

Assessing the Impact of Classical Risk Factors on Myocardial Infarction by Rate Advancement Periods

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The risk or rate advancement period (RAP) proposed by Brenner et al. (Epidemiology 1993;4:229–36) conveys information on the impact of a risk factor on the age dimension of chronic disease occurrence and may thus facilitate communication of epidemiologic findings. The RAP expresses how much sooner a given risk or rate of disease occurrence is reached among exposed than among unexposed individuals. The purpose of the present analysis was to derive estimates of RAPs for cardiovascular risk factors in relation to incident nonfatal and fatal myocardial infarction in middle-aged men of the Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA) Augsburg cohort, Germany, between 1984 and 1995. RAPs were estimated based on Cox proportional hazards models. After multivariate adjustment, hypertension, smoking, and dyslipidemia were associated with RAPs of 8, 11, and 11 years, respectively, conditional on infarction-free survival to baseline and absence of competing risks. The RAP may be interpreted as that, on average, smokers are expected to advance their risk of myocardial infarction approximately 11 years compared with never/former smokers; for example, 50-year-old smokers are expected to carry the same risk of infarction as 61-year-old nonsmokers. The authors encourage the use and evaluation of the RAP as an effective risk communication tool in actual counseling situations. *Am J Epidemiol* 2000;152:884–8.

cohort studies; methods; myocardial infarction; risk

The risk or rate advancement period (RAP) as developed by Brenner et al. (1) has been proposed as a novel and informative measure of risk factor impact on chronic disease occurrence. Similar to the concept of years of life lost, the risk or rate advancement period estimates the impact of a risk factor on the *timing* of disease occurrence; that is, the risk is phrased in terms of *premature* disease risk or rate among exposed individuals.

The purpose of this study was to estimate the impact of the classical cardiovascular risk factors hypertension, smoking, and dyslipidemia on the prematurity of occurrence of myocardial infarction. We applied the concept of risk or rate advancement periods in the Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA) Augsburg cohort and critically appraised properties and usefulness as a potential risk communication tool.

MATERIALS AND METHODS

Study design

The design of the study has been described in detail before (2). In brief, the MONICA Augsburg cohort was initiated in 1984–1985 in the city of Augsburg, Germany, and two adjacent counties. Participants aged 25–64 years were interviewed with respect to medical history, alcohol intake, smoking habits, and medication use, including antihypertensive drugs. Systolic and diastolic blood pressure, body weight, and height were subsequently measured. A nonfasting, venous blood sample was drawn and analyzed with respect to serum total cholesterol and high density lipoprotein cholesterol. These analyses focus on the 1,014 men aged 45–64 years (83 eligible men had missing data on a relevant variable and were excluded) who comprise 50 percent of the entire male cohort.

Follow-up was conducted from 1984 through 1995, and cases of nonfatal and fatal myocardial infarction were ascertained via the MONICA Augsburg coronary event registry. A coronary heart disease event was considered as incident if it was the first event during follow-up in a person reporting no history of heart attack in the 1984–1985 survey. The World Health Organization MONICA diagnostic categories (derived from electrocardiogram, enzyme, symptom, and necropsy findings) included as coronary heart disease events in this cohort study are definite and possible nonfatal acute myocardial infarction and fatal coronary heart disease (combining definite and possible fatal coronary events and

Received for publication August 3, 1999, and accepted for publication February 4, 2000.

Abbreviations: MONICA, Monitoring Trends and Determinants in Cardiovascular Diseases; RAP, risk or rate advancement period.

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unclassifiable deaths). Detailed descriptions of the definitions and applications of these diagnostic categories have been published (3). A total of 81 cases of incident myocardial infarction occurred among 1,014 men over the course of 11.5 years.

The classical cardiovascular risk factors considered in these analyses were defined as follows. Subjects having blood pressure values of ≥ 160 mmHg systolic or ≥ 95 mmHg diastolic were defined as having hypertension. Those who were aware of their hypertension and were taking medication against hypertension were also considered hypertensive. The total cholesterol/high density lipoprotein cholesterol ratio was derived and categorized as ≥ 5.5 (dyslipidemia) and < 5.5 . Individuals who reported current regular smoking of one or more cigarettes per day were classified as smokers.

The present analyses extend the previously published report on the association of the risk factors hypertension, cigarette smoking, and dyslipidemia with incident nonfatal and fatal myocardial infarction occurrence over 8 years (2). In this report, we have shown that hypertension, cigarette smoking, and the high total cholesterol/high density lipoprotein cholesterol ratio were statistically significant, independent predictors of myocardial infarction in the male MONICA Augsburg cohort.

For comparison purposes, we used published parameter estimates to derive the RAP of smoking from other European cohort studies focusing on incident coronary heart disease that included middle-aged men and were conducted at a similar time.

Statistical methods

The derivation of the risk and rate advancement periods has been described in detail by Brenner et al. (1). Briefly, the RAP describes the advancement in time of the risk or rate of a chronic disease among subjects exposed to some risk factor in the absence of competing risks; that is, it expresses how much sooner a given risk or rate of disease occurrence is reached among exposed than among unexposed individuals.

Exposures conferring an increased risk will result in a positive value of the RAP (i.e., disease risk will be advanced to a younger age), while exposures conferring a protective effect will result in a negative value (i.e., disease risk will be postponed to an older age).

The fundamental assumption underlying the RAP concept that the disease under study exhibits a monotonic increase in disease rates (risk) with age is met by many chronic diseases including atherosclerosis. The definition of the RAP implies that it is inversely related to the age gradient of the disease rate (risk). For computation of a RAP, age needs to be coded continuously. Interactions between exposure and age can be accommodated but, for the purpose of these analyses, the situation of no interaction was used.

Estimation of rate advancement periods. RAPs may be derived from any linear model of the general form

$$g(R) = a + b_1E + b_2A + \text{covariates}$$

with rate R , exposure E , and age A and the respective regression coefficients b_1 and b_2 . From this model, a point estimate of the RAP is obtained as

$$\frac{b_1}{b_2} (\text{if } E_1 - E_0 = 1);$$

that is, the increase in disease risk for each year of age (b_2) and for each unit of exposure (b_1) is used to estimate the RAP. The RAP estimated in this way can thus be interpreted as the number of years of age that are associated with the same increase in disease rate as one unit of exposure. Alternatively, the RAP can be understood as an age difference between a group of exposed and a group of unexposed individuals who experience the same risk or rate of disease.

For our analyses, we chose dichotomous risk factors; however, continuous risk factors may also be used. Since our study was a cohort study with person-time data, we applied a Cox proportional hazards model.

With hypertension as an example, from a multivariate model of the simplest form

$$g(R) = a + b_1\text{HYPERTENSION} + b_2\text{AGE},$$

the rate advancement period for hypertension (unadjusted for all other risk factors) in relation to myocardial infarction was estimated as follows:

$$\text{RAP for HYPERTENSION} = \frac{b_1}{b_2}.$$

Adjusted estimates of the RAP can be derived in the same way from models including additional covariates. For smoking, RAPs were also estimated from published literature.

Estimation of confidence intervals. Confidence intervals were calculated as described by Brenner et al (1). With the notation introduced above, large sample approximations of 95 percent confidence intervals of RAP were obtained as

$$\frac{b_1}{b_2} \pm 1.96\sqrt{\text{var}\left(\frac{b_1}{b_2}\right)},$$

where

$$\text{var}\left(\frac{b_1}{b_2}\right) = \frac{1}{b_2^2} \left[\text{var}(b_1) - 2\left(\frac{b_1}{b_2}\right)\text{cov}(b_1, b_2) + \left(\frac{b_1}{b_2}\right)^2 \text{var}(b_2) \right].$$

Confidence intervals estimated for rate advancement periods from published studies shown in table 4 were calculated omitting the covariance component of the algorithm, since it was not included in the publications. It has been shown empirically that the contribution of this component is typically negligible for the risk factors in this paper (4).

TABLE 1. Baseline characteristics (mean and standard deviation or prevalence), grouped by categorized risk factors, of 45- to 64-year-old men, MONICA* Augsburg cohort study, 1984–1995

Groups	Characteristics								
	Age (mean years)	Smokers (%)	Dyslipidemics (%)	TC*/HDL-c* ratio (mean)	Total cholesterol (mean mg/dl)	HDL-c (mean mg/dl)	Systolic blood pressure (mean mmHg)	Diastolic blood pressure (mean mmHg)	Hypertension (%)
Hypertensive† (n = 253)	54.8 (5.8)‡	26.9	42.7	5.4 (1.9)	250 (46)	50 (17)			
Nonhypertensive (n = 761)	53.9 (5.8)	31.5	33.5	5.2 (2.2)	243 (45)	51 (16)			
Smoker§ (n = 308)	53.6 (5.8)		45.5	5.6 (2.2)	248 (44)	50 (16)	136 (17)	83 (11)	22.1
Nonsmoker (n = 706)	54.4 (5.9)		31.6	5.1 (2.1)	243 (46)	52 (16)	138 (18)	85 (11)	26.2
Dyslipidemic¶ (n = 363)	54.2 (5.7)	38.6					138 (18)	85 (12)	29.8
Nondyslipidemic (n = 651)	54.1 (5.9)	25.8					136 (18)	84 (11)	22.3

* MONICA, Monitoring Trends and Determinants in Cardiovascular Diseases; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol.

† Hypertensive: subjects aware of hypertension, taking medication against hypertension, and/or having blood pressure values of ≥ 160 mmHg systolic or ≥ 95 mmHg diastolic.

‡ Numbers in parentheses, standard deviation.

§ Smoker: current regular cigarette smoking of ≥ 1 cigarette per day.

¶ Dyslipidemic: TC/HDL-c ratio ≥ 5.5 .

RESULTS

Table 1 shows baseline characteristics of the male cohort grouped by the presence or absence of the risk factors hypertension, cigarette smoking, and dyslipidemia. A clear positive relation between hypertension and dyslipidemia and between smoking and dyslipidemia and a weak negative relation between hypertension and smoking were apparent.

The risk of myocardial infarction associated with hypertension, cigarette smoking, and dyslipidemia is shown in table 2 in terms of both hazard rate ratios and rate advancement periods. Results are presented by a multivariate model. Each of the three risk factors was independently associated with a two- to threefold risk of experiencing a nonfatal or fatal myocardial infarction.

Estimates of the RAP for hypertension, smoking, and dyslipidemia were 9.4, 11.3, and 14.2 years in models containing one risk factor at a time in addition to age (table 2). These estimates were slightly reduced but still remained substantial after simultaneous adjustment for the other risk factors.

Table 3 lists the RAP of incident coronary heart disease associated with current regular smoking calculated from published coefficients of a variety of other cohort studies among middle-aged men. Most of these studies included a larger number of participants and events, resulting in more narrow confidence intervals for the RAP estimates. All studies adjusted simultaneously for systolic blood pressure and total cholesterol and some for additional risk factors. Across these studies, the RAP estimates of incident coronary heart disease associated with smoking ranged from 6.4 years to 10.5 years.

TABLE 2. Hazard rate ratios (HRRs) and rate advancement periods (RAPs) of incident nonfatal and fatal myocardial infarction in men associated with the risk factors hypertension, cigarette smoking, and dyslipidemia derived from various models, MONICA* Augsburg cohort study, 1984–1995

Model	Risk factors in models	Risk factor			Age		RAP (years)	95% CI*
		Regression coefficient	Variance	HRR	Regression coefficient	Variance		
1	Hypertension†	0.6428	0.0524	1.9	0.0681	0.0004	9.4	0.7, 18.1
2	Cigarette smoking‡	0.8702	0.0501	2.4	0.0771	0.0004	11.3	3.6, 19.0
3	TC*/HDL-c* ratio ≥ 5.5 §	1.0205	0.0512	2.8	0.0719	0.0004	14.2	4.4, 24.0
4	Hypertension	0.6461	0.0534	1.9	0.0792	0.0004	8.2	1.1, 15.2
	Cigarette smoking	0.8321	0.0519	2.3			10.5	3.3, 17.7
	TC/HDL-c ratio ≥ 5.5	0.8860	0.0522	2.4			11.2	3.3, 19.1

* MONICA, Monitoring Trends and Determinants in Cardiovascular Diseases; CI, confidence interval; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol.

† Hypertensive: subjects aware of hypertension, taking medication against hypertension, and/or having blood pressure values of ≥ 160 mmHg systolic or ≥ 95 mmHg diastolic.

‡ Smoking: current regular cigarette smoking of ≥ 1 cigarette per day.

§ Dyslipidemic: total cholesterol/HDL-c ratio ≥ 5.5 .

TABLE 3. Rate advancement periods (RAPs) associated with cigarette smoking estimated from prospective studies of incident coronary heart disease among middle-aged men

Study	No. of subjects	No. of events	Event type	Age (years)	Smoking		Age		RAP (years)	95% CI*
					Regression coefficient	Variance	Regression coefficient	Variance		
FINMONICA*	7,090	520	Incident coronary heart disease	25–64	0.5716	0.00792	0.0899	0.00003	6.4	4.3, 8.4
GRIPS*	5,639	299	Incident myocardial infarction	40–60	0.9040	0.01769	0.0900	0.00017	10.0	6.0, 14.1
PROCAM*	4,639	258	Incident coronary heart disease	40–65	0.9266	0.02028	0.1001	0.00013	9.3	5.8, 12.8
MONICA Augsburg*	1,014	81	Incident fatal or nonfatal myocardial infarction	45–64	0.8321	0.05186	0.0792	0.00042	10.5	2.7, 18.3

* CI, confidence interval; FINMONICA, Finnish Monitoring Trends and Determinants in Cardiovascular Diseases ((P. Jousilahti et al. *Circulation* 1999;99:1165–72) (P. Jousilahti, personal communication)); GRIPS, Göttingen Risk, Incidence, and Prevalence Study (P. Cremer et al. *Atherosclerosis* 1997;129:221–30); PROCAM, Münster Heart Study (G. Assmann et al. *Am J Cardiol* 1996;77:1179–84); MONICA Augsburg, Monitoring Trends and Determinants in Cardiovascular Diseases, Augsburg, Germany.

DISCUSSION

Rate advancement periods as applied here express the risk associated with the three classical risk factors hypertension, cigarette smoking, and dyslipidemia in terms of the timing of occurrence of myocardial infarction. Literally, an adjusted RAP for hypertension of 8.2 years is an age difference. Hypertensives who have a certain risk or rate of infarction at one age would be expected to have had the same risk or rate of disease at a later age (+8.2 years) had they been normotensive, given that all other covariates are equal and in the absence of competing risks. Furthermore, our results suggest that the average time period by which the age-related increase of risk of myocardial infarction could be postponed among men with dyslipidemia if these men had normal values is more than 11 years. Men smoking regularly (one or more cigarettes per day, i.e., on average nine cigarettes per day in our population) will reach the same infarction risk level as nonsmoking men about 10.5 years earlier.

Like other measures of risk factor impact, the RAP of one risk factor of disease should be carefully controlled for other, potentially confounding risk factors to quantify the net impact of the risk factor of interest. In our example, simultaneous inclusion of all three risk factors reduced the RAP estimates to some extent, which mainly results from the positive association among risk factors (see table 1). Since the addition of covariates into a multivariate model can influence the parameter estimate of both the risk factor of interest and the age variable, both of which are used in the computation of the RAP, prediction of the direction of the resulting change in the RAP estimate is somewhat less straightforward, however, than prediction for measures based on a single parameter, such as the relative risk.

We compared the RAP estimate for cigarette smoking for the men of the MONICA Augsburg cohort with that of other prospective European studies of incident coronary heart disease among middle-aged men (5–7). With various methodological study differences in mind, such as the definition of endpoints, the variable follow-up time or age range, or the statistical adjustment for other risk factors, we found that the RAP estimates for smoking were quite consistent with a range from 6.4 to 10.5 years (median, 9.7 years). In particular, the RAPs estimated from two German occupational

cohorts of incident myocardial infarction, 10 years in the Göttingen Risk, Incidence, and Prevalence Study (GRIPS) (5) and 9.3 years in the Münster Heart Study (PROCAM) (6), were remarkably similar to the estimates obtained in our study.

The magnitude of the rate advancement period is inversely related to the strength of the age effect. It is important to realize that the estimate of the RAP depends on the form in which age enters the regression model and on potential interactions with the exposure variable. In the present analysis, age was included as a simple, continuous variable with no interaction with the exposure. This assumes a monotonic increasing risk of myocardial infarction with increasing age, where the relative risk increase with each additional year of age is constant across the entire 45- to 64-year age range. Comparison of other studies that have included age in the same form has shown that the age effect is fairly similar across study populations (8), even if somewhat different inclusion criteria are used.

Another assumption to be considered in the interpretation of the concept of the rate advancement periods is the assumption of the absence of competing risks. In our case of incident myocardial infarction, potential competing risks that will remove the individual from the risk of having a myocardial infarction are essentially limited to deaths not due to myocardial infarction, that is, due to cancer, injuries, suicides, and so on, which are relatively rare in this middle-aged population. In elderly populations, however, where comorbidities and competing risks are much more frequent, rate advancement periods become increasingly theoretical.

Brenner et al. (1) suggest that rate advancement periods may be a useful tool in communicating risk factor impact on disease. Intuitively, translating the complex concepts of risk into the more easily understandable measure of time seems appealing. Literature on risk communication and perception demonstrates that many issues including the format of the information need to be considered (9, 10). For example, Weinstein et al. (11) used time intervals between expected events to convey a difference in risk probabilities in a trial on perceived threat and action intention. Participants perceived more threat and expected to take more action when the absolute risk (of cancer) of 1 in 100,000 was expressed in terms of one case in 35 years (in a city of 200,000 inhabitants) versus one case in 3,500 years (in a small town of

2,000). This effect on perceived threat and action intention was almost as large as that achieved when the absolute risk level was manipulated, that is, increased by a factor of 100. Thus, Weinstein et al. (11) could observe a substantial effect of framing risk levels on the perception of risk.

Using the RAP in risk communication settings such as counseling on risk factor modification poses conceptual challenges that are shared with all other statistical measures of probability. The concept of disease risk (be it as absolute or relative risk) is usually expressed and interpreted by the epidemiologist, physician, nurse, or health educator in an objective manner as the relative frequency of occurrence over time (12). The patient or layperson, however, is interested in the risk to him- or herself and will have a subjective interpretation of a given probability as in the degree of confidence that someone has that an event will occur (12, 13). Most individuals, however, are quite aware of the fact that chronic diseases become more frequent with increasing age. The practical appeal of the RAP may therefore lie in the ability to convey disease risk information as that of premature "aging," that is, disease occurrence, especially since it can be easily adapted to the individual consultation. For example, a RAP of 11 years can be used to explain to a 50-year-old smoker that he has the same risk of myocardial infarction as does a 61-year-old nonsmoker.

In conclusion, we have outlined several issues of both the estimation and the interpretation of the RAP. The practical usefulness of the RAP in terms of risk communication still awaits thorough evaluation. However, its simple calculation and intuitive appeal should make this a worthwhile endeavor.

ACKNOWLEDGMENTS

The authors acknowledge the contribution of Andrea Schneider and Dr. Jürgen Wellmann for data management and verification, the staff of the MONICA Augsburg 1984–1985 survey including Angela Döring and Jutta Stieber, and the coronary event register team.

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