasound Protocols

We determined multiple sources of heterogeneity between the studies. These include the details of the ultrasound protocol, namely the precise definitions of the carotid segments investigated, the use of mean or maximal IMT, the measurement of near and far wall or only far wall IMT, and whether IMT was measured only on 1 side or on both sides. Reproducibility has improved considerably over the past decades. The study populations differed with respect to age distribution, selection criteria, and length of follow-up. With the exception of the duration of follow-up, none of the sample and measurement properties significantly explained the heterogeneity between the studies. The fact that parameters such as the position of the carotid segment (Figure 1) do not significantly influence the hazard estimate puts the multiple differences between the ultrasound protocols into perspective. However, with only 5 studies to compare, the statistical power of the meta-regression is limited.

There are good arguments for and against each IMT measurement protocol used. Nevertheless, we strongly recommend the use of a standardized protocol for future studies. A recent consensus paper[24] has given some guidance on this. It is noteworthy that this consensus paper recommends measurement of IMT in plaque-free areas. The ultrasound protocols of the epidemiological studies discussed in the present study do not explicitly state how to deal with plaques, but, given that all of them use clear anatomic landmarks, it is likely that, in the IMT measurements, plaque thickness would have been incorporated and measurements would not all have been in plaque-free regions. However, in a general population-based survey with low prevalence of plaque, this is unlikely to be a major confounding factor. For epidemiological studies of low-risk populations, we suggest adherence to exact anatomic definitions. Whenever risk populations are surveyed, the consensus paper[24] recommendation applies. To ensure clinically meaningful results, we suggest adoption of the ultrasound protocol of one of the large studies mentioned in the present study (Table 1), preferably of a study with a target population similar to that of the intended study. If a single protocol is established in future, it should have demonstrated good reproducibility and a solid database that demonstrates the clinical relevance of IMT measured by this method. Both are true for the measurement and analysis protocol of CAPS.[12]

Nonlinear Relationship Between IMT and Risk

When IMT is used as a risk predictor, it is often assumed that the relationship between IMT and risk is linear. Our analysis

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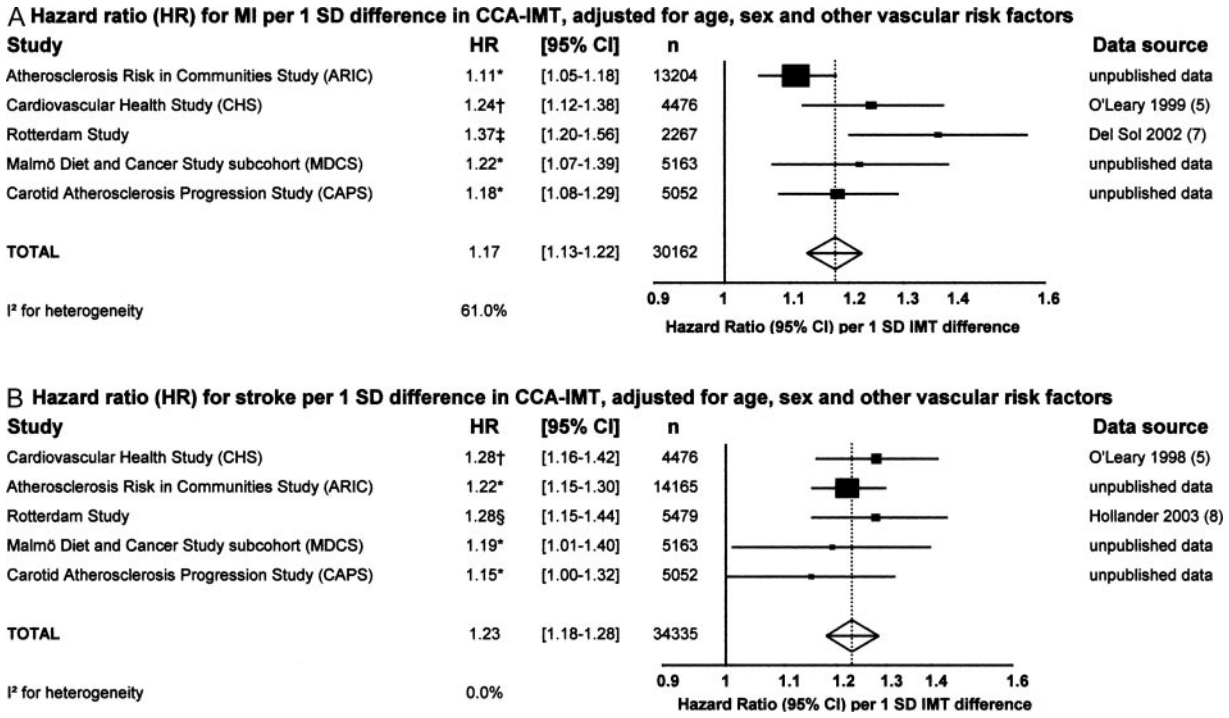

Figure 5. Forest plots of the HRs per 1 SD difference in the CCA-IMT, adjusted for age and sex and other vascular risk factors. *Adjusted for age, sex, body mass index, systolic and diastolic blood pressure, LDL cholesterol, smoking and diabetes. †Adjusted for age, sex, systolic and diastolic blood pressure, smoking, and diabetes. ‡Adjusted for age, sex, BMI, systolic and diastolic blood pressure, total and HDL cholesterol, smoking, and diabetes. §Adjusted for age, sex, systolic and diastolic blood pressure, total and HDL cholesterol, smoking, diabetes, and cardiovascular disease.

demonstrates that the relationship between CCA IMT and the relative risk of vascular events is not strictly linear in most populations. This deviation from linearity was first observed by the ARIC investigators[4,6] and found to be statistically significant for MI ($P=0.002$ for men, $P=0.04$ for women)[4] and nearly significant for stroke ($P=0.08$ for men, $P=0.06$ for women).[6] To understand this relationship, we have to be aware of the link with age: Young individuals with increased IMT are at considerably lower absolute risk but higher relative risk of vascular events.[12] Furthermore, individuals with a high risk factor load (and consequently higher IMT) are more frequently under a physician's surveillance and pharmacological intervention, which may reduce their individual risk more than the corresponding IMT.

Vascular events are rare in young individuals, which makes IMT particularly attractive as an end point in epidemiological and treatment studies in young populations. The nonlinear relationship has major implications for the design of IMT studies in young populations, as it limits the transferability of the results from older samples. It is of the utmost importance to investigate the actual risk linked with increased IMT. More studies are needed to provide a larger database on the association between IMT and vascular risk in young individuals. As long as the data on the risk in young individuals are limited, we recommend that IMT studies on young populations should adopt the ultrasound protocol of a study that provides prospective data (at the time of submission there was only one such study[12]) to be able to express the IMT findings as a relative risk of clinical events.

Limitations

Our review and meta-analysis has a number of potential limitations. First, there is the issue of potential publication bias. We have tried to identify all those studies that calculated the relative risks of future cerebrovascular or cardiovascular events or death that depend on individual baseline carotid IMT. By means of an extensive Medline-based search, we aimed to retrieve all published data. Given that such observational studies require large samples and long follow-up periods to facilitate the detection of a considerable number of events, it seems very unlikely that a study of this dimension will have been published and not identified by our search. The trim-and-fill procedure, a statistical technique to detect imbalances within the data that possibly indicate the existence of unpublished studies, found no evidence of such an imbalance in the data discussed here.

Second, the graphical method used to investigate the linearity of the IMT-risk relationship relies on the assumption of section-wise linearity. The exact underlying function is determined by polynomial regression, where the maximal power of the function depends on the number of categories. With a minimum of 3 categories, the spline curves can be second-order, which is sufficient to detect the nonlinearity described. A more complex function may be overlooked.

A third potential limitation stems from the multiple sources of heterogeneity between the studies. To obtain compound estimates, we had to take into account the large number of heterogeneities on the one hand and the possible selection bias on the other. Selection bias could be introduced if the heterogeneities were informative, eg, if the proportion of

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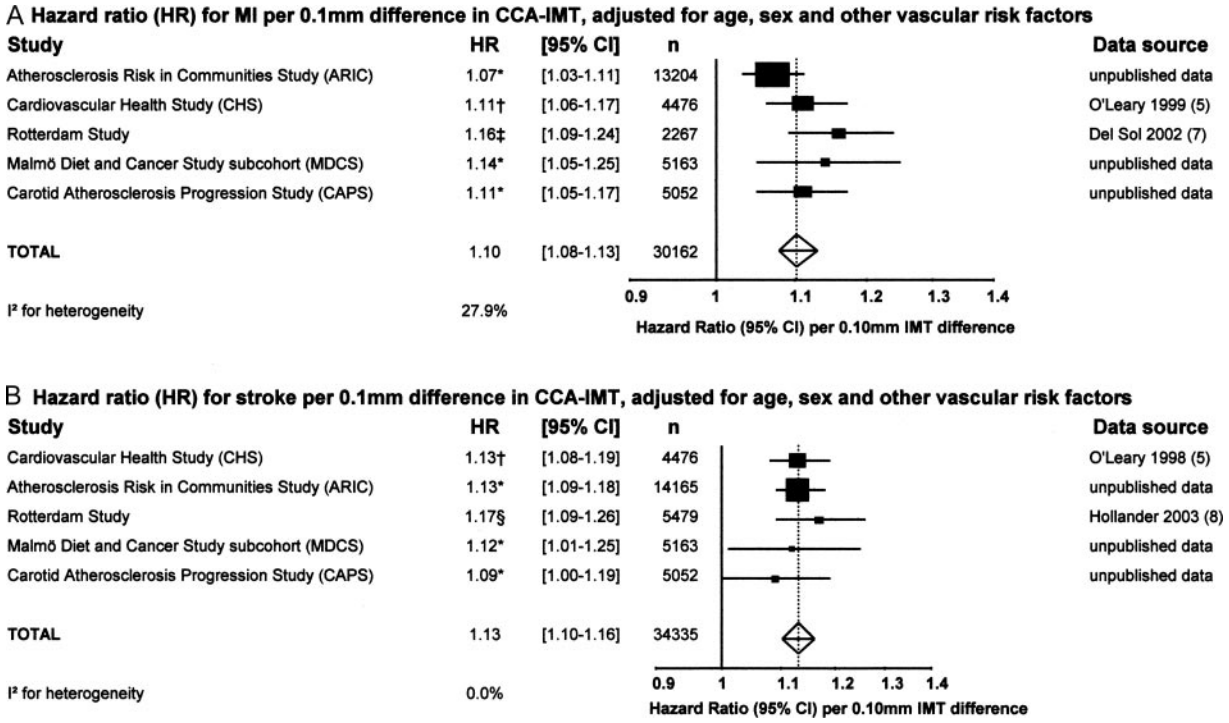

Figure 6. Forest plots of the HRs per 0.10-mm difference in the CCA-IMT, adjusted for age and sex and other vascular risk factors. *Adjusted for age, sex, body mass index, systolic and diastolic blood pressure, LDL cholesterol, smoking and diabetes. †Adjusted for age, sex, systolic and diastolic blood pressure, smoking, and diabetes. ‡Adjusted for age, sex, BMI, systolic and diastolic blood pressure, total and HDL cholesterol, smoking, and diabetes. §Adjusted for age, sex, systolic and diastolic blood pressure, total and HDL cholesterol, smoking, diabetes, and cardiovascular disease.

advanced atherosclerosis and the frequency of plaques in a population could influence the author's decision to report mean or maximal IMT, depending on how well either measurement algorithm accounted for plaques. To account for both problems, we provided calculations and forest plots for both selected and unselected studies.

Fourth, a potential limitation is the use of HR per (linear) IMT difference. The use of categorized data has other problems, as the choice of the cutoff points must not be data dependent to avoid introduction of a new bias factor. For the higher age group, however, the linear model still fits surprisingly well. The results of this meta-analysis must be interpreted with caution if young populations with low IMT are of interest.

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TABLE 3. Pooled Estimates of HRs per Absolute IMT Difference of 0.1 mm

End Point	MI			Stroke		
IMT Definition and Segment	Studies*	HR (95% CI)	I^2 for Heterogeneity	Studies*	HR (95% CI)	I^2 for Heterogeneity
Maximal CCA IMT	CHS,[5] Rotterdam Study[7]	1.17 (1.12 to 1.21)†	0.0%	…	…	…
		1.13 (1.08 to 1.17)‡	11.6%			
Mean CCA IMT	ARIC,[4] MDCS[10]	1.14 (1.11 to 1.18)†	75.0%	ARIC,[6] Rotterdam Study,[8] MDCS[11]	1.17 (1.13 to 1.22)†	0.0%
		1.08 (1.04 to 1.12)‡	41.7%		1.14 (1.10 to 1.18)‡	0.0%
Mean ICA IMT	ARIC,[4] CAPS[12]	1.07 (1.06 to 1.09)†	88.2%	ARIC,[6] CAPS[12]	1.08 (1.06 to 1.10)†	54.7%
		1.04 (1.02 to 1.06)‡	0.7%		1.06 (1.04 to 1.09)‡	13.8%

*Studies were selected by comparability of carotid segment definition.
†Adjusted for age and sex.
‡Adjusted for age, sex, and other vascular risk factors. For details, see the legend of Figure 5.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Carotid intima-media thickness (IMT) is increasingly used as a surrogate and intermediate end point of early atherosclerosis. With modern ultrasound scanners, IMT can be easily and quickly assessed in clinical routine as well as in clinical and epidemiological research. As several large population-based studies have shown, IMT can predict future clinical events, such as myocardial infarction or stroke, and IMT contains information beyond the classic cardiovascular risk factors. The present work pools the results of the existing studies to improve the precision of estimating the risk that is associated with IMT. With data of 200 000 person-years in 8 studies, we calculated compound hazard ratios for myocardial infarction and stroke and searched for sources of heterogeneity between studies and for important differences respective to study design and ultrasound protocol. We give an overview of the existing longitudinal IMT data and their limitations and attempt to derive consequences for future research.

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