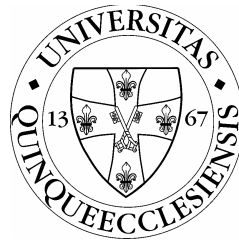


"Seasonal and Diurnal Variation in the Occurrence of Acute Myocardial Infarction, and the Effects of Weather Changes"

Ph.D. THESIS

Ildikó Kriszbacher

Accredited Ph. D. Program: D-171 Cardiovascular Health Sciences
Supervisor: Prof. Dr. Bódis József MD, PhD



**University of Pécs
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Cardiovascular Diseases

The incidence of cardiovascular diseases continues to increase in both developed and developing countries. In 2001 56 million people died all over the world, and 29% of these deaths resulted from a cardiovascular illness. Cardiovascular diseases are responsible for nearly 40% of deaths in Europe. Although western countries demonstrate a 20-30% decreasing tendency in mortality rates from 1970, in Hungary this rate has been increasing until the 1990s, when a slow increase has first occurred in mortality rates. In Hungary around 25,000 heart-attacks (AMI) are diagnosed each year, and unfortunately 50% of these patients die within a year.

Risk Factors - Causes

The primary risk factors of cardiovascular diseases are well known, such as high blood pressure, diabetes, disturbance in fat metabolism, lack of physical activity, improper eating habits, being over-weight, smoking, stress, etc. Most of these can be controlled, and many can even be prevented or eliminated. Studies of recent years have found that certain genetic defects, the increase of blood viscosity, increased fibrinogen concentrations, the propagation of homocystein, high C-reactive protein levels, periodontal bacteria and the changes of weather conditions also mean a great threat.

Prevention of Cardiovascular Diseases

In the fight against cardiovascular diseases the most important task is prevention (primary, secondary and tertiary prevention). In the prevention and treatment of cardiovascular diseases the recommendations and guidelines of certain professional groups have been applied for a long time. Nowadays, numerous guidelines are being adjusted, so that strategies support one another. In accordance with the recommendations of the Hungarian Therapeutic Consensus (Magyar Terápiás Konszenzus) the application of the Framingham table is also indicated in addition to the SCORE table.

Therapeutic Opportunities in the Treatment of Cardiovascular Diseases

Application of prophylactic medication: the most common drug for platelet inhibition is acetyl salicylic acid (aspirin) and tienopyrids (ticlopidin, clopidogrel). Besides its known side-effects, the successful application of *Aspirin* may also be limited by intolerance towards the drug, allergic reactions or resistance. Wald and colleagues have formulated in 2003 that it would be beneficial for all patients suffering from cardiovascular diseases to receive a *Polypill* drug combination, combined of aspirin, statin, anti-hypertension medication and folic acid, as a result of which 88% reduction could be realized in the occurrence of cardiovascular events. Hormone substitutive treatments applied after menopause have not met expectations with respect to cardiovascular conditions.

Characteristics of Cardiovascular Diseases

The biological functioning of the human organism follows a certain circadian rhythm. Several studies have pointed out that cardiovascular events do not occur on a general periodical basis, rather they follow a predictable critical time variation with daily, weekly and seasonal occurrence.

Peak periods are also influenced by weather conditions. The effects of ambient weather on the human body have been realized more than fifty years ago.

The circadian rhythm of diseases is a known fact these days, thus the timing of medication may also significantly influence the effectiveness of the treatment. The aim of *chrono-therapy* is to adjust the treatment to the intrinsic rhythms of the illness. The treatment is optimal if the given medication is received by the organism in the appropriate dose and at the most appropriate time.

OBJECTIVES

The onset of acute myocardial infarction (AMI) shows certain circadian and seasonal variation, which is also influenced by sex, age and changes in weather conditions. The spatial and temporal changes of weather factors depend on geographical location, the season of the year and the time of the day.

The objective of this thesis is to explore whether there is a difference in the time of onset of a heart attack between 2000 and 2004 with consideration to the days of the week, and whether the occurrence of events demonstrates a certain seasonality. We wished to examine whether certain meteorological factors (temperature, atmospheric pressure, front effects) influence the occurrence of AMI. We investigated whether a relationship could be found between the sales data of acetyl salicylic acid products and the frequency of vascular illnesses.

Further aims of this dissertation is the formulation of such recommendations by which current preventive strategies could be modified, and with the application of which cardiovascular diseases could be prevented or decreased more reliably and permanently.

Questions to be Investigated in Particular:

- ▶ How did the frequency of AMI vary with consideration to the days of the week;
- ▶ Is there a seasonality present in the occurrence of AMI;
- ▶ Is there a relationship between the occurrence of a heart attack and the changes of weather conditions;

in Hungary between 2000 and 2004?

We also investigated whether:

- ▶ there is a marked relationship between cardiovascular diseases and the rate of application of the preventive drug acetyl salicylic acid.
- ▶ the time of taking acetyl salicylic acid influences the frequency of cardiovascular events.

SUBJECTS AND METHODS

We have analyzed the data of 81,956 patients diagnosed with a heart attack between 1. January 2000 and 31. December 2004 in Hungary. Data was received from the database of the National Health Insurance Fund Administration (OEP), based on the International Classification of Diseases (ICD) (ICD I21, I22). AMI cases have been categorized according to the day, month and year of admission, and for year 2002 according to the sex and age of patients as well. The time of hospitalization has been considered as the onset of the event. Whenever the same patient has appeared more than once in the data-base, it has been considered as a new case each time, thus the actual number of patients is lower than the number of events considered.

For these five years we have collected average daily temperature, atmospheric pressure and front effect data from the Hungarian National Institute of Meteorology. The average daily temperature and average atmospheric pressure of 34 meteorology stations have been analyzed together with cold-, warm- and mixed-front movements.

We have examined the sales turnover of the lowest dose acetyl salicylic acid (100 mg) products in Hungary between 1. January 2000 and 31. December 2004 based on data received from IMS HEALTH Inc. Drug Products' Market Research Institute. The lowest dose products of acetyl salicylic acid are Astrix capsules (100 mg), Aspirin tablets (100 mg), and Aspirin protect tablets (100 mg). The dosage (UNIT) has been converted to tablets, which resulted in a total of 134,181,440 tablets sold annually by year 2004.

The analysis of statistical data was carried out through variance analysis (ANOVA), Pearson and Spearman correlation factor, χ^2 -test and double t-test. Data have been processed with SPSS 11.0 for Windows statistic, and Microsoft Excel programs.

RESULTS

Through a retrospective analysis we have examined the incidence of AMI with consideration to the days of the week, and months of the year for each year, and we sought a relationship with respect to seasons:

Hungarian hospitals have received and treated 81,956 patients diagnosed with AMI during the five years in question. During the investigated five year period the occurrence of AMI shows a steady increase. There is a marked difference between the number of cases in 2000 and in 2004 ($F=36.068$; $P<0.001$; $N=81,956$).

The seasonal distribution of AMI incidence:

With consideration to seasonal distribution, during the examined time period the peak period of AMI events was in spring, with lowest number of events during the summer season. This was followed by a sudden

increase during autumn, and a minor decrease during winter months. There was a significant difference between the seasons, with the exception of autumn and winter. (F=34.741; P<0.001; N=81,956).

Monthly distribution of AMI events

Examining the monthly occurrence of AMI, the highest rate of events was in April, then it gradually decreased, reaching its minimum in August. This was followed by a steep increase with a second peak in October month. (F=11.658; P<0.001; N=81,956).

Weekday distribution of AMI events

With respect to the weekday distribution of AMI, the peak of events was on the first day of the week, Monday, with a gradually decreasing tendency until reaching its minimum on Saturday and Sunday. A gradual 15% decrease was demonstrated from Monday to Friday, with a marked 23.7% drop from Friday to Saturday. Variance analysis of the first five days of the week and the weekends showed a significant difference in the number of events (F=4.162,101; P<0.001; N=81,956).

Ratio between males and females

Data of year 2002 have been analyzed in more detail. The number of patients treated with AMI in 2002 was 16,418. The proportion of men (56%) was slightly higher than women (44%). 88% of patients were from the age group above the age of 50. With consideration to the monthly distribution of AMI events variance analysis showed a significant difference (F=4.744; P<0.001; N=16,418). The incidence of AMI was lowest during summer months in case of both men and women and in the age groups below and above 50 as well. A secondary peak period was found in October in case of both sexes.

With respect to morbidity there was no significant, numeral difference between the days of the week in the age group below 50, while in the age group above 50 a similar rate of decrease was found from the first days of the week until the weekend in case of both men and.

In the course of the study we sought a relationship between the data of patients diagnosed with AMI and the average daily temperatures, average atmospheric pressure and front movement data received from OMSZ:

TEMPERATURE

During the spring season the number of AMI events increased in parallel with the increase of the average daily temperature. During summer the higher average temperature (above 20 C°) decreases, and with temperatures dropping during the fall season, the number of AMI events increases again. Considering summer months, when the average daily temperatures are above 20 C°, a negative correlation is shown between the average temperatures of the preceding three days (P<0,05). The daily average of events is lower on three subsequent days with a daily average above 20 C° (40.04, 39.62, 39.77.), while below 20C° events are more frequent (42.04, 42.8, 42.53).

AMI events and average monthly temperatures

The moving average (k=7) of AMI events has been contrasted with the average temperatures of the preceding, the following and the third days. The value of the Pearson-type correlation coefficients demonstrate a weak negative correlation in 2001 ($r \cong -0,12$), while in years 2000, 2002 and 2003 a medium strength negative relation has been found ($r \cong -0,42$).

FRONT MOVEMENTS

Analyzing the years between 2001-2004 an average of 96 warm, 103 cold and 50 mixed fronts have moved through Hungary annually. Based on our results the peak period of warm fronts was during the fall season, that of cold fronts during the spring season, while mixed fronts were most characteristic of summer months. Most fronts occurred during winter.

AMI events and the number and type of fronts

During the period under investigation the number of cold fronts increased during the spring season, the number of warm fronts increased during the fall season, at the same times when the number of AMI events also showed an increasing tendency. No statistical relationship could be demonstrated between the number of AMI events and the number or types of fronts preceding the events.

AMI events and front movements

Analyzing year 2002 in detail with consideration to front movements and the seasonal occurrence of AMI a weak positive correlation was found in case of both sexes ($r = 0.053$, $P < 0.05$).

ATMOSPHERIC PRESSURE

Based on the results of the examined five years, a low AMI incidence during summer months was accompanied by a decrease of the monthly average pressure. Analyzing each year separately, a significant relationship was found during the summer season ($P < 0.01$, $r = 0.329$).

In year 2002 the lowest monthly average of average pressure change and the minimum of front movements was during August, while during the months of autumn the increase of atmospheric pressure and the higher number of front movements was accompanied by a higher frequency of AMI events. Average pressure change, the number of front movements and the number of AMI events all demonstrate a similar seasonal variation.

Seasonal distribution of air pressure on days without front movements

Based on the data of the years analyzed, on days without front movements the peak value of seasonal pressure averages was at noon, with a minimum at 6 o'clock in the evening.

In the further analysis we examined the preventive status of acetyl salicylic acid with respect to national drug sales records and the sales data of acetyl salicylic acid per county in year 2004 have been contrasted with the Hungarian ESKI data-base population data, and the number of cardiovascular illnesses:

In Hungary the sales rate of the lowest dose ASA tablets shows similar increase as that of the number of AMI events.

In 2004 the capital city of Hungary and 6 counties of the 19 have reached or exceeded the national average sales rate of the lowest dose ASA tablets (13.23 tablets/person). The highest turnover was found in Budapest (16.61 tablets/person), with lowest sales in Nógrád county (8.56 tablets/person), where the frequency of cardiovascular diseases was also the lowest.

In year 2004 the sales rate of ASA products per person was an average 21 tablets, considering all citizens above the age of 30 (6,238,477 subjects). In 13 counties the sales rate was below the national average.

In 7 counties of our country the morbidity rates of cardiovascular diseases exceeded the national average number of events in 2004 (5697 persons/100thousand citizens), and 5 of these counties demonstrated a lower average sales rate of ASA tablets per person than the national average.

Considering a 24 hour rhythm, AMI events occur most frequently during 6-12 o'clock in the morning. The highest therapeutic effect of aspirin is reached 3.5-4 hours after administration, then showing a decreasing tendency during the day.

CONCLUSIONS

Based on our results it may be stated that in Hungary the occurrence of a heart attack shows an increasing tendency between 2000 and 2004, in which seasonal and weekly characteristics, and differences by age group are demonstrated.

One peak period of AMI events in Hungary is during the spring season, with a minor secondary peak during autumn, and lowest number of events during the months of summer. Distribution of monthly morbidity rates between the age groups above and below 50, and between men and women did not show any marked differences. Seasons are regulated by the laws of nature, and the resulting differences in AMI occurrence are significantly influenced by the natural environment, however this is not the one and only factor. Besides weather conditions, seasonality is also influenced by blood pressure, blood viscosity, vasoconstriction, fibrinogen levels and platelets. Low AMI incidence during the summer may also be a result of summer holidays.

Analyzing the weekly variation of heart attacks we found that with consideration to the onset of AMI in the age group above 50, the first days of the week carry a higher risk than weekends. Within the age group below 50 no such difference has been found. No difference was demonstrated between the two sexes with consideration

to weekly variation. This may be explained by the fact that social differences between men and women are less expressed nowadays with respect to work. The reason for highest number of events on Mondays may be that stress induced by psychological and physical factors related to the first work-day of the week means an increased load to the vascular and nervous system of the older age group, also carrying the burden of their previous lives with them. From this data-base no difference could be drawn up between the means of work with consideration to active or inactive jobs.

With respect to meteorological factors, our results show that the marked temperature increase during spring, and a strong temperature decrease during autumn, both result in an increase of AMI events, however other factors must also be taken into consideration.

Annually more than 200 fronts pass over Hungary. Cold fronts during spring and warm fronts during autumn may play a role in the increasing of AMI event numbers. The minimum number of front movements was during August, when AMI event numbers were also the lowest.

In Hungary the variation of atmospheric pressure is lowest during spring and autumn, when the seasonal distribution AMI events is the highest. The low number of AMI incidence during summer months is accompanied by a decreasing average monthly pressure, however no definite relationship could be proved in this respect. Changes of air pressure also demonstrate a circadian rhythm on days without front movements, when air pressure values are lowest during the morning hours and afternoon hours, at the time when the number of AMI events starts showing an increasing tendency.

Based on literature data it may be assumed that the changes of atmospheric pressure may contribute to the development of plaque ruptures. During the times of decreasing external pressure, mechanical pressure is increased on the atherosclerotic plaque, which could provide an explanation to the above mentioned relationship. However, changes of atmospheric pressure do not explain all AMI events, thus it is possible that such changes only effect certain plaques.

Contrasting our results with foreign data, some differences occur, which may be due to different geographical positions and weather conditions. We only had aggregate data of infarcts and weather data, thus the regional distribution of events could not be examined, we did not have an opportunity to eliminate errors resulting from the national span, and differences may also occur from the regional, numeral compilation of the population and differences in general health as well.

With respect to bio-meteorological considerations the combined effect of certain meteorological factors, such as the changes of temperature, types of fronts, number of front movements and the circadian rhythm of daily atmospheric pressure changes may all be related to the occurrence of AMI. Risk factors may add up and have an increased effect. The more risk factors one bares, the higher the chance of having a cardiovascular event.

The most frequently applied drug of preventing cardiovascular diseases is acetyl salicylic acid. From the sales rate of acetyl salicylic acid in Hungary we concluded that not even those suffering from a known cardiovascular disease apply ASA medication regularly. The results of these analyses are rather of informational nature, thus no far gone conclusions could be drawn, for which further examination would be necessary.

Large-scale studies have already proven the preventive effects of ASA treatment. Based on our results the turnover of ASA products in Hungary, and the number of AMI events both show an increasing tendency during the years under investigation. Based on such findings the preventive effect of ASA could be questioned, however if we acknowledge the well based results of multi-central studies, we need to find other explanations to

straighten up this contradiction. Many research is being carried out with consideration to the effective dosage of ASA, however no studies have addressed the question of time of application of the drug. With the morning administration of aspirin its lowest protective effect is reached at night and early in the morning. At the same time, lack of physical activity further increases platelet aggregability at this time of the day, which is in favor of the development of thrombo-embolic complications. The best preventive effect is at the same time when normal physical activities are carried out, which in itself provides greater protection against complications. With the 10 o'clock p.m. administration of aspirin, its peak effect might already be over, but due to the irreversibility of its anti-platelet effect, its preventive effects may still be stronger than with its administration after the morning AMI peak period.

Summary

The most critical periods of having a heart attack in Hungary is during spring and autumn, on the first days of the week, and early in the morning, which may all be influenced by the changes of temperature, warm and cold fronts and the daily rhythms of air pressure changes.

Based on our observations, the night-time administration of low-dose (75-100 mg) aspirin could be more adjusted to the 24 hour circadian rhythm of cardiovascular diseases, thus a better preventive effect could be achieved. At the start of an ASA treatment some already developed pathological conditions must also be taken into consideration, together with the risk factors remaining in the course of the preventive treatment.

For such reasons the results of our study shall be applied for the preparation of a more thorough and more successful preventive strategy. For this we plan the conduction of a randomized, multi-central trial in the future.

RECOMMENDATIONS

- ▶ In the course of preventing cardiovascular diseases the seasonality, the weekly variation and circadian rhythm of the disease, and the influence of current meteorological factors must also be taken into consideration,

- ▶ With the optimally timed application of a therapy in the most critical periods, during spring and autumn, on the first days of the week and in the morning hours, and with the administration of drug combinations, primary and secondary prevention could be made more effective,

- ▶ General practitioners should recommend the application of a cardiovascular risk factor evaluation sheet for all patients above the age of 40,

- ▶ For the prevention of cardiovascular diseases we recommend the administration of aspirin in the evening, by which the platelet inhibiting effect of the drug may be increased during the critical period.

What could health-care professionals do in their daily work to improve conditions and promote preventive concepts?

- ▶ Providing regular instruction with the application of persuasive methods, and by following an exemplary behavior,
- ▶ Developing self-responsibility towards oneself,
- ▶ Evaluation of cardiovascular risk factors,
- ▶ Calling attention to times with increased risk.

Application of the latest recommendations in therapy, and the complex application of preventive methods shall perhaps help to decrease the number of cardiovascular events in Hungary. We hope that the results of our study can be applied in the preventive system of the health-care program.

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ABBREVIATIONS

AMI	Acute Myocardial Infarction
ASA	Acetyl Salicylic Acid
ICD	International Classification of Diseases
CRP	C-Reactive Protein
ESKI	Health Strategy Research Laboratory
EU	European Union
KSH	Central Bureau of Statistics
OEP	National Health Insurance Fund Administration
OLEF	National Population-Based Health Survey
OMSZ	National Institute of Meteorology
SCORE	Systematic Coronary Risk Evaluation
WHO HFA	World Health Organization Health for All

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