*Acute coronary events in general practice:*

# the Imminent Myocardial Infarction Rotterdam study

TEXT

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PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT TE ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. B. LEIJNSE
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATS VINDEN OP
VRIJDAG 27 JANUARI 1978 DES NAMIDDAGS
TE 3.00 UUR PRECIES

DOOR

EMANUEL VAN DER DOES

GEBOREN TE ROTTERDAM

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TE 4.15 UUR PRECIES

DOOR

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R. VAN STRIK

*"Yet, what is medicine, if it is not a personal philosophy tempered by science and experience, put into practice"*

*Apley*

Opgedragen aan alle Rotterdammers door wier medewerking, inspanning en offervaardigheid het I.M.I.R. project gerealiseerd kon worden.

Dedicated to the people of Rotterdam. Their cooperation, effort and generosity made the I.M.I.R. study a reality.

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door steun van de Nederlandse Hartstichting.

## VOORWOORD

In dit geschrift worden de resultaten vermeld en besproken van de I.M.I.R. studie. I.M.I.R. is een afkorting van: Imminent Myocardial Infarction Rotterdam, welke naam aanduidt dat de studie met zijn hoofddoelstelling was gericht op de opsporing van mensen met een verhoogd risico op het krijgen van een acute coronaire episode (A.C.E. is: plotse dood of myocard infarct) in de naaste toekomst. Tevens werd getracht de zin te evalueren van een diagnostisch centrum, waarheen personen met klachten welke zouden kunnen wijzen op een dreigend A.C.E., verwezen moesten worden nadat zij tot de studie waren toegelaten op grond van bepaalde omschreven klachten en nadat de huisarts een voorlopige diagnose had gemaakt. Het centrum werkte op een 24-uurs basis en de resultaten (uitslagen van E.C.G. en serumenzymbepalingen) bereikten de huisarts gemiddeld binnen twee uur, afhankelijk van de urgentie. Interpretatie van de gevonden resultaten werd geheel aan de huisarts overgelaten, die ook het verdere beleid uitstippelde. Gezien het bovenstaande kan men stellen dat het I.M.I.R. project geheel in de ontwikkelingen van de gezondheidszorg past, met name waar het gaat over versterking van de 1e lijns gezondheidszorg. Zowel de ontwikkeling van de vroeg-diagnostiek op het gebied van coronaire hartziekten alsmede diagnostische hulp voor die diagnostiek passen in dit kader. Als zodanig draagt dit proefschrift argumenten aan voor het organiseren van een vorm van diagnostiek, voor scholing van de huisartsen en om de verdere research op het gebied van de coronaire hartziekten met kracht te bevorderen, waarbij tevens voortdurend op het punt van de samenwerking actie zal moeten worden genomen. Ook bij een omvangrijk klinisch-epidemiologisch onderzoeksproject zoals het I.M.I.R. is gebleken hoe belangrijk de samenwerking is. Meer dan 50 personen met zeer uiteenlopende deskundigheid namen eraan deel, zij worden allen op blz. 27 van dit proefschrift genoemd.

Het is ons daarnaast een behoefte het bijzondere belang van het werk van bepaalde mensen en groepen extra te belichten. Aan het begin van de geschiedenis van dit project staat Verhey, die niet aflieť om bij discussies met huisartsen er in het eind van de jaren zestig, begin zeventig, op te wijzen dat het van het grootste belang was om te onderzoeken of het mogelijk was hartinfarcten reeds in het dreigende stadium op te sporen. Zijn ideeën vonden weerklank en het was Arntzenius, die het daarop gerichte I.M.I.R. project operationeel maakte,

waarbij, Van der Does als coördinator van de huisartsengroep optrad. Tot die mensen van het eerste uur behoren ook Hugenholtz en Miettinen zonder wier hulp en nimmer aflatende steun het project niet had kunnen worden gerealiseerd. De huisartsengroep, waarvan er tien de gehele onderzoeksperiode hebben meegewerkt, komt lof toe voor de wijze waarop zij hebben gewerkt om het project operationeel te maken en te houden, voor hun inbreng tijdens de I.M.I.R. vergaderingen en vooral voor de wijze waarop zij zichzelf discutabel wilden stellen, niet alleen met betrekking tot de diagnostiek, maar ook in het kader van het enquêteonderzoek naar hun toelatingsbeleid (hoofdstuk 2). Naar onze mening is een dergelijk onderzoek nog nooit uitgevoerd. Na de benoeming van Arntzenius tot hoogleraar te Leiden, nam Pool mede de leiding van het project op zich en trad Lubsen tot de werkgroep toe. Wij, Van der Does en Lubsen, zijn van mening dat het aandeel van Pool met betrekking tot alle aspecten van de I.M.I.R. studie (d.w.z. huisartsgeneeskundig, cardiologisch en epidemiologisch) van essentieel belang is geweest bij het tot stand komen van deze dissertatie. Van de huisartsgeneeskundige kant was Van Trommel, destijds lector, bij de voorbereidende besprekingen betrokken. Hij werd in 1973 door Dokter opgevolgd, die met grote interesse en toewijding het project en de verslaggeving mede heeft begeleid. Dataverwerking ten behoeve van projecten zoals de I.M.I.R. studie zijn niet denkbaar zonder de steun van computerdeskundigen. Ook vroegen diverse onderdelen van het project om aparte organisatie en tevens coördinatie waarvoor de dagelijkse leiding was aangewezen. Deze aktiviteiten omvatten: het funktioneren van het I.M.I.R. diagnostisch centrum, de tape monitoring, toepassing van de Minnesota code, de data-codering en de verzorging van de apparatuur. De namen der medewerkers aan al deze aktiviteiten staan vermeld op blz. 27 van dit proefschrift. Voorts achten wij de uitkomsten van het enquêteonderzoek, verricht door student-assistenten (zie hoofdstuk 3 van dit proefschrift) van essentieel belang voor de interpretatie van de uitkomsten. Vele anderen hebben ons met raad en daad terzijde gestaan zonder direckt bij het dagelijks werk betrokken te zijn en van sommigen zal men de namen ook niet terugvinden. Echter is voor een multidisciplinair onderzoek, waarbij cardiologen, computerdeskundigen, epidemiologen, huisartsen en laboratoriumdeskundigen samenwerken, een multidisciplinaire adviesraad nodig (zie blz. 27).

Als alles dan is gedaan, zijn er mensen, die de moeizame arbeid op zich nemen om alles duidelijk op schrift te stellen. Paula van Wassenaar van het Huisartsen Instituut komt veel waardering toe voor de wijze waarop zij het manuscript mede in de vorm heeft gebracht, waarin het nu voor ons ligt. Voorts is het ons een behoefte te vermelden dat de kontakten met Hugenholtz intensief en zeer leerzaam zijn geweest. Het is nauwelijks te schatten hoeveel tijd en energie Pool aan de begeleiding en bewerking van dit project heeft besteed. Uitgebreid overleg en geduld heeft bijgedragen tot onderling begrip, het verstaan van elkaars taal en het begrijpen van een ieders invalshoek, zodat hierna een poging tot synthese van drie vakgebieden kon volgen (cardiologie,epidemiologie en huisartsgeneeeskunde). Een dergelijk proces kan slechts verlopen bij goede relatie en wederzijds respect.

Omvangrijke, langlopende projecten zoals I.M.I.R. kosten veel geld. Nadat de Wetenschappelijke Advies Raad van de Nederlandse Hartstichting de opzet positief had beoordeeld, heeft de Hartstichting het project gefinancierd met gelden, door de afdeling Rotterdam bijeengebracht. Wij vermelden de inspanning en offervaardigheid van velen uit de Rotterdamse bevolking. Dankzij de financiële steun van Z.W.O. kon Lubsen gedurende een jaar het epidemiologische studieprogramma volgen en het met succes afsluiten aan de Harvard School of Public Health, afdeling Epidemiologie in Boston, Mass., U.S.A. Tijdens dit verblijf werden door hem onder supervisie van Miettinen de data van I.M.I.R. bewerkt. Voorts vermelden wij gaarne de financiële steun van Boehringer Ingelheim Nederland voor de ontwikkeling van het diagnostisch lineaaltje (AMI-RO-METER).

De vraag kan worden gesteld waarom in dit proefschrift het werk van twee promovendi is gecombineerd. De aard en het ontwerp van de studie vereiste een nauwe samenwerking tussen huisarts, kliniek (cardioloog) en epidemioloog. Dientengevolge is het aandeel van huisarts en cardioloog enerzijds en epidemioloog anderzijds zo nauw verweven, dat aparte bewerking slechts geleid zou hebben tot duplicaturen en een mindere integratie. Het zou onzes inziens een demonstratie vormen tegen samenwerking, welke juist op het gebied van de gezondheidszorg zo nodig is.

Er wordt wel eens gesproken over het "lijden" van de direkte omgeving van promovendi tijdens het bewerken van een proefschrift. Wij willen liever eindigen met onze grote dank uit te spreken aan onze

gezinnen voor de wijze waarop zij naast ons stonden bij ons pogen een bijdrage te leveren aan de gezondheidszorg.

TABLE OF CONTENTS

N.B. Chapters 2-8 of this thesis are self contained papers intended for separate publication. At the time of printing, chapters 2, 3 and 7 had appeared in the "Hart Bulletin" while chapter 8 was in press. All tables and figures appear in a separate volume.

# 1. INTRODUCTION

## 1.1. MOTIVATION (E. van der Does)

With the advent of coronary care units in the early sixties, the first concentrated effort was made to reduce mortality from myocardial infarction. Subsequent experience has demonstrated that in-hospital deaths, particularly those from arrhythmias, have decreased from some thirty-five per cent to below ten per cent. However, several studies had indicated that up to 60% of the total mortality from acute coronary events, i.e. sudden cardiac death and acute myocardial infarction, took place in pre-hospital phase 1-6 and as early as the late sixties, both clinicians and epidemiologists began to realize that the greatest further gains had to be achieved by decreasing mortality in that particular phase. In 1969, Bondurant[7] stated: "the pre-hospital mortality due to ischaemic heart disease is greater ( ) than the total mortality due to any other single cause of death" and also: "the pre-hospital phase of acute myocardial infarction poses the greatest single medical problem of our nation in terms of loss of potential salvageable life". This seems to apply to the U.S.A. as well to the entire western world of today. Fulton et al. from Edinburgh, Scotland, concluded also in 1969: "The majority of deaths occur before patients with acute myocardial infarction reach hospital. Most of these are sudden and unattended medically. In many, symptoms of ischaemic heart disease have been present, but often they have passed unnoticed or at least undeclared. It is difficult to conceive of any system which would allow effective treatment of these patients. Therefore, reliable identification of those prone to sudden death and the development of prophylactic measures would do as much or more to combat the problem of acute coronary attacks as any other approach."[6] Thus, the emphasis began to swing away from further intra-hospital efforts at reducing death from coronary atherosclerotic heart disease (C.A.H.D.) to the out-of-hospital pre-coronary phase. For instance, Lown and Wolf stated in 1971: "Coronary care units, while effective in lowering hospital mortality, can not significantly reduce sudden cardiac death, which occurs primarily out-of-hospital and accounts for the majority of deaths from coronary heart disease."[8]

How might a reduction of especially out-of-hospital mortality be achieved? In an editorial "On Sudden Death", which appeared in

Circulation in January 1971, O. Paul and M. Schatz discussed several different approaches.[9] The three main ones were:

1. A system of early admission or treatment of patients sustaining an acute coronary event which aims at the reduction of the delays between the onset of the attack and the institution of proper treatment by a combination of public education, doctor's education and improved ambulance services.
2. Completely opposite to this thrust at relieving the sequelae of the disease by prompt reaction of emergency services are attempts at primary prevention. Stamler urged in 1970 that "the main strategic thrust must be prevention, especially primary prevention."[10] In this context, the study of precursors of C.A.H.D. is emphasized since, as stated by Chiang et al. "presumably any regimen which corrects the conditions predisposing to coronary heart disease in general, might also be benificial in the prevention of sudden death."[11]
3. Then, there are the "inbetween" approaches. A working group of the W.H.O. advocated the search for early warning symptoms: "Attention has ( ) turned to the identification of patients who are liable to have an acute heart attack within a short time interval. If a high-risk group could be defined precisely, anti-arrhythmic or other drugs could be given in the hope of preventing the development of the ventricular arrhythmias responsible for sudden deaths."[12] In fact, Bondurant had argued much along the same lines already in 1969: "There is a great need to increase the presicion of the identification of the patient at risk, both to allow more effective study of the problem and to begin to apply preventive and early interventions."[7]

It must be clear that these different strategic approaches each have their place in the attempt at reduction of sudden death from C.A.H.D. In fact, they appear interrelated. While the first approach has found its culmination in the successes of the presently operated ambulance services in the cities of Moscow, U.S.S.R.[13], Belfast, U.K.[14] and Seattle, Washington, U.S.A.[15], it must be borne in mind that the majority of the patients so resuscitated have advanced stages of C.A.H.D. and thus are treated in an end-stage of their disease. In fact, 80% of patients resuscitated from out-of-hospital ventricular fibrillation, who underwent subsequent cardiac catheterization had

several abnormal coronary arteriograms.[15]

Although in recent years some have advocated that these patients might have been protected from ventricular fibrillation and sudden death by timely coronary bypass grafting, it is clear that this is no fundamental solution to the problem.[16] The net salvage through this approach must remain limited and the question must also be raised whether the effort and expense involved is worth the goal.

The second approach has much more to recommend for it and seems recently to have gained much favor although firm evidence that it can achieve a reduction of the incidence of C.A.H.D. is still lacking. This however has not deterred those recommending it from pursueing their goal. Furthermore, it must be clearly realized that primary prevention certainly can not help the patient already afflicted in the clinical stage of the disease; even if primary prevention can result eventually in an appreciable reduction of sudden cardiac death, the latter will remain with us for several decades to come. Nevertheless, it does represent the most fundamental approach to reducing C.A.H.D.

All these considerations inevitably lead to renewed emphasis on the study of early warning symptoms. In fact, the special article by Lown and Wolf devoted to "Approaches to sudden death from coronary artery disease" specifically spells this out: "In view of the frequent precipitous nature of sudden cardiac death, only a program which identifies and protects the victim prior to the event can hope to be successful in preventing the majority of sudden cardiac death. Since it is likely that sudden cardiac death is due to an arrhythmia, drug prophylaxis might prove effective."[8]

Such an approach hinges on the identification of the potential victim. There is strong evidence that a major part of the patients who sustain an acute coronary event have had "warning symptoms". Kuller[4] reported that 24% of the patients who died suddenly had seen an physician during the week prior to the event. This finding was corroborated by many other studies in various countries.[17-21] The working group of the W.H.O. observed however that the data collected came nearly exclusively from retrospective studies and concluded therefore that their value for prediction was open to doubt since "hindsight often assists in the interpretation of atypical symptoms" and since such studies "do not supply information on how often 'prodromal'

symptoms are not followed by heart attacks."[12] The same working group recommended that studies should be undertaken to investigate prospectively symptoms and signs that may have predictive value for A.M.I. or sudden death within a short period of time.[12] This view and the fact that so many patients did visit a physician shortly before the acute coronary event occurred were starting points for the Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study. When symptoms arise which induce a visit to a doctor, this doctor will in the Dutch health care system nearly always be a general practitioner. It was therefore natural that patients seen by G.P.s were the objects of inquiry in the I.M.I.R. study. Its main goal was the recognition of those patients who are at high risk to sustain an A.C.E. in the near future in a population which consults a G.P. for a set of specified symptoms. Details of design and methods may be found in chapter 2 of this thesis.[22]

## 1.2. METHODOLOGY (J. Lubsen)

### 1.2.1. THE MAIN OBJECTIVE IN EPIDEMIOLOGICAL TERMS

In the previous section, the main-objective of the I.M.I.R. study was stated as "the recognition of those patients who are at high risk to sustain an A.C.E. in the near future in a population which consults a G.P. for a set of specified symptoms".

In epidemiology, the term "risk" is used to characterize individuals; it is the probability that an individual will develop the disease at issue within a particular period of time.[23] Numerically, such a probability is commonly expressed as a number between zero and one, reflecting the a priori degree of certainty about the eventual disease outcome. Zero and one indicate certainty about the non-occurrence and occurrence respectively of the disease within the time period considered. Between these extremes, lesser degrees of certainty are expressed by numbers greater than one but smaller than zero. For instance, a risk of 0.5 indicates that the disease is as likely to occur as not to occur. Often, risks are expressed as a percentage between 0% and 100%.

Risk is a theoretical concept and not directly observable in the individual.[23] For, even the occurrence of disease in a certain individual does not indicate *a posteriori* the risk of that individual since

risk has to do with the *a priori* probability of the occurrence of disease. Risks are estimable only by studying a group of individuals of a certain kind and determining the relative frequency of disease occurrence. For instance, in Edinburgh, Scotland, Duncan et al.[24] studied the prognosis of unstable angina in men under 70 years of age. Of 251 such men suffering from the condition, 39 developed an A.C.E. within six months after the onset of symptoms. Consequently, the relative frequency of A.C.E.-occurence in that study was 39/251 or 0.16. By the frequency concept of probability[25], this number represents the probability, or risk, that a patient entered in that study sustains an A.C.E. within six months after entry.

It must be emphasized that a risk-statement is devoid of meaning unless specifications are added of: (i) the kind of individual for which the statement is given, (ii) the disease event to which it applies, and (iii) the period of time to which it applies. In the above example, the description of the individual would be "male under 70 years of age, suffering from unstable angina", the disease event would be "acute coronary event" and the period of time "six months". In general, an individual's risk will depend on certain characteristics, such as for instance age, sex, symptoms and signs. In many an epidemiological study, I.M.I.R. included, the object of inquiry is the relationship between risk and such characteristics, the aim being to uncover as many independently to risk related characteristics as possible. Preferably, the results are given in terms of a mathematical function which describes the risk(s) as a function of a set of characteristics. The stronger the relationship to risk of the joint set of characteristics is, the more precise a prediction can be given by such a function, that is to say, the closer to zero or one respectively are the risks yielded by the function for the individuals to which it applies.

With these concepts in mind, the main objective of the I.M.I.R. study may now be understood as follows. The "population which is seen by a G.P. for a set of specified symptoms" will consist of patients at varying levels of short-term A.C.E.-risk. Within that population, the objective implies the study of the association between observable patient-characteristics and A.C.E.-risk and the results will, possibly, form a basis for "the recognition of those patients who are at high risk to sustain an A.C.E. in the near future".

## 1.2.2. CHOICE OF STUDY DESIGN

Once the objective of a study has been defined, a design must be chosen which will allow the objective(s) to be met. In many instances, different options in study design are possible but a particular design will usually suggest itself on practical and/or theoretical grounds.The main consideration in choosing a design is the type of information which is required. As outlined in the previous section the main objective of the I.M.I.R. study called for the assessment of A.C.E.-risk in relation to the characteristics of patients who belong to a particular population. It must be emphasized that such an objective involves a distinct directionality in time. For, the interest is in the relationship between the characteristics of patients who do not yet have sustained an A.C.E., i.e. are "at risk", and its subsequent development. Such relationships involving time directionality can in principle be investigated either within the framework of a case-referent study or within the framework of a follow-up study.[26] In the first type of study, a series of cases of the disease are compared as to the previous presence of the characteristics of interest with a series of healthy referents. In the second type, individuals "at risk" in various categories of the characteristics under study are followed in time to determine whether disease develops or does not develop. But, there are limitations. It will be apparent that the first type of study is feasible only if the occurrence of disease does not by itself affect the characteristic under study or if historical information about the characteristic may be collected irrespective of the occurrence or non-occurrence of the disease. For instance, the relationship between electrocardiographic information and risk of a future A.M.I. can not be determined from a case-referent study in which current E.C.G.s, recorded in cases of A.M.I., are compared with E.C.G.s recorded in healthy subjects since A.M.I. itself affects the recording. Such a study would only meet its objective if the E.C.G.-information could be obtained from already available historical records. In the absence of such records, a further problem would be caused by the fact that only cases of A.M.I. who survive up to a certain point in time can be studied. Such cases would form but a subset of all cases of A.M.I. and can therefore not be assumed representative for A.M.I. in general. By virtue of their design, follow-up studies do not suffer from the limitations which are imposed on case-referent stu-

dies by the time directionality of disease processes. Since it is difficult if not impossible to envision, in the face of its limitations, a case-referent type of design which would meet the objectives of I.M.I.R., a follow-up study was the natural choice in the present instance.

### 1.2.3. INTRODUCTION TO THE DESIGN OF I.M.I.R.

In the previous section, the conclusion was reached that a follow-up study was the design-of-choice to meet the objectives of I.M.I.R. Particulars of design and methods are described in detail in the next chapter[22] but an introduction is given here.

In a follow-up study, patients who fulfil certain inclusion criteria are included and followed for a certain amount of time during which occurring disease events of interest are detected. Since I.M.I.R. was to investigate by such a design the short-term A.C.E.-risk of patients who belonged to a population which consulted a G.P. for a set of specified symptoms, these symptoms took on the role of inclusion criteria in a procedure which required from the participating G.P.s the inclusion of all patients who fulfilled these criteria whenever they were seen.The symptoms described were of such nature that the procedure would also lead to the inclusion of patients who were sustaining an A.M.I. at the moment of inclusion. Although they were "at risk" to sustain an, in this case recurrent, A.C.E. in the near future, such patients do not belong to the population of patients whose short-term A.C.E.-risk was the primary scientific and practical concern and therefore had to be identified for future exclusion from the analysis. To this end, E.C.G. recordings and enzyme tests were part of the inclusion procedure. At the same time, it was the purpose of that procedure to collect information on all patient-characteristics of possible interest in the search for associations between such characteristics and the occurrence of an A.C.E. in the near future.As follow-up period, a length of 10 months was chosen. Since the interest was primarily with the patient who was to sustain an A.C.E. shortly after inclusion, follow-up investigations were specified to take place one week and one month after inclusion. Ten months after that moment, follow-up was concluded by collecting all relevant information on the patient's clinical course since inclusion.

To attain validity of information is the prime concern in the de-

sign and execution of an epidemiological study. Validity is defined in this context as the property which ensures that, were the study to be expanded to "infinite" size, completely accurate information in reference to its object results.[23] It has two major dimensions: internal validity and external validity. Internal validity has to do with the validity of the inferential conclusions which are made in reference to the subjects actually studied while external validity has to do with attempted generalization, i.e. with the generalizability of those conclusions.[23]

To ensure internal validity, the design must be such that selection-biases can not affect the composition of the obtained sample from the "population which consults a G.P. for a set of specified symptoms". It was to avoid such a bias that the protocol specified the inclusion of *all* patients who were seen by the participating G.P.s with symptoms meeting the inclusion criteria and that adherence to the inclusion procedure by the G.P.s was such an important issue during the execution of the study. Other concerns in the context of internal validity were the completeness of data collection and of follow-up in included patients and the criteria used for the detection of A.C.E.s. With respect to these aspects the protocol provided strict rules and procedures.

In the context of external validity, it is noted here only that the participating G.P.s were selected on the basis of their interest in cardiology and their willingness to cooperate. Therefore, they do not form a representative probability sample of Dutch G.P.s or even of G.P.s in the Rotterdam area. The implications of this will be taken up in the context of the discussion in chapter 11 of the external validity of the results of I.M.I.R.

### 1.2.4. CONCLUSIONS

Since the object of inquiry in the I.M.I.R. study was short-term A.C.E.-risk in relation to patient characteristics observable before and A.C.E. occurred, a follow-up study was the necessary choice of study design. Internal validity was the prime concern both in designing the study and during its execution. The participating G.P.s were selected on the basis of their interest and willingness to cooperate.

REFERENCES


1. Pell, S., D'Alonzo, C.A., Acute myocardial infarction in a large industrial population. Report of a 6 year study of 1,356 cases. J.A.M.A. 185: 831-835, 1963

2. Kannel, W., Dawber, T., McNamara, P., Detection of the coronary prone adult. The Framingham study. J. Iowa. Med. Soc. 56: 26-32, 1966

3. Kuller, L., Lilienfeld, A., Fisher, R., Epidemiological study of sudden and unexpected death due to arteriosclerotic heart disease, Circulation 34: 1056-1068, 1966

4. Kuller, L., Sudden death in artherosclerotic heart disease. Amer. J. Cardiol. 24: 617-628, 1969

5. Pantridge, J.F., Geddes, J.S., A mobile intensive-care unit in the management of myocardial infarction. Lancet 2: 271-273, 1967

6. Fulton, M.B., Julian, D.G., Oliver, M.F., Sudden death and myocardial infarction. Circulation, suppl. IV: 182-191, 1969

7. Bondurant, S., Problems of the pre-hospital phase of acute myocardial infarction. Amer. J. Cardiol. 24: 612-616, 1969

8. Lown, B., Wolf, M., Approaches to sudden death from coronary heart disease. Circulation 44: 130-142, 1971

9. Paul, O., Schatz, M., On sudden death. Editorial. Circulation 43: 7-10, 1973

10. Stamler, J., Prevention of atherosclerotic coronary heart disease by change of diet and mode of life. Ischaemic heart disease, Boerhaave Series, University Press, Leiden: 311-362, 1970

11. Chiang, B.N., Perlman, L.V., Fulton, M.B., Ostrander, L.D., Epstein, F.H., Predisposing factors in sudden cardiac death in Tecumseh, Michigan; A prospective study. Circulation 41: 31-37, 1970

12. World Health Organization. Regional office for Europe. The prodromal symptoms of myocardial infarction and sudden death. Report of a working group, Copenhagen, 1971

13. Chazow, E., Experience with the work of special first aid service and special units for treating patients with myocardial infarction. Arch. Klin. Med. 216: 258-266, 1969

14. Pantridge, J.E., Adgey, A.A., Prehospital coronary care. The mobile coronary care unit. Amer. J. Cardiol. 24: 666-673, 1969

15. Cobb, L.A., Baum, R.S., Alvarez, H. III, Schaffer, W.A., Resuscitation from out-of-hospital ventricular fibrillation. Circulation 51/52, suppl. III: 223-228, 1975

16. Kouchoukos, N.T., Kirklin, J.W., Surgical treatment of coronary atherosclerotic heart disease. Heart, arteries and veins. Eds. Hurst, J.W. et al., McGraw Hill Book Comp. Ltd., New York, London; 1132-1140, 1974

17. Solomon, H.A., Edwards, A.L., Killip, T., Prodromata in acute myocardial infarction. Circulation 40: 463-466, 1969

18. Stowers, M., Short, D., Warning symptoms before major myocardial infarction. Br. Heart J. 32: 833-840, 1970

19. Tibblin, G., Holmberg, S., Prodromal symptoms of acute myocardial infarction. Working document W.H.O.-conference, Copenhagen, March 1-3, 1971

20. Bekker, B.V., Interim verslag resultaten W.H.O. registratie projekt, ischaemische hartziekten. Nijmegen, 1972

21. Goldstein, S., Moss, A.J., Greene, W., Sudden death in acute myocardial infarction: relationship to factors affecting delay in hospitalization. Arch. Intern. Med. 129: 720-724, 1972

22. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G., Arntzenius, A.C., Acute coronary events in general practice. Objectives and

design of the I.M.I.R. study. Hart Bull. 7: 91-98, 1976. This thesis, chapter 2

23. Miettinen, O.S., Principles of epidemiologic research: an introductory course, Boston, Harvard School of Public Health, 1977

24. Duncan, B., Fulton, M., Morrision, S.L., Lutz, W., Donald, K.W., Kerr, F., Kirby, B.J., Julian, D.G., Oliver, M.F., Prognosis of new and worsening angina pectoris, B.M.J. 1: 981-985, 1976

25. Freund, J.E., Mathematical statistics, Englewood Cliffs, Prentice Hall, 1971

26. Miettinen, O.S., Estimability and estimation in case-referent studies, Am. J. Epidemiol. 103: 226-235, 1976

2. ACUTE CORONARY EVENTS IN GENERAL PRACTICE: OBJECTIVES AND DESIGN OF THE I.M.I.R. STUDY

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SAMENVATTING

De belangrijkste doelstelling van de Imminent Myocardial Infarction Rotterdam (I.M.I.R.)studie was de herkenning van patiënten met een hoog risico op een acute coronaire episode (hartinfarct en/of plotse dood) in de naaste toekomst.

Retrospectieve studies hebben uitgewezen dat vele patiënten met een acute coronaire episode in de weken daaraan voorafgaand prodromale klachten hadden. In de I.M.I.R. studie werd de betekenis van de prodromale symptomen, gecombineerd met bevindingen afkomstig van anamnese, lichamelijk onderzoek en electrocardiogram, prospectief onderzocht.

Alle patiënten die hun huisarts consulteerden met recente nieuwe of verergerde angina pectoris, recente pijn of onaangenaam gevoel in de borst, recente onverklaarde kortademigheid, hartkloppingen, duizeligheid, flauwvallen, bovenbuiksklachten en stemmingsveranderingen, werden tot de studie toegelaten. Anamnese en lichamelijk onderzoek werden door de huisarts op gestandaardiseerde wijze vastgelegd, evenals een voorlopige diagnose.

Deze gegevens werden aan het I.M.I.R.-centrum doorgegeven, waarna de patiënt onmiddellijk òf thuis òf op de polikliniek werd onderzocht. Een laborante nam een aanvullende anamnese op, maakte een standaard 12-afleidingen E.C.G. en nam bloed af voor enzymbepalingen. E.C.G. en bloedonderzoek werden herhaald na 3 dagen en 1 week. Na 1 en 10 maanden werd nogmaals een E.C.G. gemaakt. Aan het einde van de vervolgperiode van 10 maanden werden alle relevante aanvullende medische gegevens verzameld van de patiënt, de huisarts en de behandelende specialist.

Het onderzoek werd gecoördineerd en dagelijks begeleid door een cardioloog en een huisarts. Regelmatig werden bijeenkomsten gehouden met de laborantes, deelnemende huisartsen, andere medewerkers en externe adviseurs, teneinde een goed contact te onderhouden en eventuele problemen bij de verzameling van de gegevens en de voortgang van de studie te bespreken.

SUMMARY

The main goal of the Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study was to recognize patients who are at high risk of sustaining an acute coronary event in the immediate future. The study originated from the fact that retrospective studies showed many patients to have prodromal symptoms in the weeks preceding acute myocardial infarction and sudden death. The predictive value of these symptoms, in combination with other data of the patient's history, results of physical examination, and electrocardiographic and biochemical findings, was studied prospectively.

All patients who consulted their general practitioner with recent pain or discomfort in the chest, recent new or worsening angina pectoris, recent unexplained dyspnea, palpitations, collaps, dizzyness, upper abdominal pain, tiredness, irritability or anxiety, were included in the study. Detailed history and physical findings were recorded in a standardized manner by the general practitioner who also recorded his provisional diagnosis. The patient was reported to the I.M.I.R.-center and immediately examined either at home or at the out-patient clinic. A technician completed an additional questionnaire, obtained a standard 12-lead electrocardiogram and drew blood for serum enzyme level determinations. Electrocardiogram and bloodtests were repeated after 3 days and 1 week, and 1 month and 10 months later the electrocardiogram (E.C.G.) was repeated once again. At the end of the 10-month follow-up period further medical information was obtained from the patient, the general practitioner and consulted specialists.

The I.M.I.R. study was coordinated on a day to day basis by a cardiologist and a general practitioner. Regularly, meetings were held with the technicians, participating general practitioners, advisors and other consultants to maintain good cooperation and discuss progress of the study.

## 2.1. INTRODUCTION

Recently, it has become quite evident that the timecourse of coronary atherosclerotic heart disease (C.A.H.D.) extends over an individual's entire life. From the moment of conception until the time when a first acute coronary event (A.C.E.) is sustained, which may be fatal, several phases with more or less well recognizable demarcation points, can now be distinguished.

After conception, the unborn fetus is exposed early to several influences predisposing to the onset of C.A.H.D. In addition to genetic factors, smoking by the mother has been shown to alter the endothelium of the umbilical artery, a finding which may be the first manifestation of the disease.[1]

After birth, there appears to be no period during which western man can develop or live without being influenced by several risk factors which may lead to the development of an acute coronary event.[2,3] Various foodstuffs, the high fat content of cow's milk, early smoking are all suspected to play a part in the pathogenesis of C.A.H.D. already in early life.

Gradually, with increasing age the risk factors grow in importance.[4] De Haas reviewed recently the entire literature on risk factors for ischaemic heart disease in childhood and stated that the primary prevention of ischaemic heart disease has now become a sociopediatric problem.[3] Everest in 1971 spoke of the long "incubation" (=presymptomatic) period of ischaemic heart disease.[5]

At a given moment, the damage to the cardiovascular system mediated by these partly still obscure mechanisms has progressed to such an extent that symptoms arise. These may be initiated by an acute myocardial infarction or, alternatively, they may precede an acute coronary event. To the phase in which such "prodromal symptoms" occur, the I.M.I.R. study is pointed. A conceptual picture of the natural history of ischaemic heart disease is given in fig. 2.1.

In The Netherlands, the increase in mortality from ischaemic heart disease has relatively been the greatest in the younger age-groups. From 1950 to 1968 the mortality risk for men aged 35-44 increased threefold whereas it doubled for men aged 45-59.[6]

After 1972, a slight decrease in the mortality rate has set in, but at present in The Netherlands with its population of 13,5 million people, about 52,000 persons sustain an acute myocardial infarction each year and more than 50% of these are believed to die with the first attack.[7] A similar early mortality rate of about 50% of myocardial infarction has been found in the United Kingdom.[5] From the investigations of Fieren[8] in Wageningen and of Bekker[9] in Nijmegen, both in The Netherlands, it has become evident that a large portion of these people die before adequate help can be provided for. Fieren reported that more than half of

the fatal cases died within half an hour after the occurrence of symptoms and more than 60% within four hours.[8] In the United Kingdom it was found that 45% of all fatal attacks from myocardial infarction occurred within the hour.[10,11] Bekker reported that about 50% of the patients who died from a myocardial infarction had consulted a doctor in the two weeks prior to the acute attack.[9] In the study of Kuller et al. 23% of patients, who died suddenly, had seen a physician in the week prior to death.[12] Possibly the symptoms of these patients could have indicated the imminence of the acute event. Solomon et al. found that of 100 patients with acute myocardial infarction, 65 reported significant symptoms in the four weeks prior to hospitalization.[13]

Since the symptoms are mostly vague and often difficult to interpret, their significance is frequently not recognized at the first patient-doctor contact. Furthermore the patient's own denial and ignorance of the symptoms are probably equally important factors.[11,14-20]

All these studies are retrospective. As a W.H.O. working group in 1971 stated: "Useful though retrospective studies are, their value as guides to prediction is open to doubt, firstly because hindsight assists in the interpretation of atypical symptoms, and secondly because they do not supply information on how often 'prodromal' symptoms are not followed by heart attacks".[21]

It was this opinion which gave the final stimulus to carry out a prospective study in the out-of-hospital population in the city of Rotterdam based on the first warning symptoms presented to a group of general practitioners.

## 2.2. OBJECTIVES OF THE STUDY

The main goal was the recognition of those patients who were at high risk to sustain an A.C.E. in the near future in a population which consulted a general practitioner (G.P.) for a set of specified symptoms. Such recognition was to be based on information on history, symptoms and signs of the patient obtained by the G.P. and on an expanded history, electrocardiographic and biochemical findings, gathered by technicians.

A second goal to be pursued at the same time was the evaluation of the diagnostic support provided by the program to the participating G.P.s.

## 2.3. DESIGN AND METHODS

### 2.3.1. GENERAL OUTLINE

In I.M.I.R., the medical histories of patients who consulted their G.P. with symptoms which could be regarded as suspect for the occurrence of an A.C.E. in the near future were studied prospectively. Directly after inclusion into the study, information about the patient's symptoms and signs was collected, and data regarding the presence of an acute myocardial infarction were obtained. During the follow-up period of 10 months careful registration of all acute coronary events took place. Sudden deaths assumed to be due to a cardiac cause in all other patients within the practices of the participating G.P.s were registered. Retrospective information about symptoms preceding inclusion or registration as "sudden death" was also collected. A "flow-diagram" of all activities is depicted in fig. 2.2. It reflects the protocol[22], which the participating G.P.s had agreed upon and followed throughout the period of the study.

### 2.3.2. G.P. AND PATIENTS

INCLUSION PROCEDURE

When a patient consulted a participating G.P. with symptoms which met the inclusion criteria, the patient was included in the study.

The inclusion criteria were:†

- recent pain or discomfort in the chest
- recent unstable angina pectoris
- recent unexplained dyspnea
- recent unexplained palpitations
- recent unexplained upper abdominal pain
- recent unexplained collaps
- recent unexplained dizzyness
- recent unexplained tiredness, irritability or anxiety
- other reasons to think of an imminent or acute myocardial infarction
- sudden death, without evident extra-cardiac cause.

† For definitions see: "Definitions and abbreviations", page 29

Exclusion criteria were: lack of consent to cooperate, or an age of 20 years or younger for male patients and 25 years or younger for female patients.

INCLUSION EXAMINATION BY THE G.P.

Directly after inclusion the G.P. took a detailed history and performed a physical examination. A special inclusion form was designed for easy collection of data about the history and physical findings of the patient.[22] This form was filled out in each instance by the G.P.

INCLUSION DIAGNOSIS OF THE G.P.

After performing the inclusion examination, the G.P. recorded on the form his own provisional diagnosis which had to be classified into one of the following diagnostic categories:

- acute myocardial infarction
- imminent myocardial infarction
- other somatic disease
- psycho-social disorder
- no provisional diagnosis

Next the G.P. decided whether the patient's condition demanded immediate hospitalization. Information about the indications, if any, was also filled out on the I.M.I.R. inclusion form.

QUESTIONNAIRE AT CONCLUSION OF FOLLOW-UP

At the end of the follow-up period, approximately 10 months after inclusion, the G.P. received a questionnaire by mail. In this form he was asked for additional details on medical history, possible referrals of the patient to other physicians or hospitals and about medication during the follow-up period. All of this was included in the standardized protocol.

2.3.3. I.M.I.R.-CENTER AND PATIENTS

FIRST I.M.I.R. EXAMINATION

After a patient had been included and reported to the center, a trained technician went as soon as possible to the home of non-hospitalized patients. When a patient was ambulatory he was seen at the I.M.I.R.-center by a technician as early as possible. The I.M.I.R.-technician was then to take a standard 12-lead E.C.G.

and to draw a blood sample for assessment of serum enzyme levels of $\alpha$-H.B.D.H., C.P.K. and G.O.T. An additional questionnaire about the status of the patient, smoking history and physical activities was completed and, when compatible with the activities of the patient and available, an Avionics portable tape recorder (no. 350) was connected to the patient. An 8 hour single-lead E.C.G. record was obtained in an effort to detect arrhythmias.

When the patient had to be admitted to hospital, no time was lost to record the E.C.G. etc. first. Through the courtesy of the hospital doctors, E.C.G.s and other relevant data collected at admission could be used to complete the I.M.I.R. files.

FOLLOW-UP.

During the follow-up period, the E.C.G. and enzyme studies were repeated 3 days and 1 week after inclusion. After 1 month, the E.C.G. was repeated once again. At each of these occasions, a brief questionnaire was taken. When the patient was hospitalized, the discharge summary records of clinical and laboratory findings and a copy of the admission E.C.G. were requested. At the end of the 10th month follow-up, the patient was seen again by the technician. An E.C.G. was made and a detailed questionnaire about symptoms and medical history was taken. This patient questionnaire served partly as check on the G.P. questionnaire. Supplementory information was obtained from specialists in case they had treated the patient in the interim period.

DIAGNOSTIC SUPPORT.

Diagnostic support was given to the participating G.P.s by reporting abnormal E.C.G. and/or enzyme findings by telephone. For this purpose, a cardiologist interpreted the E.C.G.s as soon as they became available. After the 8th day examination, a summary of all E.C.G. and enzyme findings and of the main characteristics of the patient was sent to the G.P. On this summary, the conclusion of the cardiologist was also reported. In addition, the G.P. received copies of all E.C.G. tracings made and, where available, of the findings of the 8 hour tape recording of the E.C.G.

2.3.4. FINAL DIAGNOSIS

Based on all available clinical data (history, serial E.C.G.s, enzyme levels, clinical findings, discharge letters, autopsy reports) at inclusion and during follow-up, a final diagnosis was made. At inclusion, symptoms typical for A.M.I. were given a score of two points. Suspect symptoms were given one point. E.C.G.s and enzymes were scored similarly. The scores were added. A total score of four points or more was considered as definite, two or three as possible A.M.I. For complications during follow-up the same scoring procedure was used where all these data were available. If only history and serial E.C.G.s were available a score of three or more points was considered as definite A.M.I. and of two points as possible A.M.I. In the final interpretation of E.C.G., enzymes and total score, the history of a former M.I. and of other clinical or autopsy data were taken into account. A precise description of the scoring system is available upon request to the authors.[22]

2.3.5. ORGANIZATIONAL ASPECTS

In the I.M.I.R. study participated directly:

- general practitioners whose 14 practices were located at various districts in the Rotterdam area
- physicians,an administrator, technicians, data analysts and clerks at the I.M.I.R.- center
- collaborators of the Department of Cardiology of the Thoraxcenter at the Erasmus University, Rotterdam
- collaborators of the Department of Clinical and Experimental Information Processing of the Thoraxcenter at the Erasmus University, Rotterdam
- collaborators of the Department of General Practice at the Erasmus University, Rotterdam

Before the study started the cooperating G.P.s were trained in the uniform handling of the inclusion criteria. Also the manner of interpreting and filling out the forms and questionnaires was standardized as much as possible. The design was such that entry into the I.M.I.R. study did not interfere with the prevailing management and treatment of the patients. In fact all these aspects remained the responsibility of the G.P. On the other hand the group of G.P.s decided to adopt certain guidelines for treatment of

cases of myocardial infarction or cases suspected of imminent acute coronary event as they became acquainted with the study. Details of these guidelines are given in the protocol.[22]

Three rooms in the Department of Cardiology at the Thoraxcenter of the University Hospital Rotterdam-Dijkzigt provided the base of operations of the I.M.I.R.-center. Six technicians performed all examinations and administrative activities required by the study. Daily management was provided for by one of the coordinators and the administrator. A cardiology fellow was available to read incomming E.C.G.s. A data analyst supervised the entry of data on punch cards, provided ad hoc analysis on an ongoing basis, and prepared the final data tape. The technicians were not only trained in the technical aspects of their work but also to meet the patient with a confident attitude and an open eye for his or her general clinical problems. In this manner they supported the care given by the physician.

The center was staffed on a 24 hour basis to receive messages of new inclusions and to perform the necessary examinations. A time lag of maximally one hour between inclusion and examination was strived for. To this end, most of the time a radio dispatched car was at the disposal of the center. The center was open during normal working hours for ambulant follow-up and for inclusion examinations.

During the course of the study, several regular meetings were held. Three levels of discussions were distinguished.

"Small I.M.I.R. meetings" took place every week. In attendence were the daily managers, the available I.M.I.R. technicians and the project coordinators. Practical matters in the daily execution of tasks and in the acquisition of data were discussed.

"Large I.M.I.R meetings" were organized once a month under chairmanship of the coordinating G.P. All G.P.s, all co-workers of the I.M.I.R-center and other interested people attended these meetings. Minutes were kept and mailed to all participants and advisors. The purpose of these meetings was primarily to maintain good contact between everyone involved in the execution of the study and to discuss executional problems. Also, progress of the study was discussed on the basis of interim data. The contribution of experts and the occasional discussion of literature were an educational element in the meetings.

"0-day meetings" took place half-yearly with biostatistical advisors. These were attended by the heads of the departments of cardiology and general practice, coordinators and managers of the I.M.I.R.-center. At times these meetings were attended by the G.P.s and the medical director of the Netherlands Heart Foundation. Their purpose was to review progress of the study and larger management issues on the basis of interim data.

## 2.4. DISCUSSION

### 2.4.1. THE INCLUSION CRITERIA

The inclusion criteria were originally derived from the report of a working group convened by the Regional Office for Europe of the World Health Organization.[21] This report deals with the prodromal symptoms of myocardial infarction and sudden death. The participants were: Fulton, Julian, Lown, Tibblin and Tybjaerg Hansen. This group was struck by the fact that several investigators found that up to 50% of the patients who sustained an acute coronary event had seen their G.P. in the previous 4 weeks. They stressed however the limitations of conclusions based on retrospective studies.

Aware of the fact that a prospective study of people suspect of sustaining an acute coronary event in the near future was to be carried out, the definition of inclusion criteria became of critical importance. What, for example, does the syndrome "unstable angina" really contain? Classical angina recurring after a free interval and increasing in frequency or severity but also angina occurring for the first time and rapidly increasing in severity? This syndrome is reported to be the most specific prodromal sign for an acute coronary event.[14,15,23] With its exact description as given in these reports, one could assume that the syndrome should be well known to the G.P.s and fairly easily recognized. Practical experience has shown however, that this is not the case.[24] Furthermore, many more patients visit their doctor one or more weeks prior to the occurrence of the acute coronary event than are recognized as such, even when their symptoms in retrospect appear "typical". Many other patients present symptoms different from unstable angina yet ultimately prove to get an

acute coronary event. Clearly then, much wider inclusion criteria are needed.

Specifically with the aim of including as many patients as possible who might ultimately sustain an acute coronary event, all patients with recent chest pain, all those with recent unexplained dyspnea, upper abdominal pain, collaps, dizzyness, tiredness, irritability and anxiety were admitted to the study, in addition to those with the classical syndrome of "unstable angina". Furthermore, in an effort to allow "clinical judgement" to play a role the opportunity was given to the G.P. to include also those patients, in whom he, for whatever other reason, suspected an imminent or acute myocardial infarction.

The inclusion criteria as described were established irrespective of the opinion expressed by the W.H.O. working group that symptoms other than chest pain were of little or no value in providing evidence of impending myocardial infarction or sudden death. On the contrary, it was expected that by so broadening the scope of the inclusion criteria the "non-detection" rate could be kept as low as possible.

Since Vakil in 1961 found in 30% within 3 months subsequent coronary events in a group of patients with "intermediate coronary syndrome"[25] and Fulton et al. in 1972 observed in 14% sequelae in a study of unstable angina in Edinburgh within a similar period,[11] it was expected that the I.M.I.R. study would yield less than 14% of such events. But, by broadening of the inclusion criteria it was hoped that the risk implications of other symptoms than "intermediate coronary syndrome" or "unstable angina" could also be assessed and the total incidence rate be ascertained.

### 2.4.2. INVOLVEMENT OF THE GENERAL PRACTITIONERS

In The Netherlands, the G.P. has a central role in the health care system. He is a "family doctor" in the true sense of the word. As a general rule, a family is assigned to one G.P. and changes are not very frequent. A patient rarely consults a specialist, visits an out-patient clinic or goes to a hospital without first being referred by his own G.P. Even in case of an emergency occurring outside the home, the patient's G.P. is informed first. In this context, the design of this study without the detailed cooperation with G.P.s would not only have been ill advised but

also would have yielded data of little practical relevance. While through special discussion groups and in repeated contacts with the cardiologist supervisor the correct admission procedure was constantly emphasized and verified, the possibility remains that a person experiencing symptoms will not tell his G.P. about them, let alone visit him. In fact, the system present here in The Netherlands has been considered to provide a delay by making the potential patient think "twice" before he consults his physician. It remains therefore probable that not all potential patients have been included.

In spite of these considerations, it appeared reasonable to restrict the study only to those individuals whose symptoms were such that the patient himself decided to consult a G.P. By providing rapid and accurate diagnostic support, the G.P. in turn was induced to admit to the study as many patients as he recognized. While there is also a danger in providing such support by making it too "easy" for the G.P., the "bias problem" was counterbalanced by providing repeated training periods to the G.P.s in order to increase their objectivity and awareness of the limitations of the study.

### 2.4.3. THE INCLUSION AND FOLLOW-UP EXAMINATIONS

The nature of the inclusion criteria results in the inclusion of patients who sustain at that time an acute myocardial infarction. To study *IMMINENT* coronary events, these patients with established acute myocardial infarction had to be removed from the study material. The first function of the inclusion examination therefore was the detection and verification of an acute myocardial infarction. To this end, the E.C.G. at inclusion as well as the enzyme levels reported within 24 hours provided sufficient evidence. A second function of the inclusion examination was the compilation of data of possible relevance for the prognosis of a later acute coronary event. This "profile of information" together with knowledge about the outcome of the patient under study (i.e. the occurrence or non-occurrence of an acute coronary event during the 10 month follow-up) forms the body of information that was collected to fulfil the main objective of this study.

The scheme of follow-up examinations called for examinations

after 3 days, 1 week, 1 month and 10 months. The 3rd day examination served partly the purpose of verification of the diagnosis of an acute myocardial infarction present at inclusion. The one-week examination also contributes to this aspect. In the design stage of the study, it was expected that most new events would take place in the first 30 days. Therefore, the 30th day examination was designed to be the conclusion of this period. However, the 300th day examination was added to document other acute coronary events which might have taken place between the 30th and 300th day. Clinical information and comparison of E.C.G.s provided the main basis of this documentation.

### 2.4.4. FUNCTION OF THE I.M.I.R. CENTER

In the preceding section, the purpose of the examinations performed by the I.M.I.R.-technicians has been discussed. The justification for a special I.M.I.R.-center is given here. While technical aspects of most examinations could have been handled by the cardiac out-patient department of the Thoraxcenter, it was considered that a "non-personal" handling of these examinations might have been counterproductive in that the patient's consent to continued participation might have been adversely influenced. The creation of a special unit for the purposes of this study also facilitated to a significant extent the cooperation with the G.P.s. It permitted better quality control of the data and it made to individual patients specific technicians available who could focus solely on these patients. Despite some shortcomings, largely from an organizational nature, the operation of the center was a great success, which to a large extent secured the long term cooperation with the G.P.s and the 1,343 patients.

### 2.4.5. TIME COURSE OF STUDY

The study was planned in 1971 and was designed in joint deliberation between the departments of Cardiology and of General Practice. In the first phase of the study, the training of the future collaborators was an important feature. It concentrated particularly on the tasks of the G.P.s and I.M.I.R.-technicians. In addition, the study and its aims were introduced to the departments of Internal Medicine and Cardiology of various Rotterdam hospitals, to the wives and assistants of the G.P.s and to the

ambulance service of the city of Rotterdam.

From February, 1972 - June, 1972, a pilot study was performed. Its results were reported at the European Congress of Cardiology in Madrid.[26] As a result of the pilot study, several changes were made in the execution of the study. The definite study began on the 1st of October, 1972 and the inclusion of the last patient took place on the 31st of May, 1974. The follow-up period of the last patient lasted until April, 1975. From this time until mid 1976, the data were analysed and the various manuscripts prepared. Preliminary results of the study have been reported in the interim period.[27]

The study started with fourteen practices, of which three contained more than one G.P. Four doctors terminated their cooperation in the first half of the study. A fifteenth practice joined the I.M.I.R. study on the first of October, 1973 and cooperated until the end of the study. As a result only ten of fifteen practices took part throughout the entire study. The collected data of the ten practices are considered in some studies,[29,30] while the data of all fifteen practices appear in others.[31,32]

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The study was supported by the Netherlands Heart Foundation. J. Lubsen was supported in part by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.)

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APPENDIX

INCLUSION CRITERIA

Symptoms of patients leading to inclusion into the I.M.I.R.-study. The symptoms are regarded as suspect for the occurrence of acute or imminent coronary events.

The inclusion criteria are:

1. recent pain or discomfort in the chest
2. recent unstable angina pectoris
3. recent unexplained dyspnea
4. recent unexplained palpitations
5. recent unexplained upper abdominal pain
6. recent unexplained collaps
7. recent unexplained dizzyness
8. recent unexplained tiredness, irritability or anxiety, described together as "mood changes"
9. other reasons to think of an imminent or acute myocardial infarction
10. sudden death, without evident extra-cardiac cause

Recent = in the last four weeks

Unexplained = without evident extra-cardiac cause

Unstable = occurring for the first time, occurring anew after a symptom free period of one month or more, sudden and unexpected increase of frequency and/or severity of symptoms.

Angina pectoris = pain in the middle of the chest, which can radiate to the jaw, left arm and/or back, often described as a feeling of tightness or oppression.

DEFINITIONS

Target population: All men, older than 20 years and all women, older than 25 years belonging to the Dutch population, registered with a general practitioner.

Sampled population: All men, older than 20 years and all women, older than 25 years, who belong to the practices of the practitioners participating in the I.M.I.R.-study.

Study population: All men, older than 20 years and all women, older than 25 years who have consulted their family doctor during the study period for symptoms, which met the inclusion criteria of the I.M.I.R.-study, and were included.

Study patient: A patient, belonging to the study population.

Acute coronary event: Acute myocardial infarction or sudden death.

Sudden death: Death occuring within 24 hours after onset of suspected symptoms.

Typical exercise induced angina: Chest discomfort, related to exercise, disappearing at rest within 10 minutes.

Possible exercise induced angina: Chest discomfort related to exercise, disappearing at rest, not within 10 minutes (atypical form).

Probably no exercise induced angina: Chest discomfort related to exercise not (quite) disappearing at rest (atypical form).

Definitely no exercise induced angina: Chest discomfort, not related to exercise, not disappearing at rest.

Unknown if exercise induced angina: Chest discomfort occurring for the first time of longer duration than 10 minutes despite rest.

Atypical exercise induced angina: Possible exercise induced angina and probably no effort angina together.

ABBREVIATIONS

| | |
|---|---|
| I.M.I.R | - Imminent myocardial infarction Rotterdam |
| G.P. | - general practitioner |
| C.A.H.D. | - coronary atherosclerotic heart disease |
| A.C.E. | - acute coronary event |
| A.M.I. | - acute myocardial infarction |
| I.M.I. | - imminent myocardial infarction |
| S.D. | - sudden death |
| O.S.D. | - other somatic disease |
| P.S.D. | - psycho-social disorder |
| N.P.D. | - no provisional diagnosis |
| E.C.G. | - electrocardiogram |
| $\alpha$-H.B.D.H. | - alpha hydroxy butyric dehydrogenase |
| C.P.K. | - creatinine phosphokinase |
| G.O.T. | - glutamic oxaloacetic transaminase |

REFERENCES


1. Asmussen, I., Kjeldson, K., Observations in arteries from newborn children of smoking and non-smoking mothers. Circ. Res. 3: 579-589, 1975

2. Editorial: Hart Bull. 4: 1-2, 1973

3. De Haas, J.H., Primary prevention of coronary heart disease. A socio-pediatric problem. Hart Bull. 4: 3-12, 1973

4. Dalderup, L.M., Lim, M., van Wezel, L.A., Het hartinfarct, risicofactoren en preventiemogelijkheden. Nederlandse Hartstichting en Voorlichtingsbureau Voeding, Den Haag, 1974

5. Everest, M.S., Presymptomatic diagnosis of ischaemic heart disease. Update 3: 1355-1359, 1971

6. De Haas, J.H., Sterfte aan ischaemische hartziekten naar gemeentegrootte. Hart Bull. 2: 69-76, 1971

7. Centraal Bureau voor de Statistiek. Hart en vaatziekten, een statistische verkenning. Staatsuitgeverij, Den Haag, 1972

8. Fieren, C.J., Het myocardinfarct, een prospectief onderzoek naar de morbiditeit en de sterfte, speciaal in de acute fase, in het woongebied Neder-Veluwe. Thesis, Wageningen, 1972

9. Bekker, B.V., Interim verslag resultaten W.H.O. registratie projekt ischaemische hartziekten. Nijmegen, 1972

10. Armstrong, A., Duncan, B., Oliver, M.F., Julian, D.G., Donald, K.W., Fulton, M., Lutz, W., Morrison, S.L., Natural history of acute coronary heart attacks. A community study. Brit. Heart J. 34: 67-80, 1972

11. Fulton, M., Duncan, B., Lutz, W., Morrison, S.L., Donald, K.W., Kerr, F., Kirby, B.J., Julian, D.G., Natural history of unstable angina. Lancet 1: 860-865, 1972

12. Kuller, L., Sudden death in arteriosclerotic heart disease. The case for preventive medicine. Amer. J. Cardiol 24: 617-628, 1969

13. Solomon, H.A., Edwards, A.L., Killip, T., Prodromata in acute myocardial infarction. Circulation 40: 463-471, 1969

14. Vakil, R.J., Pre-infarction syndrome - Management and follow-up. Amer. J. Cardiol. 14: 55-60, 1964

15. Hudson, W.A., Pre-infarction. Update 3: 1083-1091, 1971

16. Durrer, D., Ischaemische hartziekten en de huisarts. Ned. T. v. Geneesk. 110: 1771-1781, 1966

17. Snellen, H.A., Practische cardiologie voor de huisarts. Amsterdam, Bohn, 1975

18. Goodwin, J.F., Differential diagnosis of chest pain. Update 7: 1219-1226, 1973

19. Killip, T., Management of the patient with acute myocardial infarction. Med. Clin. of North Am. 52: 1016-1025, 1968

20. Wellens, H.J.J., Prodromale verschijnselen van het hartinfarct. Hart Bull. 3: 15-18, 1972

21. World Health Organization. Regional Office for Europe. The prodromal symptoms of myocardial infarction and sudden death. Report of a working group. Copenhagen, 1971

22. Pool, J., Van der Does, E., Lubsen, J., Arntzenius, A.C., Protocol of the I.M.I.R.-study, including used forms, diagnosis scoring system and guidelines for treatment. Thoraxcenter, Erasmus University, Rotterdam, 1972. Available upon request to the authors

23. Durrer, D., Enige anamnetische criteria bij diagnostiek en verloop van angina pectoris en hartinfarct. Ned. T. v. Geneesk. 115: 1141-1143, 1971

24. Wellens, H.J.J., Chamuleau-Loonen, W.L.J.M., Remme, M.A.J., Durrer, D., Het dreigend hartinfarct. Ned. T. v. Geneesk. 115: 652-657, 1971

25. Vakil, R.J., Intermediate coronary syndrome. Circulation 24: 557-571, 1961

26. Arntzenius, A.C., van der Does, E., Hugenholtz, P.G., Miettinen, O.S. Pool, J., van der Voorde, F., I.M.I.R.-Imminent Myocardial Infarction in Rotterdam (the preliminary results of the pilot study). Proc. of the VIth. Eur. Congress of Cardiol: Communicaciones B.C.-4, Madrid, 1972

27. Presentations: Pool, J., Van der Does, E., Het I.M.I.R.-project. At the common meeting of the "Klinisch Genootschap Rotterdam" and the "K.N.M.G. Rotterdam en Omstreken", Rotterdam, April, 1974
Verbaan, N., Detection and analysis of rhythm disturbances in a group of patients with a high risk of an acute coronary event. At the "15e Federatieve Vergadering van Medisch Biologische Verenigingen", Nijmegen, April, 1974
Pool, J., Ventricular arrhythmias and sudden death. At a conference of the American Heart Association on Sudden Coronary Death Outside Hospital, Minneapolis, October, 1974
Pool, J., Prodromale symptomen van acuut hartinfarct en plotse dood. At the "Wetenschappelijk Rapport" of the Department of Cardiology of the University Hospital, Leiden, November, 1974
Pool, J., Lubsen, J., Parameters in clinical epidemiology of ischaemic heart disease. At the Computers in Cardiology Meeting, Rotterdam, 1975

28. Fox, III, S.M., Robins, M., Incidence, prevalence and death rates of cardiovascular disease. Some practical implications. Heart, arteries and veins. p. 602, Ed. Hurst, J.W. et al. McGraw-Hill Book Comp. Ltd., New York, London, 1974

29. Van der Does, E., Lubsen, J., Pool, J., van Strik, R., van der Sijde, J., Stroink, J., Acute coronary events in general practice. Early warning symptoms of acute myocardial infarction and sudden death in general practice. Hart Bull. 7: 99-106, 1976. This thesis, chapter 3

30. Lubsen, J., van der Does, E., Pool, J., Acute coronary events in general practice. Incidence of acute myocardial infarction and sudden death. Hart Bull. 7: 107-113, 1976. This thesis, chapter 7

31. Lubsen, J., Pool, J., van der Does, E., Acute coronary events in general practice. Acute risk of myocardial infarction and early death in a symptomatic patient. Hart Bull. 7: 114-117, 1976. See also this thesis, chapter 4

32. Van der Does, E., Lubsen, J., Pool, J., Gorter, S., Acute coronary events in general practice. Diagnostic power of the general practitioner without laboratory assistance. Hart Bull. 7: 118-121, 1976. See also this thesis, chapter 5 and 6

3. ACUTE CORONARY EVENTS IN GENERAL PRACTICE: EARLY WARNING SYMPTOMS OF ACUTE MYOCARDIAL INFARCTION AND SUDDEN DEATH

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SAMENVATTING

Bij de Imminent Myocardial Infarction Rotterdam (I.M.I.R.)studie waren gedurende de gehele studieperiode tien huisartsenpraktijken betrokken. In deze praktijken gezamenlijk waren 11.160 mannen boven de 20 jaar en 10.926 vrouwen boven de 25 geregistreerd.

Gedurende de toelatingsperiode zijn 1.255 in leven zijnde patiënten tot de studie toegelaten. Deze patiënten consulteerden hun huisarts (H.A.) voor recente of recent verergerde pijn op de borst en/of recente onverklaarde bovenbuiksklachten, hartkloppingen, kortademigheid, duizelingen, wegrakingen of stemmingsveranderingen. Ondanks veel inspanning om consequente uitvoering van het protocol door de H.A.en te verkrijgen zijn grote onderlinge verschillen in het toelatingsbeleid geconstateerd. Uit een schriftelijke enquête onder een steekproef uit alle patiënten die hun H.A. bezochten, bleek dat 55% van de patiënten die op grond van hun klachten voor toelating in aanmerking kwamen, desondanks niet werden toegelaten. In de meeste gevallen was de oorzaak hiervan dat de H.A. een duidelijke extracardiale oorzaak aanwezig achtte voor een geval van recente of recent verergerde pijn op de borst. De enquête wees wél uit, dat geen gevallen van angineuze borstpijn werden gemist; de gegevens over deze categorie van klachten zijn daarom als betrouwbaar te beschouwen. Voor andere klachten zijn de gegevens over het voorkomen slechts een benadering die het werkelijke voorkomen onderschat.

De meeste patiënten (71%) hadden pijn op de borst als hoofdklacht; bij nog eens 20% was pijn op de borst aanwezig als bijklacht. Van alle patiënten met pijn op de borst had 10% recente en 13% recent verergerde met inspanning samenhangende angina pectoris. In de populatie van mannen ouder dan 20 en vrouwen ouder dan 25 werd de incidentie van met inspanning samenhangende angina pectoris geschat op 3 per 1.000 per jaar.

In een gemiddelde H.A.-praktijk van 3.000 patiënten consulteerden ongeveer 117 patiënten per jaar hun H.A. voor recente of recent verergerde klachten die een waarschuwing kunnen zijn voor

een acute coronaire episode. De bevindingen van de enquête wijzen er op dat regelmatig patiënten hun klachten niet voorleggen aan hun H.A. en dat soms, als de klachten wél worden gemeld, verscheidene contacten met de H.A. nodig zijn voordat deze adequate aandacht aan de klachten schenkt.

SUMMARY

With 10 general practices participating in the Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study during the whole study period, 11,160 men over 20 years of age and 10,926 women over 25 years were registered.

During the 20 months of intake, 1,255 patients were included into the study alive. These patients presented to the general practitioner (G.P.) recent or recently worsened chest pain and/or recent unexplained upper abdominal pains, palpitations, dyspnea, dizzyness, fainting or mood changes. Notwithstanding a major effort to obtain optimal protocol compliance, considerable variability in inclusion policy of the G.P.s was observed. Through a mail inquiry of a sample of all patient-G.P. contacts, it was found that 55% of all patients with symptoms meeting the inclusion criteria were not included by the G.P. The reason for non-inclusion was in the majority of cases the presence of an evident extra-cardiac cause for an instance of recent or recently worsened chest pain. The inquiry showed however that no instances of anginal chest pain were missed. The data pertaining to this category of symptoms are therefore reliable. For other symptoms meeting the inclusion criteria, the data on the incidence are rough and the absolute incidence will be underestimated.

Most patients (71%) had chest pain as the primary symptom; in another 20% chest pain was present as secondary symptom. Of all patients with chest pain, 10% had recent onset and 13% recently worsened exercise induced angina. In the population of men over 20 and women over 25 years, incidence of exercise induced angina could be estimated at 3 per 1,000 per year.

In an average practice of about 3,000 patients, some 117 patients per year consulted a G.P. for recent or recently worsened warning symptoms of a coronary event. The mail inquiry suggested that quite frequently patients do not tell their symptoms

to their G.P. and that sometimes several consultations are needed before the G.P. pays proper attention to the symptoms

## 3.1. INTRODUCTION

A number of case history studies have shown that about half of the cases of acute coronary event (A.C.E.)†, i.e. acute myocardial infarction (A.M.I.) or cardiac death within 24 hours after onset of symptoms (sudden death), are preceded by so-called prodromal symptoms.[1] Also, frequent visits to a physician preceding an A.C.E. have been reported. In a case-history study of instances of sudden death, Kuller found that 23% of these patients had seen a physician in the week prior to the event.[2] These findings have been corroborated by many other studies.[3] Bekker reported that in Nijmegen, The Netherlands, about half of the patients who had sustained an A.C.E., visited a physician in the last 2 weeks before the event occurred.[4]

These findings would imply that physicians are frequently confronted with patients presenting symptoms that could possibly be prodromal for an ensueing A.C.E. In The Netherlands, a patient has to see a general practitioner (G.P.) first before a referral can be made. Under such circumstances it will be the G.P. who, as "first line" physician, is primarily confronted with such symptoms. For the G.P. a situation is thereby created full of diagnostic pitfalls. If he is consulted by a patient presenting unstable, i.e. recent or worsening, symptoms of suspected cardiac origin, there are three possibilities. First, the patient may be sustaining an A.M.I. at that moment. Second, the pain could be an "early warning symptom" of an impending coronary event and, third, the problem may not be a cardiac one at all. To handle such a situation properly, considerable diagnostic skills are required. The G.P. is expected to diagnose the presence of an A.M.I. with a high degree of accuracy. But he must also estimate the prognostic significance with respect to impending coronary events of various symptom complexes in combination with other characteristics of, and findings in, the patient.

Providing answers to the last question was the main objective of the I.M.I.R. study,[5] which was designed as a prospective out-of-hospital study of patients consulting a G.P. for unstable symptoms of suspected cardiac origin. Relevant patient-doctor

† For criteria, definitions, and abbreviations see Appendix on page 29

contacts were ascertained and followed-up to determine whether an A.C.E. was present at the time of the contact, ensued after it or remained absent. Symptomatic patients were not actively searched for however. In fact, the patient-doctor contact had to be established on the initiative of the patient. But the G.P.s participating in the study had committed themselves to include all patients presenting symptoms meeting the inclusion criteria and to do so irrespective of their judgement about the presence or absence of an acute or imminent coronary event.

To provide for the possibility to establish the prognostic significance of a wider range of complaints of suspected cardiac origin as "early warning symptom", the I.M.I.R. study did not confine itself to unstable angina only. Results of the study with respect to its main objective are reported elsewhere.[6] The present report is confined to the following questions:

1. What are the characteristics of patients consulting a G.P. for unstable symptoms of suspected cardiac origin?
2. Which is the nature of such symptoms and how often are they seen by a G.P. with an average practice?
3. Do the patient-doctor contacts ascertained by the methods of I.M.I.R. represent the full magnitude of the occurrence of such symptoms?

As the decision to include a patient after a relevant patient-doctor contact was the task of the G.P., the third question could not be answered directly from the I.M.I.R. study. Therefore, during a two-month period parallel to the I.M.I.R. study, a mail inquiry was held among a sample of all patients who consulted a G.P. participating in I.M.I.R. The purpose was to investigate whether all patients who had symptoms meeting the inclusion criteria actually had been included.

In the study, 14 general practices in Rotterdam participated. The present analysis was restricted to data from 10 practices serving a population of about 22,000 people in the age-categories under study. Data from the 4 other practices were excluded because the G.P.s concerned did not participate during the whole study period.

## 3.2. METHODS

### 3.2.1. INCLUSION

Details of design and methods are described in a companion paper.[5] Briefly, all patient-G.P. contacts were registered under a common protocol if the patients presented symptoms meeting the following inclusion criteria:

- recent or worsening chest pain,
- recent unexplained, i.e. without apparent extra-cardiac cause, upper abdominal pains, palpitations, dyspnea, dizzyness, syncope and/or mood changes.

The G.P. was also given the opportunity to include a patient with symptoms not meeting the inclusion criteria if the presence of an acute or imminent coronary event was suspected by him. Furthermore, all instances of sudden death occurring in patients not previously included into the study were registered. Men younger than 20 years of age and women younger than 25 years were excluded. On inclusion, the G.P. took a clinical history and performed a simple physical examination after which the G.P. was asked to indicate a provisional diagnosis by choosing between: acute myocardial infarction, imminent myocardial infarction, other somatic disease, psycho-social disorder and no provisional diagnosis. In order to determine whether an A.M.I. was present or absent at that moment, a technician took an electrocardiogram (E.C.G.) and a blood-sample for enzyme tests. After inclusion a follow-up period of 10 months ensued during which occurring A.C.E.s were detected by repeating E.C.G. and enzyme tests at protocol-fixed moments. All data were collected on standardized forms. The protocol did not provide for registration of patient-G.P. contacts occurring during follow-up or for re-inclusion of patients who had already completed their follow-up.

From October 1972 through May 1974, 1,255 alive patients were included from the 10 general practices taken into account in the present report. Data on the composition of the target population, i.e. the entire Dutch population, were derived from a publication by the Central Bureau for Statistics[7] and reflect the state on January 1, 1973. Data on the composition of the sampled population, i.e. all people registered with participating general practices, were obtained from the administrations of the health insurance systems in Rotterdam and by individual counting of persons not at all or otherwise insured. These data reflect the

state on January 1, 1974.

### 3.2.2. INQUIRY

During April/May 1974, the last two months that inclusion into the I.M.I.R. study was open, all patient-G.P. contacts regardless for which cause but excluding the ones for administrative reasons only, were registered in 9 general practices of the 10 considered in the present report. One of the G.P.s refused to cooperate because he feared possible embarrassment for the patient. Every third recorded patient received by mail a questionnaire asking "did you experience chest pain in the last four weeks" and similar questions for upper abdominal pains, palpitations, dyspnea, dizzyness, syncope and mood changes. Also, it was asked whether the symptoms had been reported to the G.P. For every returned questionnaire, inclusion into the I.M.I.R. study was verified. Where this was not the case while the patient stated that the G.P. was consulted for the symptoms mentioned, the G.P. was interviewed about the possible reasons for non-inclusion. During this interview it was determined whether the patient's symptoms had indeed met the inclusion criteria. When it was found that non-inclusion was not justified on the basis of the established inclusion criteria, the reason for non-inclusion was recorded.

Of 2,495 questionnaires sent, 1,933 (77%) were returned. No attempt was made to trace the reasons for non-compliance with the questionnaire.

## 3.3. RESULTS

### 3.3.1. TARGET- AND SAMPLED POPULATION

In comparison to the target population, the sampled population was found to be slightly older. Of the target population, 7.4% are men of 65 and older and 9.6% are women over 65. For the sampled population, these figures were 8.2% and 11.5% respectively. Also, the target population contained more men than the sampled population: 52.7% Vv. 50.5% (table 3.1.).

### 3.3.2. STUDY POPULATION

In the age-category up to 50 years, men predominated over women (25.1% Vv. 13.4% of the study population).

In the age-category 50-64, both sexes were about equally represented whereas women predominated over men in the age-category of 65 years and older (16.0% Vv. 11.8%). The study population contained more men than women: 54.5% Vv. 45.5% (table 3.2.). Per participating general practice, the contribution to the study population was found to vary considerably. The number of inclusions ranged from 55 to 158 with a median of 136,5. When corrected for the size of the practice, differences still remain. The number of inclusions ranged from 2.3% to 10%, median 6.0%, of the practice size. These differences were statistically significant ($p < 0.001$, chi-square test with 9 degrees of freedom) and could not be attributed to differences in age and sex composition of the practices (table 3.3.).

### 3.3.3. SYMPTOMS AT INCLUSION

The most frequent symptom recorded at inclusion was chest pain, which was present in 1,135 (90%) of the 1,255 patients. In 889 (71%) patients, chest pain was the primary symptom. Other symptoms than chest pain were less frequent as primary symptom; palpitations were the primary symptom in 92 (7.3%) and dyspnea in 81 (6.5%) patients. Mood changes, while rare as primary symptom, was present as secondary one in 734 (58%) patients. Symptomatology at inclusion was multifarious: on the average, 3 different symptoms were recorded per patient (table 3.4.). If chest pain was present, it was most often of recent onset and of "atypical" nature, i.e. did not meet the strict criteria for angina pectoris. Such chest pain was present in 544 (43%) patients. Recent onset angina was recorded 118 and recently worsened angina 138 times or in 9.4% and 11.0% of the patients respectively. In 290 (23%) patients, recently worsened "atypical" chest pain was found (table 3.5.).

### 3.3.4. INQUIRY

In 1,172 (61%) of the 1,933 instances of patient-G.P. contact for which an inquiry form was returned, the patient stated that one or more of the symptoms into which the questionnaire inquired, i.e. chest pain, upper abdominal pains, palpitations, dyspnea, dizzyness, syncope and mood changes ("inquiry symptoms"), had been present and were told to the G.P. In 167 (8.6%) instances the

contact concerned a patient who had been included into the I.M.I.R. study before the inquiry was held. Of the remaining contacts for "inquiry symptoms", an interview with the G.P. showed that 98 (5.1%) had been for symptoms that met the I.M.I.R. inclusion criteria, i.e. were recent or recently worsened or were, in the absence of chest pain, recent and unexplained. In 44 of these instances, the complaints had led to inclusion into I.M.I.R. In 54 instances however, inclusion did not result although the symptoms did meet the inclusion criteria. Consequently, of the total number of patients that should have been included 55%, i.e. 54 out of 98, were "missed". In 336 (17%) contacts, the patient stated that "inquiry symptoms" had been experienced but that they were not reported to the G.P. In 425 (22%) contacts, the reasons for consulting the G.P. were not related to the presence of "inquiry symptoms" as the patient answered all questions about these symptoms negatively (table 3.6.). Of the 54 patients unjustifiably not included, 46 (85%) had recent or recently worsened chest pain. In the majority of such instances, 25 patients, the reasons given for non-inclusion by the G.P. was the presence of an evident extra-cardiac cause, such as acute respiratory disease, pneumonia, lung cancer, acute leukemia, oesophagitis, herpes zoster, inflammation of the breast and fear of breast cancer. In 10 other patients with chest pain the cause was "not evidently extra-cardiac" but nevertheless judged to be "unrelated to the heart". Psychic causes, hyperventilation and atrial fibrillation were mentioned in such instances. In 7 further patients with chest pain, inclusion was omitted because the patient was "too nervous" or had refused. The G.P. "forgot" to include another 4 patients with chest pain; "too busy" was among the reasons given. No chest pain but other recent symptoms which met the inclusion criteria were present in 8 of the missed patients. Details are given in table 3.7.

## 3.4. DISCUSSION

### 3.4.1. TARGET-, SAMPLED- AND STUDY POPULATION

In comparison to the target population, i.e. the population of The Netherlands, the sampled population registered with participating practices was found to be older and to contain less men. The differences, however, are small. In generalizing the results of

the present study it has to be kept in mind that the study was conducted in an industrialized and urban area and therefore may not be representative for the general population. Regional differences in incidence rates of A.C.E. have been reported[8] and it is possible that these differences are reflected in the occurrence of the symptoms under study.

The study population differed considerably in composition from the sampled population; particulary women under 50 are underrepresented. In the entire study population, men predominate women. In The Netherlands, women visit a G.P. two to three times more often than men.[9] By the inquiry it was found that no selection towards men by the G.P. took place. Results of the present study indicate therefore that the symptomatology under study is indeed more frequently found in the male than in the female. With increasing age the difference disappeared in the present study.

### 3.4.2. INCLUSION POLICY OF THE G.P.

Much effort was made to achieve optimal cooperation and uniformity of interpretation of the inclusion criteria of the participating G.P.s. Nevertheless, variations in the proportion of the sampled population included were found to occur that exceed chance alone. In fact, the inquiry was held to investigate the reasons for this finding. Its results indicate that 55% of all patients presenting symptoms meeting the inclusion criteria were not included. The most frequent reason for non-inclusion given by the G.P. was "evident extra-cardiac cause" for an instance of recent or recently worsened chest pain. During the interviews held with G.P.s to determine the reasons for non-inclusions, it appeared that some of them hesitated to include patients with "explained" chest pain although it was required by the protocol. Probably, this circumstance forms the most important explanation for the observed variability in the number of inclusions. In addition, behavioural differences both between patients and doctors could have played a role.

Despite the inclusion variability observed, the authors remain of the opinion that the data taken together represent the real problem as it is seen by an average G.P. in an average practice in a big city in The Netherlands. Since the inquiry did not show that any cases of anginal chest pain were missed, the data

pertaining to this sub-category of pain are considered to be the most reliable. The results pertaining to other symptoms were shown by the inquiry to reflect the lower limit of the real magnitude of occurrence.

### 3.4.3. SYMPTOMS AT INCLUSION

Symptoms varied considerably as to their distribution over primary and secondary ones. Chest pain was common. Of the included patients, 90% had some form of chest discomfort, in 71% it was the primary symptom and in 20% exercise induced angina was present. Non chest pain symptoms were of minor importance as the primary one but their frequency increased at least five fold when a primary and secondary symptom were taken together. For mood changes, this increase was even 25 times. It was present as primary or secondary symptom in 61% of the patients but only 2.5% presented it as primary symptom. These findings underscore the importance of careful listening and asking for other symptoms in taking a history. Even if a clinically important symptom as chest pain was not presented as the primary one, it proved to be present in 20% of the patients after eliciting secondary symptoms; apart from a primary symptom, at least two other symptoms were present on the average.

### 3.4.4. INQUIRY

In the two months during which the inquiry was held, about 7,500 contacts were registered in nine practices. The degree of completeness of these contacts could be verified indirectly. Oliemans reported from a morbidity study in The Netherlands, 4,176 patient-G.P. contacts per year per 1,000 population of all ages.[10] Fry, in a study in the United Kingdom, found that one quarter of the G.P.'s work is done in the younger age-groups.[11] In the practice of one of the present authors (E. van der Does), the number of contacts for administrative reasons only was estimated at 800 per 1,000 persons per year. When the British and Dutch data are taken together and it is assumed that 1/4 of all contacts are with patients younger than 20 (men) or 25 (women), 3/4 of 4,176 – 800 = 2,532 contacts per 1,000 per year could have been expected. In fact, from the inquiry the number of contacts per year per 1,000 sampled population could be estimated.

For, 7,500 contacts in nine practices during two months represent, neglecting possible seasonal variations, 5,000 (6/9 of 7,500) contacts per year per G.P. Since the average contribution to the sampled population per practice was 2,200, 5,000/2.2 or 2,273 contacts per 1,000 per year result.

It is possible that the inquiry influenced the behaviour of the G.P. during the period it was conducted. The G.P.s were aware of the inquiry and the reasons for which it was held. Therefore, it could have influenced their alertness on symptoms meeting the inclusion criteria, resulting in an increased number of inclusions into I.M.I.R. during the inquiry period. The data do not provide strong evidence that this was the case. In the corresponding period in 1973, there were fewer inclusions: 134 in April/May 1973 Vv. 157 during the inquiry, April/May 1974 (table 3.8.). This difference is comparatively small however. Also, the somewhat larger number of inclusions during the inquiry than during a corresponding period a year earlier could have been caused by the "Heart week", a national drive organized by the Netherlands Heart Foundation during the inquiry period and accompanied by much attention in the press and on television, which could have influenced the number of visits to G.P.s by patients with cardiac symptoms. In conclusion, the authors are of the opinion that the inquiry provided a reliable and comprehensive picture of the occurrence of symptoms meeting the inclusion criteria of the I.M.I.R. study and of the way these symptoms were dealt with by the patient and the G.P.

Some other findings of the inquiry warrant emphasis. Of 1,508 patients experiencing "inquiry symptoms", 336 (22%) did not report them to the G.P. The phenomenon that symptoms are not necessarily presented at a patient-doctor contact was already known and reported by several investigators for different symptoms and diseases.[12-16] Horder et al. found that in the United Kingdom only 25% of the total morbidity is indeed seen by the G.P.[12] Stocks[13] and Logan[14] found however that in the same country about 30-40% of all health disturbances were seen by a doctor. Data for The Netherlands gave a higher percentage. Bremer, practicing in a small village, found that 65% of all health disturbances were seen by him.[15] The 35% remaining unseen by that author exceed the findings of the present study but it should be noted that Bremer investigated all morbidity in the population in his

practice whereas the present study confined itself to a subset of symptoms in patients older than 20 (men) or 25 (women) visiting their G.P.

The inquiry showed however that the "resemblance of disease prevalence to an iceberg in the sea" (Folmer[16]) applies also to symptoms that could be of cardiac origin. The proportion of the iceberg which is visible is not fixed and changes with the height of the waves washing against it as is the case with the degree of alertness of the doctor, the way he shows himself accessible to the patient and the skill with which the patient verbalizes his symptoms or is willing to present them. That the degree of alertness of the doctor is of importance was shown by the inquiry since 54 out of the 98 patients with symptoms meeting the inclusion criteria were "overlooked". Another finding of I.M.I.R. was that 11% of all patients included were so only after several contacts since they had consulted the G.P. in the four weeks prior to inclusion for symptoms meeting the inclusion criteria. The percentage of patients for which this was the case did not depend on the diagnosis of the G.P. indicated at the moment of inclusion. Consequently, the G.P. seems to "overlook" an important part of the symptomatology at first contact. From these findings and those of Bremer[15] and Folmer[16] it is attractive to postulate four different ways in which patient-doctor contacts are dealt with (table 3.9.). One part of the contacts receives proper attention immediately, a second part only after two or more contacts, a third part deals with contacts for disorders already established that might however need renewed attention (the inquiry observed 167 contacts for patients already included in I.M.I.R., table 3.7.) and a fourth part is not properly attended to because the symptoms are not presented in a recognizable form to the doctor.

### 3.4.5. INCIDENCE OF UNSTABLE SYMPTOMS

Unfortunately, it is impossible to assess exactly how often a G.P. is confronted with symptoms meeting the I.M.I.R. inclusion criteria since patient-doctor contacts during follow-up were not registered. However, some conclusions can be drawn from the present data.

The 1,255 patients included alive amount to 34 inclusions per 1,000 per year. This figure is somewhat higher for men than for

women: 37 Vv. 31. In men under 50, the number of inclusions per 1,000 per year was 28, in women of the same age-category it was 18. For men over 65 the number of inclusions per 1,000 per year was 49, in women over 65 this figure was 48 (table 3.10.) These trends resemble the incidence of myocardial infarction observed by De Haas[17] for The Hague, The Netherlands, but the differences are less pronounced. For recent exercise induced angina, 3 inclusions per 1,000 per year were recorded (table 3.5.). This figure represents by definition the incidence in the sampled population of exercise induced angina. For recently worsened exercise induced angina, 4 inclusions per 1,000 per year were recorded and for recent and recently worsened "atypical" chest pain, i.e. not induced by exercise, taken together another 23. The inquiry showed that the figure for "atypical" chest pain must be approximately doubled. At least 53 (2 x 23 + 4 + 3) contacts per 1,000 per year can therefore be expected to occur for unstable chest pain on the basis of the results of the present study. As an average practice will consist of about 2,200 people in the relevant age-categories, 117 contacts per year per practice for such pain can be expected. This would imply that a G.P. finds himself at least two times a week in a situation where considerable diagnostic skills are required and where quick diagnostic support from an E.C.G. and enzyme tests could be helpful.

## 3.5. CONCLUSIONS

Early warning symptoms of A.C.E. presented to a G.P. are in 90% of the instances accompanied by chest pain in some form. The incidence of such symptoms rises with age and is higher in men than in women, these trends resemble those for myocardial infarction but are less pronounced. The present study indicated that the incidence of effort induced angina is 3 per 1,000 per year in the population of men over 20 and women over 25 years and that an average G.P. is at least twice a week confronted with a patient with unstable chest pain requiring proper diagnostic attention with respect to the presence or imminence of an acute coronary event.

Despite major efforts to achieve optimal participation of the G.P., an inquiry of a sample of all patient-G.P. contacts

showed that 55% of all patients who should have been included in the I.M.I.R. study were missed. In the majority of such instances the reason given by the G.P. was the "evident extra-cardiac cause" for an instance of chest pain meeting the inclusion criteria. It would have been more realistic to add the adjective "unexplained" to the inclusion criterion "recent or recently worsened chest pain" and the need for close surveillance of protocol compliance in a study like I.M.I.R. is to be stressed. The inquiry also showed that 1 out of 5 patients do not tell their symptoms to a G.P. when they visit him and that the symptoms, when reported, do not always get proper attention from the general practitioner.

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The study was supported by the Netherlands Heart Foundation. J. Lubsen was supported in part by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.)

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REFERENCES


1. Pool, J., Lubsen, J., van der Does, E., Hugenholtz, P.G., Acute coronary events in general practice. Overview of the problem as it presented itself in 1970 and as it is seen in 1976. Hart Bull. 7: 88-90, 1976

2. Kuller, L., Sudden death in arteriosclerotic heart disease; the case for preventive medicine. Amer. J. Cardiol. 24: 617-628, 1969

3. Feinleib, M., Simon, A.B., Gillum, R.F., Margolis, J.R., Prodromal symptoms and signs of sudden death. Circulation 51: suppl. III, 155-159, 1975

4. Bekker, B.V., Interim verslag resultaten W.H.O. registratieproject ischaemische hartziekten Nijmegen. Nijmegen, 1972

5. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G., Arntzenius, A.C., Acute coronary events in general practice. Objectives and design of the I.M.I.R. study. Hart Bull. 7: 91-98, 1976 This thesis, chapter 2

6. Lubsen, J., Pool, J., van der Does, E., Acute coronary events in general practice. Acute risk of myocardial infarction or sudden death in a symptomatic patient. Hart Bull. 7: 114-117, 1976. See also this thesis, chapter 4

7. Centraal Bureau voor de Statistiek. Statistisch jaarboek. Staatsuitgeverij, Den Haag, 1973

8. Centraal Bureau voor de Statistiek. Hart- en vaatziekten, een statistische verkenning. Staatsuitgeverij, Den Haag, 1972

9. Lamberts, H., De morbiditeitsanalyse 1972 door de groepspraktijk Ommoord. Huisarts en Wetensch. 1: 21-39, 1975

10. Oliemans, A.P., Morbiditeit in de huisartspraktijk. Thesis, Leiden, 1969

11. Fry, J., Profiles of disease. Livingstone, Edinburgh, London, 1966

12. Horder, J.P., Horder, E., Illness in general practice. Practitioner 173: 177-187, 1954

13. Stocks, P., Sickness in the population of England and Wales in 1944-1947, London, 1949

14. Logan, W.P.D., Morbidity statistics in England and Wales. Public Health Paper W.H.O. 27: 158-162, 1965

15. Bremer, G.J., Het verwijzen in de huisartsenpraktijk. Van Gorcum, Assen, 1964

16. Folmer, H.R., Huisarts en ijsberg. Thesis, Utrecht, 1968

17. De Haas, J.H., Eerste myocardinfarct in Groot-Den Haag- een retrospectieve epidemiologische survey. Hart Bull. 6: 36-49, 1975

4. ACUTE CORONARY EVENTS IN GENERAL PRACTICE: PREDICTABILITY OF FUTURE EVENTS IN PATIENTS WITH NEW OR WORSENING SYMPTOMS

E. van der Does*, J. Lubsen**, J. Pool** and P.G. Hugenholtz**

SAMENVATTING

In 14 huisartsenpraktijken in en om de stad Rotterdam werd een bevolkingsstudie uitgevoerd teneinde de betekenis te bestuderen van zogenaamde "prodromale" verschijnselen van de acute coronaire episode (A.C.E.), d.w.z. plotse cardiale dood (P.D.) of acuut myocardinfarct (A.M.I.) en van de diagnose "dreigend myocardinfarct" (D.M.I.) gesteld door een huisarts (H.A.). Gevallen van patient-huisartscontact wegens onstabiele, d.w.z. recente of recent verergerde, klachten zonder aanwijsbare extra-cardiale oorzaak werden onder een gemeenschappelijk protocol geregistreerd en vervolgd gedurende 10 maanden. Optredende A.C.E.'s werden gedetecteerd aan de hand van daartoe opgestelde criteria.

Gedurende de periode dat de toelating tot de studie opengesteld was werden 43 gevallen van P.D. geregistreerd bij patiënten die niet eerder in leven tot de studie waren toegelaten. Van de patiënten die in leven werden ingesloten hadden er op het moment van insluiting 93 een "bewezen A.M.I." en 37 een "mogelijk A.M.I."; bij 1.214 patiënten was géén A.M.I. aanwezig. Van deze laatsten maakte 7% (83/1214) een A.C.E. door gedurende de vervolgperiode. Van de 83 nieuwe A.C.E.'s werden er 19 geclassificeerd als "P.D.", 34 als "bewezen A.M.I." en de resterende 30 als "mogelijk A.M.I."; 44 nieuwe episodes traden op gedurende de eerste maand na toelating. In 64% (53/83) van de nieuwe A.C.E.'s was de episode juist voorspeld door de H.A. aangezien hij bij de betrokken patiënten op het moment van toelating de diagnose "D.M.I." had gesteld. Echter, het aantal fout-positieve diagnoses "D.M.I." was groot aangezien deze diagnose werd gesteld bij 26% (310/1214) van de patiënten die bij toelating géén A.M.I. hadden. Toelating wegens onstabiele angina pectoris ging vooraf aan 40% (33/83) van de nieuwe A.C.E.'s die optraden gedurende de vervolgperiode en aan 13% (33/256) van alle A.C.E.'s die werden geregistreerd Van de patiënten zonder A.M.I. had 21% (252/1214) bij toelating onstabiele angina pectoris; van deze patiënten maakte 13% een A.C.E. door binnen 10 maanden. Patiënten met andere onstabiele klachten hadden een laag risico op het optreden van een A.C.E. gedurende 10 maanden.

Lineaire Discriminant Functie (L.D.F.) analyse toonde aan dat in de patiëntenpopulatie die de huisarts consulteert wegens onstabiele klachten maar zònder infarct, het geslacht, de leeftijd, de aanwezigheid van Q- en T-golf afwijkingen in het E.C.G., diabetes, hypertensie en van vochtige ronchiën waren geassocieerd met het risico op een A.C.E. optredend op korte termijn. Bij patiënten met een L.D.F.-score in de laagste 10% van zijn distributie werd geen A.C.E. gedetecteerd gedurende de vervolgperiode. Van de patiënten met een L.D.F.-score in de hoogste 10% maakte 31% een A.C.E. door binnen 10 maanden. De evaluatie aan de hand van de L.D.F.-score van het risico van een patiënt op een A.C.E. optredend op korte termijn kan in de praktijk van waarde blijken.

SUMMARY

To investigate the significance of so-called "prodromal" symptoms of acute coronary event (A.C.E.), i.e. sudden cardiac death (S.D.) or acute myocardial infarction (A.M.I.), and of the diagnosis "imminent myocardial infarction" (I.M.I.) made by a general practitioner (G.P.), a community study was conducted in 14 general practices in and around Rotterdam, The Netherlands. Instances of patient-G.P. contact for unstable, i.e. new or worsening, coronary-type symptoms without apparent extra-cardiac cause were registered and followed for 10 months under a common protocol. Instances of A.C.E. were detected according to preset criteria.

While inclusion into the study was in progress, 43 instances of S.D. were registered in patients not previously included alive. Of the patients included alive, 93 had "definite A.M.I." and 37 had "possible A.M.I." at the moment of inclusion and in 1,214 patients no A.M.I. was present. Of these 7% (83/1214) sustained an A.C.E. during follow-up. Of the 83 new A.C.E.s, 19 were classified as "S.D.", 34 as "definite A.M.I." and the remaining 30 as "possible A.M.I."; 44 new events occurred within the first month after inclusion. In 64% (53/83) of the new A.C.E.s was the event correctly predicted by the G.P. since he made the diagnosis "I.M.I." at inclusion in the patients concerned. The number of false-positive diagnosis of "I.M.I." was large however since this diagnosis was made in 26% (310/1214) of the patients free of A.M.I. at inclusion. Inclusion for unstable angina preceded 40% (33/83) of the new A.C.E.s which occurred during follow-up and 13% (33/256) of all A.C.E.s detected.

In patients free of A.M.I., it was present at inclusion in 21% (252/1214) and it was associated with a 13% (33/252) rate of A.C.E. within 10 months. Patients with other unstable symptoms had a low 10-month A.C.E.-rate.

Linear discriminant function (L.D.F.) analysis showed that in patients presenting to a G.P. with unstable symptoms but without A.M.I., short-term risk of A.C.E. was associated with age, sex, unstable angina, Q- and T-wave abnormalities in the E.C.G., diabetes, hypertension and with râles. Among patients with a L.D.F.-score in the lowest 10% of its distribution, no events during follow-up were detected. Patients with a L.D.F.-score in the highest 10% had a 31% rate of A.C.E. within 10 months. The L.D.F.-score may be useful in practice as a basis for the evaluation of a patient's short-term risk of A.C.E.

## 4.1. INTRODUCTION

Instances of acute corornary event (A.C.E.), i.e. acute myocardial infarction (A.M.I.) or sudden cardiac death (S.D.), are a major cause of disability and death in most industrialized countries[1]. The case fatality rate is high, especially in the first few hours after the attack and attempts to decrease the early mortality have not been very successful. Of interest therefore is the question whether the occurrence of an A.C.E. can be predicted on the basis of prodromal symptoms or other phenomena which precede the event. For, if such a prediction is possible with an acceptable degree of certainty, a more timely institution of treatment could in principle be envisioned.

The notion that prodromal symptoms frequently precede an A.C.E. is primarily based on case-history studies[2]. Such studies have however rarely given much insight into questions of predictability. Only a few follow-up studies have been reported. Most of these, such as for instance the studies of Vakil[3] and of Lie et al.[4], were concerned with patients hospitalized for well defined syndromes. More comprehensive follow-up studies have been advocated[5] but have rarely been done. Only the study by a group of investigators working in Edinburgh, Scotland[6], concerned with the prognosis of patients with unstable angina referred to a special clinic by general practitioners (G.P.s), involved patients irrespective of hospitalization. The Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study[7]

was similar in objectives and design to the Edinburgh study. However, its scope was more comprehensive in that included were not only patients consulting their G.P. for unstable angina but also patients with other unstable, i.e. recent or recently worsened, symptoms without apparent extra-cardiac cause. Based on data from this study, the present report addresses itself to the question whether future A.C.E.s occurring in patients free of A.M.I. who consult a G.P. for unstable symptoms without apparent extra-cardiac cause, are predictable.

Such prediction would be of little relevance if the G.P. actually saw only a small fraction of all patients who sustain an A.C.E. before the event occurred for reasons possibly related to the impending event. The design of the I.M.I.R. study was such that an indication of the size of this fraction could be obtained. Other results from the I.M.I.R. study have been described elsewhere[8-10].

## 4.2. METHODS

Design and methods of the I.M.I.R. study have been described in detail elsewhere[7]. Nevertheless, some features relevant to the present report are given here.

In 14 general practices situated in and around the city of Rotterdam, instances of patient-G.P. contact were registered from October, 1972 through May, 1974 whenever the patient complained of recent or recently increased chest pain and/or recent and unexplained dyspnea, palpitations, upper abdominal pains, dizzyness, syncope, mood changes; "recent" referring to the last four weeks and "unexplained" to "without apparent extra-cardiac cause". Also, all instances of sudden cardiac death, defined as death within 24 hours after the onset of the attack and without apparent extra-cardiac cause, were registered upon notification by the G.P. Inclusion was restricted to men of 20 years and older and women of 25 and older. Management of included patients was left at the G.P.'s discretion although common opinion led to the adoption of some general policies.

After verifying that the inclusion criteria were met, the G.P. took a detailed history and performed a simple physical examination, using a standardized questionnaire for data recording. Then, the G.P. recorded his provisional inclusion diagnosis by opting for one of the following diagnostic categories: "myocardial infarction" (M.I.), "imminent myocardial infarction" (I.M.I.), "other somatic di-

sease" (O.S.D.), "psycho-social disorder" (P.S.D.) or "no provisional diagnosis" (N.P.D.). The last option was to be used only when the G.P. was hesitating between O.S.D. and P.S.D. Finally the G.P. decided whether immediate hospitalization was necessary and gave, if applicable, the indications for it.

If no immediate hospitalization followed the patient-G.P. contact, the patient was seen directly either at the patient's home or at a special clinic by a technician, who completed an additional questionnaire, recorded a standard 12-lead electrocardiogram (E.C.G.) and took a blood sample for assessment of the serum levels of the enzymes alpha-hydroxybutyric dehydrogenase ($\alpha$-H.B.D.H.), glutamic oxaloacetic transaminase (G.O.T.) and creatinine phosphokinase (C.P.K.). For these investigations, technicians were kept available on a 24-hour basis. When the patient was hospitalized, test results and other clinical information were obtained from the hospital.

After inclusion, there was a 10-month follow-up period for the collection of further data on the clinical course of the patient. E.C.G. and enzyme studies were repeated after 3 days and after 1 week, another E.C.G. was recorded 1 month after inclusion. At all these occasions, a short questionnaire on the current status of the patient was completed also. At the conclusion of follow-up, i.e. 10 months after entry into the study, an E.C.G. was recorded and a detailed questionnaire was completed on current symptoms and medical events during follow-up. Also, information was obtained from the patient's G.P. and, if applicable, from consulting specialists or from hospitals.

Acute coronary events at inclusion or during follow-up were classified as either "definite" or "possible" A.M.I. or as "sudden cardiac death". A modified version of the World Health Organization criteria for A.M.I.[11] was used, details of which are available from the authors upon request.

In the analysis, conventional statistical methods were employed. To select from all information recorded at inclusion a set of variables which were independently associated with the future occurrence of an A.C.E. in patients free of A.M.I. at inclusion, linear discriminant function (L.D.F.) analysis[12] was used. By the same technique, a weight was attached to each information variable selected. For the purpose of L.D.F.-analysis, the variable "age" was coded in years

while attributes, such as "male sex", were represented by indicator variables coded as 0 = attribute absent, 1 = attribute present. Multiplying the weights with the value of its associated information variable and adding the results yields a composite risk-score. On the coding used, high values of this score indicate high risk of a future A.C.E. A positive weight indicates that a future A.C.E. is more likely in the presence of the associated attribute than in its absence. The dependence of actual risk on the risk-score was studied as follows. First, for all patients free of A.M.I. at inclusion, the risk score was calculated. Next, patients were arranged in order of increasing score and divided into 10 strata consisting of an equal number of patients, the 10% of the patients with the lowest scores forming the first stratum, the 10% with the next lowest scores forming the second stratum, etc. Finally, the numbers of actual A.C.E.s which occurred during follow-up in each stratum were counted.

## 4.3. RESULTS

### 4.3.1. TOTAL OCCURRENCE OF ACUTE CORONARY EVENTS

Of the 1,387 patients included, 43 were registered as "sudden cardiac death". Of the remaining 1,344, 130 (10%) patients had either "definite" or "possible" A.M.I. at inclusion (table 4.1.).

Of the 1,214 patients free of A.M.I. at inclusion, 83 (7%) sustained an A.C.E. during follow-up. Of these events, 19 (23%) were classified as "sudden cardiac death". Of the remaining 64 instances of "definite" or "possible" A.M.I., 4 were fatal (table 4.1.).

### 4.3.2. RELATIONSHIP TO INCLUSION DIAGNOSIS

The diagnosis made by the G.P. at inclusion in patients free of A.M.I. at that moment and the subsequent A.C.E.s which occurred during follow-up are presented in table 4.2. Of the 1,214 patients free of A.M.I., 40 were diagnosed by the G.P. as "M.I.". In this subgroup, the one-month rate of A.C.E. was 5% (2/40) and the 10-month rate was 18% (7/40). Another 310 patients were diagnosed as "I.M.I.", one- and 10-month rates of subsequent A.C.E. were 8% (26/310) and 17% (53/310) respectively in these patients. In the remaining 864 patients, the G.P. diagnosed either "O.S.D.", "P.S.D." or "N.P.D.". For these patients taken together, one- and 10-month A.C.E.-rates were observed of 2% (16/864) and 3% (23/864)

respectively.

### 4.3.3. RELATIONSHIP TO SYMPTOMS AT INCLUSION

Of the 1,214 patients without A.M.I. at inclusion, 4 were excluded from further analysis because of incomplete data. One of these sustained an A.C.E. during the first month of follow-up. Of the remaining 1,210 patients, 252 (21%) had unstable exertional angina at inclusion, which was "worsening" in 134 patients and "new" in the remainder. In another 841 patients (69%), other (non-anginal) chest pain was among the symptoms recorded at inclusion while in the remaining 117 (10%) patients, unstable symptoms other than chest pain were present (table 4.3.).

Worsening angina was associated with the highest rate, 9% (12/134), of A.C.E. within one month after inclusion. This rate was lowest, less than 1% (1/117), in patients without chest pain among their symptoms. Unstable angina and other chest pain were associated with one-month A.C.E.-rates of 8% (20/252) and 3% (22/841) respectively. Of the 43 patients who sustained an A.C.E. within one month after inclusion, less than half, 20, had unstable angina at entry into the study but only one patient had other symptoms than chest pain at that moment (table 4.3.).

Patients with unstable angina had a 10-month rate of A.C.E. of 13% (33/252). Within this group, a higher rate, 16% (22/134), was associated with "worsening" than with "new" angina, which had a 10-month rate of 9% (11/118). The difference was however not statistically significant ($p = 0.1$, table 4.3.). In patients who did not have angina, a 10-month rate of 5% (49/958) was observed. Their prognosis did not depend on the presence of chest pain at inclusion (table 4.3.).

### 4.3.4. COMPOSITE RISK-SCORE

The nine variables selected by L.D.F.-analysis which were independently associated with the future occurrence of A.C.E.s. in patients free of A.M.I. at inclusion are presented in table 4.4. Also given are the respective weights and, for cases of A.C.E. and non-cases respectively, the age and sex composition and the prevalences of the remaining attributes. All weights were statistically significant at the 5% level. Apart from "male sex" and an older age, the presence of Q-wave and of T-wave abnormalities in the E.C.G., which

was recorded at inclusion, were predictors of future A.C.E. Of all information which was recorded about symptoms, only "unstable angina" was retained. Furthermore, the presence of hypertension and of diabetes were found to be predictive, as were râles found at the physical examination by the G.P. All weights were positive, which is in accordance with the fact that all attributes were more prevalent among cases than among non-cases and that cases were older.

The dependence of A.C.E.-rate on the composite risk-score is shown in fig. 4.1. Among the 121 patients with the lowest scores, i.e. a score $\leq 1.5$, no A.C.E.s. during follow-up were observed. On the other hand, the 121 patients with the highest scores, i.e. a score $> 5.5$, had a 10-month A.C.E.-rate of 31% since 37 A.C.E.s were counted in this patient group during follow-up. For the strata between these extremes, the figure shows a gradual increase of risk with increasing score value.

## 4.5. DISCUSSION

"Imminent myocardial infarction" as a diagnosis is a prediction of which the correctness cannot at present be verified immediately by further diagnostic investigation. Only the occurrence or non-occurrence of an A.C.E. within the period of time implied in the prediction can prove its (in)correctness. Our findings do not show that the G.P. is able to predict accurately the early occurrence of a future A.C.E. in a symptomatic patient who is still free of A.M.I. In 310 such patients, an A.C.E. was predicted by the G.P. since he diagnosed "I.M.I." at inclusion (table 4.2.). This diagnosis was correct in only 8% (26/310) of the patients so diagnosed with respect to events occurring within one month and in 17% (53/310) with respect to events occurring within 10 months after the moment that the diagnosis "I.M.I." was made. Of the 44 A.C.E.s which occurred in patients free of A.M.I. at inclusion during the first month of follow-up, 59% (26/44) were predicted by the G.P. by a diagnosis of "I.M.I." made at inclusion. Although this figure seems to be rather high, it should be remembered that it was attained at the cost of a large number of false-positive diagnosis. During a further nine months of follow-up, another 39 A.C.E.s occurred. Of these, 69% (27/39) were correctly predicted by the G.P. It may be questioned however whether these events can in fact be considered as having been "imminent" at the moment of inclusion since at least in some

instances a considerable amount of time expired before the event took place. On the other hand, the data of table 4.2. reflect the possibility that the G.P. is too early with his diagnosis. Of the patients who sustained an A.C.E. during follow-up and were free of A.M.I. at the moment of inclusion, two were diagnosed by the G.P. as having "A.M.I." at that moment and this was the case in another five patients who sustained an A.C.E. during the next nine months of follow-up. It seems questionable whether great accuracy of prediction can be expected from the G.P., who has to base his diagnosis primarily on symptoms and signs, if there are no specific symptoms and/or signs which precede an A.C.E. Unstable angina is considered to be the most important prodromal symptom of A.C.E.[14] Although our data support this notion, its mere presence was not an accurate predictor of a future A.C.E. Of 252 patients with unstable angina who did not have A.M.I. at inclusion, 13% (33/252) sustained an A.C.E. during 10 months of follow-up (table 4.3.). Also, of all the patients who sustained an A.C.E. during follow-up and were free of A.M.I. at inclusion, only 40% (33/82) had unstable angina at that moment. This figure can however not be taken to represent the fraction of all patients who sustain an A.C.E. and who are seen by the G.P. before the event occurs with unstable angina. In fact, this fraction must be much smaller. In our study, 43 instances of S.D. were registered in patients not included into the study before decease; furthermore, 93 cases of "definite A.M.I." and 37 cases of "possible A.M.I." were detected at the moment of inclusion (table 4.1.). In these instances, unstable angina must have been either absent or not recognized by the G.P. or not presented to him by the patient before the event occurred since inclusion into the study would otherwise have preceded the event. If the total of 256 A.C.E.s which were detected either at inclusion or during follow-up (table 4.1.) are assumed to represent all A.C.E.s which occurred in the participating practices during the study period[9], the fraction of all patients sustaining an A.C.E. who were seen by the G.P. at most 10 months before the event occurred with unstable angina was 13%, 33 out of 256 (tables 4.1. and 4.3.) since in 33 instances was the A.C.E. preceded by inclusion into the study for unstable angina. Although this figure is in part a product of a particular study design, it indicates that unstable angina is infrequently encountered in general practice as a prodromal symptom of A.C.E.

Results published elsewhere[8] have shown that there is reason to assume that the participating G.P.s included all patients with unstable angina who were seen by him. The results mentioned above are therefore believed to be representative for the natural history of unstable angina as seen by these G.P.s.

Evidence that no combination of signs and symptoms exists which accurately predicts the early occurrence of a future A.C.E. derives also from the results of the L.D.F.-analysis to obtain a composite risk-score. This analysis took into account also E.C.G. information, which was not available to the G.P. when he had to make his diagnosis at the moment of inclusion. Nevertheless, a diagnosis "I.M.I." based on the composite risk-score (table 4.4.) would not surpass the accuracy of prediction of the G.P.'s diagnosis "I.M.I.". For instance, a L.D.F.-score-based procedure in which the diagnosis "I.M.I." is made when the score exceeds 3.5 would allocate that diagnosis to 3 x 121 or 363 patients (fig. 4.1.). The diagnosis would be correct in only 17% (61/363, fig. 4.1.) of the patients so diagnosed with respect to events occurring in 10 months of follow-up since 61 A.C.E.s were observed in these patients during that period. The same score-based procedure would predict correctly 74% (61/82, fig. 4.1.) of the total of 82 A.C.E.s which took place during follow-up in patients who were included in this part of the analysis. This figure seems high but is again attained at the cost of a large number of false-positive diagnosis of "I.M.I." These considerations led to the conclusion that a procedure for allocating the diagnosis "I.M.I." in a symptomatic patient who is seen by a G.P. and who does not have A.M.I. which is based on the present L.D.F. would have an accuracy which is comparable to that of the G.P.'s diagnosis of "I.M.I." made in such patients without E.C.G. assistance. Furthermore, the results of the present L.D.F.-analysis seems to render it unlikely that a specific combination of symptoms and signs exists which precedes a future A.C.E. and which can be recognized as a syndrome by a G.P. This is so as many variables describing comprehensively the symptoms and other features of the patient's condition at inclusion were considered for incorporation in the final L.D.F. Nevertheless, we are of the opinion that the use in general practice of a L.D.F. like the present one for estimating a patient's short-term risk of A.C.E. could be of practical value. In a health care system in which the G.P. has a central position, as is the case in The Netherlands, it

is his responsibility to make a first diagnosis in a patient who experiences symptoms and to decide on further action since the patient will as a rule consult a G.P. first. Results from the I.M.I.R. study[10] have shown a low accuracy of both the diagnosis "A.M.I." and "I.M.I." as made by the G.P. at first contact with a patient who complains of unstable symptoms without apparent extra-cardiac cause. Provided he has access to diagnostic help, the G.P. will be able to recognize the cases of A.M.I. present among such patients. But in the absence of A.M.I., he is faced with the problem to determine whether the patient in question is likely to sustain an A.C.E. in the near future. It is in this area that the use of L.D.F.-score-based risk estimation could be of help. No absolute certainty about the patient's future clinical course would result. But such risk-estimation could be an aid in solving the problem of setting indications for treatment, be it the administration of drugs or further diagnostic investigation and evaluation for bypass surgery. On the basis of the L.D.F.-score, a sub-group of patients may be identified in whom a 31% rate of A.C.E. occurring within 10 months is expected (fig. 4.1.). This seems to be a very high risk which would warrant medical intervention with the aim to avoid a future A.C.E. or at least to diminish its possible impact. On the other hand, different actions would presumably be taken if the patient in question appears to have a low risk on the basis of the L.D.F.-score. Before specific L.D.F.-score-based guidelines for treatment selection can be given, much further research is needed however. As a final note in this context, the above problem of treatment selection would be of little practical relevance if the G.P. rarely saw a patient shortly before an A.C.E. is sustained with symptoms which could be related to the impending event. Our results indicated that this is not the case. Of the total of 256 A.C.E.s detected either at inclusion or during follow-up, 32% (83/256, table 4.1.) occurred during follow-up, i.e. at most 10 months after the patient had consulted a G.P. with unstable symptoms without apparent extra-cardiac cause.

A comparison of the present results to those of other reported studies is of interest. However, such comparisons have to be made with caution since differences in design, methods and in populations studied have to be taken into account. A number of case-history studies of prodromal symptoms of A.C.E. have been done. Bekker[16] reported from an A.M.I. registration project[17] which was carried out

under the auspices of the World Health Organization in Nijmegen, The Netherlands, that 50% of the patients who died suddenly had seen a doctor in the two weeks preceding the event. From all centers taking part in the registration project[17] combined, it was reported that 56% of the patients who sustained a non-fatal A.M.I. had any of the symptoms described in the inclusion criteria of the present study in the 28 days preceding the attack. But the results of such a study cannot be compared to those of the present one. As reported elsewhere[8], a special investigation carried out in the practices participating in I.M.I.R. showed that having a symptom does not always mean that a G.P. is consulted or that the patient is properly attended by him at first contact. To be included into the I.M.I.R. study, experiencing a symptom was not enough. It had to be presented to a G.P., who had to recognize it as complying with the inclusion criteria and consequently bring about entry into the study. In this respect, a case-history study is not comparable to a follow-up study like the present one, part of the reason being that the memory of a patient who has sustained an A.M.I. may be biased by the event itself. In design and as a community based study, the I.M.I.R. study can be compared directly only to the Edinburgh study[6]. In that study, 15.5% (39/251) of the patients with unstable angina who were free of A.M.I. at the time of entry developed an A.C.E. within six months. In the present study, a somewhat lower risk of 13% (33/252, table 4.3.) was observed for these patients for a longer period of time of 10 months. Differences in the population studied may account for this. In the Edinburgh study[6], only men aged under 70 were studied; in the present study, women were included also, who have a lower risk than men, as is apparent also from the results of the L.D.F.-analysis (table 4.4.). But other factors, such as different criteria for diagnosing unstable angina or for the occurrence of an A.C.E. may have played a role also. In the Edinburg study[6], "unstable angina" was clinically diagnosed by an experienced cardiologist on the basis of all investigations done, which included a bicycle ergometer exercise tolerance test. Such tests were not done in the present study and "unstable angina" was diagnosed solely on the basis of the Rose-questionnaire[15]. In the Edinburg study[6], "probable myocardial infarction" was included in the total event count. In the present study, "possible myocardial infarction" was included but this diagnostic category is likely to represent "probable myocardial

infarction" according to the criteria used in Edinburgh. A recent review article expressed the "consensus opinion" that worsening angina has a worse prognosis than new angina[14]. With respect to this matter, both the Edinburgh and the present study gave inconfirmative results. Although both studies observed a slightly higher risk for "worsening" than for "new" angina, the differences were not statistically significant in either case. The present L.D.F.-analysis did not yield new predictive information from the qualitative point of view. Age, sex, E.C.G.-abnormalities, unstable angina, hypertension and diabetes are all well established predictors of future coronary events[18]. Since "râles" may be caused by heart failure which will also show as an increased cardio-thoracic ratio[19], the present finding that "râles" are a predictor supports the Edinburgh-finding that the cardio-thoracic ratio is a predictor[6]. That group of investigators described the results of their L.D.F.-analysis as "poor". When viewed as a basis of an allocation procedure for diagnosing "I.M.I.", the present results are probably no better. A finding not previously reported from a community based follow-up study is the finding from the present study that, although the most specific prodromal symptom, unstable angina for which a G.P. is consulted infrequently precedes an A.C.E. This finding once more underscores that other unstable symptoms than angina may be prodromal of an A.C.E. also and require therefore proper attention of the G.P.

The present results are a reflection of a particular study of the medical history of patients seen for unstable symptoms without apparent extra-cardiac cause by a group of selected G.P.s. Although the protocol specified the inclusion of all patients with unstable chest pain irrespective of its suspected cause, it appeared[8] that the participating G.P.s in fact hesitated to include a patient with chest pain if a very obvious extra-cardiac cause, such as a pneumonia accompanied by fever, was present. But otherwise protocol compliance was shown to be very good[8] and we are of the opinion that the present results are representative for the G.P.s involved and for their management of patients with unstable symptoms if the adjective "without apparent extra-cardiac cause" is taken into account. Nevertheless, whether these results are also representative for other practices, even within The Netherlands, is a matter of conjecture. The G.P.s who participated in the I.M.I.R. study were especially se-

lected because of their interest in cardiology and differences between the way in which G.P.s act and react could lead to different results if the study were to be repeated elsewhere. Furthermore, differences between populations could lead to different results. Notably, the composite risk score procedure for estimating the risk of a future A.C.E. in a symptomatic patient free of A.M.I. which was derived from the present study will therefore require further evaluation if its general use is inteded.

We are most grateful to all general practitioners and the technicians who participated in the I.M.I.R. study, which would have been impossible without their interest and cooperation. Their names appear on page 27 of this thesis.

We wish to thank O.S. Miettinen, M.D., Ph.D., Professor of Epidemiology and Biostatistics at the Harvard School of Public Health, Boston, U.S.A., for his guidance during the execution of the study and the analysis of the data. Also, we thank R.K. Neff, Director of the Health Sciences Computing Facility at the Harvard School of Public Health, and Susan Gorter-Mayer, then at the Department of Clinical Information Processing at the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands, for their assistance in computing.

The study was supported by the Netherlands Heart Foundation. Dr. Lubsen was supported in part by the Netherlands Organization for the Advancement of Pure Science (Z.W.O.).

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Accepted for presentation on the 50th Annual Scientific Sessions of the American Heart Association, November 28 - December 1, 1977, Miami, Fla., U.S.A.

REFERENCES

1. Vedin, J.A., Wilhelsson, C., Elmfeldt, D., Tibblin, G.,Wilhelmsen,L., and Werkö, L., Sudden Death: Identification of high risk groups. Am. Heart J. 86 : 124-132, 1973

2. Gillum, R.F., Feinleib, M., Margolis, J.R., Fabsitz, R. R., Brasch,R. C., The pre-hospital phase of acute myocardial infarction and sudden death : 1. Prodromata of acute coronary events. Prev. Med. 5 : 408-413, 1976

3. Vakil, R. J., Preinfarction syndrome - management and follow-up. Am. J. Card. 14 : 55-63, 1964

4. Lie, L.I., Wellens, H.J.J., Durrer, D., Een prospectieve studie van het dreigende hartinfarct. Ned. T. Geneesk. 118 : 1218-1220, 1974

5. World Health Organization, Reginal Office for Europe, The prodromal symptoms of myocardial infarction and sudden death, Report of a working group, Copenhagen 1971

6. Duncan, B., Fulton, M., Morrison, S.L., Lutz, W., Donald, K. W., Kerr, F., Kirby, B. J., Julian, D. G., Oliver, M. F., Prognosis of new and worsening angina pectoris. B. M. J. 1 : 981-985, 1976

7. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G., Arntzenius, A.C., Acute coronary events in general practice : Objectives and design of the I.M.I.R study. Hart Bull. 7 : 91-98, 1976. This thesis chapter 2

8. Van der Does, E., Lubsen, J., Pool, J., Van Strik, R., Van der Sijde, J., Stroink, J., Acute coronary events in general practice: Early warning symptoms of acute myocardial infarction and sudden death. Hart Bull. 7 : 99-106, 1976. This thesis chapter 3

9. Lubsen, J., Van der Does, E., Pool, J., Acute coronary events in general practice: Incidence of acute myocardial infarction and sudden death. Hart Bull. 7 : 107-113, 1976. This thesis chapter 7

10. Van der Does, E., Lubsen, J., Pool, J., Gorter, S., Acute coronary events in general practice: Diagnostic power of the G.P. without

laboratory assistance. Hart Bull. 7 : 118-121, 1976. See also this thesis chapter 4, 5

11. World Health Organization, Reginal Office for Europe, Ischaemic Heart disease registers. Report of the 5th working group, Copenhagen 1971

12. Cornfield, J., Discriminant functions. Review Int. Stat. Inst., 35 : 142-153, 1967

13. Miettinen, O.S., Comment on Conover W. J. : Some reasons for not using the Yates continuity correction on 2x2 contingency tables. J.A.S.A. 69 : 380-382, 1974

14. Cairns, J. A., Fantus, I.G., Klassen, G. A., Review: Unstable angina pectoris. Am. Heart J. 92 : 373-386, 1976

15. Rose, G. A., Blackburn, H., in: Cardiovascular Survey Methods, World Health Organization, Geneva 1968, pp. 172-175

16. Bekker, B. V., Interim verslag resultaten W.H.O. registratie project ischaemische hartziekten. Nijmegen 1972

17. World Health Organization, Reginal Office for Europe, Myocardial infarction community registers. Public health in Europe 5, Copenhagen 1976

18. Moss, A.J., Profile of high risk in people known to have coronary heart disease: a review. Circulation Suppl. III to 51, 52:III-III-154, 1975

19. Hurst, J. W., Spann, J. F., in Hurst, J.W., et al. (eds.), The heart, arteries and veins, New York, McGaw-Hill, 1974

5. ACUTE CORONARY EVENTS IN GENERAL PRACTICE: DIAGNOSIS AND MISDIAGNOSIS OF MYOCARDIAL INFARCTION

E. van der Does*, J. Lubsen** and J. Pool**

SAMENVATTING

De Imminent Myocardial Infarction Rotterdam (I.M.I.R.)studie registreerde gevallen van patiënt-huisarts (H.A.) contact wegens klachten die mogelijk bij een coronair lijden passen. De aanwezige gevallen van acuut myocardinfarct (A.M.I.) werden gediagnostiseerd aan de hand van gemodificeerde W.H.O.-criteria en deze diagnose kon worden vergeleken met de voorlopige diagnose die op het moment van het contact werd gesteld door de huisarts zonder laboratoriumhulp.

Van de 1.343 patiënten die in de studie werden opgenomen hadden er, op basis van de gebruikte diagnostische criteria, 93 (7%) een "bewezen A.M.I." en 37 een "mogelijk A.M.I.". Van de 93 gevallen van "bewezen A.M.I." werden er 41 (44%) op het moment van het contact door de H.A. als zodanig herkend terwijl in 31 gevallen door de H.A. de diagnose "dreigend myocardinfarct" werd gesteld. Van de 1.213 patiënten die géén infarct hadden werden er 40 (3%) ten onrechte door de H.A. als "A.M.I." gediagnostiseerd. Bij patiënten die in werkelijkheid A.M.I. hadden was het niet herkennen ervan door de H.A. geassocieerd met de afwezigheid van afwijkingen bij het lichamelijk onderzoek; terwijl, evenzo, bij patiënten die in werkelijkheid géén A.M.I. hadden de aanwezigheid van afwijkingen bij het lichamelijk onderzoek was geassocieerd met een fout-positieve H.A.-diagnose "A.M.I.". De beslissing van de H.A. een patiënt te doen opnemen in een ziekenhuis was eveneens geassocieerd met de aanwezigheid van afwijkingen bij het lichamelijk onderzoek. De gemiddelde deelnemende H.A. had een praktijkgrootte van 2.200 mannen en vrouwen, die tenminste 20 resp. 25 jaar oud waren. Hij zag ongeveer 75 patienten per jaar voor klachten die de verdenking op aanwezig- of dreigend A.M.I. wekten.

SUMMARY

In the Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study, instances of patient-general practitioner (G.P.) contact for symptoms of potential coronary origin were registered. The instances of acute myocardial infarction (A.M.I.) present among these were

diagnosed on the basis of modified W.H.O.-criteria and this diagnisis could be compared to the initial diagnosis made by the G.P. at the moment of the contact without laboratory assistance.

Of the 1,343 patients who were included into the study, 93 (7%) had "definite A.M.I." and another 37 had "possible A.M.I." on the basis of the diagnostic criteria used. At the moment of the patient-G.P. contact, 41 (44%) of the 93 instances of "definite A.M.I." were recognized as such by the G.P. while in another 31 instances, the G.P. diagnosed "imminent myocardial infarction". Of the 1,213 patients free of A.M.I. at the time, 40 (3%) were incorrectly diagnosed by the G.P. as having "A.M.I.". In patients who in fact had A.M.I., the G.P.'s failure to diagnose it was related to the absence of physical signs; while, similarly, in patients who in fact did not have A.M.I., the presence of physical signs was related to a false-positive G.P.-diagnosis "A.M.I.". Also, the G.P.'s decision to hospitalize a patient was related to the presence of physical signs. The average participating G.P. had in his practice about 2,200 men and women of at least 20 resp. 25 years of age and he saw about 75 patients a year with symptoms raising the suspicion of present or imminent A.M.I.

## 5.1. INTRODUCTION

Little has been written about the diagnostic accuracy achieved by general practitioners (G.P.s). This question is however of considerable interest since in a health care system in which G.P.s have a central position, as is the case in The Netherlands, the G.P.'s initial diagnosis will to a large extent determine the first action which is taken in the management of a patient.

With respect to acute myocardial infarction (A.M.I.), overdiagnosis by G.P.s is a phenomenon known from coronary care experience[1]. Less information however is available about the accuracy attained in patients who are seen for symptoms possibly related to present or imminent A.M.I. but who are not admitted to a hospital. Such information was provided by the Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study, which had as its main objective the assessment of the acute risk of a coronary event, i.e. A.M.I. or sudden cardiac death, in a symptomatic patient still free of A.M.I. when seen by a G.P.[2] By virtue of its design, instances of symptomatic A.M.I. present at the time of the initial contact were included also. This

provided for the opportunity to relate the patient's symptoms and signs to the initial diagnosis made by the G.P. and to compare that diagnosis to a final one made on the basis of further diagnostic investigations which were carried out by a special clinic-based facility. Based on data from the I.M.I.R. study, the present report addresses the following questions:

1. How often does an average G.P. see a patient with "warning" symptoms, i.e. symptoms suspect for present or imminent A.M.I.?
2. What is the accuracy of the initial diagnosis "A.M.I." made by the G.P. without laboratory assistance and how frequently are patients initially diagnosed as having A.M.I. referred to a hospital?
3. How does the G.P.'s diagnosis relate to the patient's symptoms and signs?

An alternative probabilistic approach to the diagnosis of A.M.I. applicable in primary care is described in a companion paper[3]. Other results from the I.M.I.R. study have been described elsewhere[4,5].

## 5.2. STUDY DESIGN

The design of the I.M.I.R. study has been described in detail elsewhere[2]. However, some selected aspects are given here.

### 5.2.1. GENERAL PRACTITIONERS AND PATIENTS

In 14 general practices situated in and around the city of Rotterdam, The Netherlands, instances of patient-G.P. contact were registered whenever the patient had symptoms which met one or both of the following inclusion criteria:

- recent or recently increased chest pain,
- recent and unexplained dyspnea, palpitations, dizzyness, syncope, upper abdominal pains and/or mood changes.

In each criterion, "recent" refers to "the last four weeks" and "unexplained" to "without apparent extra-cardiac cause". Inclusion was restricted to men of at least 20 and women of at least 25 years of age. The participating G.P.s were selected on the basis of their special interest in cardiology and their willingness to cooperate.

### 5.2.2. PROCEDURES

After verifying compliance with the inclusion criteria, the G.P. filled out a detailed questionnaire on the history and symptoms of

the patient and performed a simple physical examination. Then, without any guidelines from the study-protocol, he made an initial diagnosis by opting for one of the following diagnostic categories:
- acute myocardial infarction (A.M.I.),
- imminent myocardial infarction (I.M.I.),
- other somatic disease (O.S.D.),
- psycho-social disorder (P.S.D.) or
- no provisional diagnosis (N.P.D.).

The last category was to be used only when the G.P. hesitated between O.S.D. and P.S.D. Finally, the G.P. indicated whether immediate hospitalization was necessary and gave, if applicable, the indications for hospital admission.

If no immediate hospitalization followed the patient-G.P. contact, the patient was seen as soon as possible by a technician who completed an additional questionnaire, recorded a standard 12-lead electrocardiogram (E.C.G.) and took a blood-sample for the assessment of the serum levels of the enzymes alpha-hydroxybutyric dehydrogenase ($\alpha$-H.B.D.H.), glutamic oxaloacetic transaminase (G.O.T.) and creatinine phosphokinase (C.P.K.). These investigations took place either at the patient's home or at a special clinic. Technicians were kept available on a round-the-clock basis. The E.C.G. and enzyme tests were repeated three days and one week later. In case of hospitalization, results of diagnostic studies were obtained from the hospital. During a 10-month follow-up, further data on the clinical course of the patient were collected. Standardized forms were used throughout for data collection. Inclusion into the study was open from October, 1972 through May, 1974. Data on practice-size reflect the state on January 1, 1974.

### 5.2.3. FINAL DIAGNOSIS

To establish, a posteriori, the final diagnosis at inclusion, a scoring system was developed which is based on the diagnostic criteria for A.M.I. adopted by the W.H.O. for A.M.I. community registers[6]. An E.C.G. "typical" for A.M.I. was given two points and a recording considered "suspect" one point, otherwise, zero was assigned. Symptoms and the results of enzyme tests were scored in a similar way each with either two, one or zero points. "Definite A.M.I." was diagnosed when the total score was four or more points. If the total score was two or three points, "possible A.M.I." was diagnosed,

while otherwise, "no A.M.I." was inferred to have been present. Details of the criteria used for scoring are given as Appendix.

### 5.2.4. ANALYSIS

Conventional statistical methods were used. Associations between patient-characteristics and the G.P.'s diagnosis were assessed as follows. First, all patients studied were divided into two sub-groups, one sub-group consisting of the patients diagnosed by the G.P. as having either A.M.I. or I.M.I. and the other sub-group consisting of the patients diagnosed otherwise. Then, for the two sub-groups respectively, the frequency of patients having a certain characteristic was determined. If the characteristic was dichotomous, a modification of Fisher's "exact" test[7] was used to assess the statistical significance of the difference observed. Otherwise, a conventional chi-square test[8] was used; "$p \leqslant 0.05$" was considered "significant". Finally, a similar analysis was performed only for the patients diagnosed as having A.M.I. or I.M.I.

## 5.3. RESULTS

### 5.3.1. NUMBER AND RATE OF INCLUSIONS

During the 20-month inclusion-period, 1,343 patients were registered. Of the 14 general practices which participated, four did only temporarily so. The remaining 10 covered a total of 22,086 people, excluding males younger than 20 and females younger than 25 years of age; from these practices, 1,255 patients were registered. Thus, the registration-rate was 34 patients per 1,000 people per year in the age-categories considered.

### 5.3.2. DIAGNOSIS AND HOSPITALIZATIONS

A comparison between the inclusion diagnosis of the G.P. and the final diagnosis is presented in table 5.1. Of the 93 patients finally diagnosed as having definite A.M.I., 41 were recognized by the G.P. to have A.M.I.; another 31 were diagnosed as having I.M.I. and the remaining 21 as having either O.S.D., P.S.D. or N.P.D. Of the 1,213 patients finally diagnosed as not having A.M.I., 40 were diagnosed by the G.P. as having A.M.I.

Of the 87 patients diagnosed by the G.P. as having A.M.I., 49 (56%) were referred to a hospital immediately.

Of these 49, 30 (61%) in fact had A.M.I. as the final diagnosis. In the remaining 38 instances of a G.P.-diagnosis of A.M.I., the patient was initially treated at home. Of these 38, 11 (29%) actually had A.M.I. as the final diagnosis and 7 were later referred to a hospital.

### 5.3.3. DIAGNOSIS AND PATIENT-CHARACTERISTICS

Sex and age data are presented in table 5.2. There were no significant differences in sex-composition between the sub-groups based on the G.P.'s diagnosis. Patients diagnosed by the G.P. as having either A.M.I. or I.M.I. were significantly older than patients diagnosed otherwise, the difference in median age being 14 years for men and 16 years for women. Men diagnosed as having A.M.I. were also older than men diagnosed as having I.M.I., the median age difference being 7 years. In women, the median age difference between these diagnostic categories was not significant.

Data on the symptoms at inclusion are presented in table 5.3. Chest pain was a predominant symptom. Only 5% of the patients diagnosed as having either A.M.I. or I.M.I. and only 11% of the patients diagnosed otherwise did not have this symptom. As the primary symptom, it was particularly frequent in patients with either A.M.I. or I.M.I. as the G.P.'s diagnosis but, within the sub-group of patients so diagnosed, no significant differences in chest pain frequencies were present. Dyspnea was a common symptom too, especially as a secondary one. If it was the primary symptom, it was associated in particular with the G.P.'s diagnosis "A.M.I.".

Data on the quality of chest pain are presented in table 5.4. A "stabbing" pain was twice as frequent in patients having either O.S.D, P.S.D. or N.P.D. as the G.P.'s diagnosis than in patients diagnosed as either A.M.I. or I.M.I. In both sub-groups, "pressure" was the most frequently recorded quality but it was significantly more frequent in the sub-group of patients diagnosed as having either A.M.I. or I.M.I. Within this last sub-group however, the quality of the pain did not seem to discriminate between A.M.I. and I.M.I. as the diagnosis. A "sharp increase" or a "sudden onset" of the pain and a "duration longer than 30 minutes" were more frequently recorded in patients diagnosed as having either A.M.I. or I.M.I. but, among patients so diagnosed, only "duration of pain longer than 30 minutes" was associated with A.M.I. as the G.P.'s diagnosis.

Data on selected findings at the physical examination are presented in table 5.5. In patients diagnosed by the G.P. as having either O.S.D., P.S.D. or N.P.D., abnormalities were infrequent. The following findings were significantly more frequent if A.M.I. or I.M.I. was the diagnosis: râles, signs of backward failure, cold clammy skin, systolic blood pressure ≤100 mmHg, irregular pulse and >3 premature beats. Within the same sub-group of patients, all these findings were also more frequent if A.M.I. was the G.P.'s diagnosis; the difference for "irregular pulse" was however not significant. Furthermore, again within the same sub-group of patients, both bradycardia (heart rate ≤60 beats/min.) and tachycardia (heart rate >100 beats/min.) were particularly associated with A.M.I. as the G.P.'s diagnosis.

## 5.4. DISCUSSION

The I.M.I.R. study had as its object of inquiry the clinical course of patients with "warning symptoms", i.e. symptoms raising the suspicion of present or imminent A.M.I. However, the results also gave insight into several issues related to the diagnosis and management in general practice of patients who sustain an A.M.I.

### 5.4.1. DIAGNOSTIC ACCURACY OF THE G.P.

Of the 93 cases of definite A.M.I. present at the moment of inclusion, 44% (41/93) were recognized at that moment by the G.P. On the other hand, 3% (40/1,213) cases of A.M.I. were diagnosed among patients who in fact did not have A.M.I. while having the I.M.I.R. complaints (table 5.1.). These findings point to an unexpectedly low diagnostic accuracy so that the question arises what the health consequences are in patients whose actual condition was, at least initially, incorrectly diagnosed. For the "missed" cases of A.M.I. which were diagnosed as having I.M.I., and this was the case in 33% (31/93, table 5.1.) of all cases of A.M.I. present, these might not be too serious as long as the policy is, as it was in I.M.I.R., to treat fresh instances of I.M.I. as A.M.I. if there was no indication for hospitalization until the presence of A.M.I. is excluded on the basis of further diagnostic investigations. But in 23% (9 + 5 + 7 out of 93, table 5.1.) of all instances of A.M.I. even the cardiac origin of the symptoms was not recognized initially. The I.M.I.R.-G.P. was subsequently in a position to reconsider the management of these cases since the results of the E.C.G.s and enzyme tests were

immediately reported to him in case of abnormal findings. In the absence of such diagnostic service however, it is possible that some of the initially "missed" cases of A.M.I. would have remained unrecognized, with unknown consequences for the health of the patient. With respect to the 3% false-positive diagnoses of A.M.I. made by the G.P., it is worthy of note that this apparently small fraction represents nevertheless 46% (40 out of 87, table 5.1.) of all patients diagnosed by the G.P. as having A.M.I. If such patients are hospitalized only because the presence of A.M.I. is suspected, an unnecessary burden could result for both patients and hospitals. In view of these considerations, we are of the opinion that the G.P. should have quick access to diagnostic facilities, enabling him not only to detect instances of A.M.I. and treat them properly but also to exclude the presence of A.M.I. if its presence is suspected, thereby reassuring himself and the patient.

### 5.4.2. SYMPTOMS, SIGNS AND (MIS)DIAGNOSIS

In the face of the low diagnostic accuracy observed, the relationship between symptoms and signs and the diagnosis of the G.P. is of interest since one possible explanation for the low accuracy is that the G.P. is basing his diagnosis to an unjustifiable extent on the presence or absence of particular symptoms and/or signs which are thought to be specific for A.M.I. With this hypothesis in mind, it was attempted to follow in the analysis what seemed to be a logical train of thought from the perspective of a G.P. For, in making a diagnosis, the G.P. will presumably first consider the question of whether the symptoms suggest a coronary origin or not, i.e. whether either A.M.I. or I.M.I. is present as opposed to either O.S.D., P.S.D. or N.P.D.; and only then decide whether the diagnosis should be A.M.I. or I.M.I. when a coronary origin seems likely.

With regards to symptoms, the associations present do not seem to support the above hypothesis. For instance, 5% of all patients diagnosed as having either A.M.I. or I.M.I. did not have chest pain at all, for A.M.I. alone, this fraction was 8% (table 5.3.). Therefore, the presence of chest pain was apparently not a prerequisite for the presence of A.M.I. or I.M.I. in the G.P.'s opinion. Also, a "stabbing" quality of the pain, generally assumed as suggesting its non-coronary origin[9], was not uniquely absent in patients diagnosed

as A.M.I. (table 5.4.), which again supports the notion that the G.P. was not unduly basing his diagnosis on "textbook" symptomatology.

With regards to the frequency of abnormal signs, considerable differences were present between the sub-groups based on the G.P.'s diagnosis (table 5.5.). For instance, râles and a cold clammy skin were present in 17% and in 23% respectively of the patients diagnosed as having A.M.I., as opposed to 1% and 1% respectively in patients who had either O.S.D., P.S.D. or N.P.D. as the G.P.'s diagnosis. These findings seemed to support the notion that the G.P. was (over)emphasizing signs in making a diagnosis and the question arose whether signs could possibly "mislead" the G.P. to make a wrong diagnosis. If this were the case, the absence of abnormal signs would, in patients finally diagnosed as having A.M.I., be expected to be more frequent if "no A.M.I." was the G.P.'s diagnosis. On the other hand, in patients finally diagnosed as not having A.M.I., the presence of abnormal signs would be expected to be more frequent if A.M.I. was the G.P.'s diagnosis. As is apparent from table 5.6., significant differences in the hypothesized directions were indeed present.

In conclusion, it seems apparent from the data that the G.P. was attaching much, and possibly too much, weight to abnormal signs in making a diagnosis of A.M.I. Although this last finding could readily be explained by the fact that the presence of abnormal signs will in general arouse alarm, it is to be emphasized that an appreciation of this finding by the G.P. would in itself not necessarily improve his diagnostic accuracy. Rather, it seems that the variability of presentation of A.M.I. in general practice is so great that the "senses and a few simple tools" on which the average G.P. has to rely in making his diagnosis are insufficient regardless of the skill and the experience with which they are used.

### 5.4.3. MANAGEMENT OF PATIENTS DIAGNOSED BY THE G.P. AS HAVING A.M.I.

Whether all patients in whom a diagnosis of A.M.I. is made should be treated in a hospital remains a matter of debate[10,11]. In the present study, not every instance of A.M.I. diagnosed by the G.P. was sent immediately to a hospital since he treated slightly less than half, 44%, of the patients diagnosed as A.M.I. at least initially at

home. Actual A.M.I. was more often present in patients selected for hospital care than in patients initially treated at home (61% and 29% respectively, $p \leq 0.01$, two-sided modified Fisher-exact test[7]), as was the occurrence of cardiac death (18% and 8% respectively, $p \geq 0.05$). It seemed likely therefore that the I.M.I.R.-G.P. tended to refer the clinically sicker patient to a hospital but treated the uncomplicated cases of A.M.I. at home. This notion found support in the fact that in patients referred to hospital, abnormal findings during the physical examination were significantly more frequent. The I.M.I.R. study was not designed to inquire into the relative merits of hospital Vv. home care and instructions as to when to hospitalize were not given in the study protocol. Nevertheless, the data presented here give some insight into the management of patients in whom A.M.I. was diagnosed by a particular group of G.P.s.

### 5.4.4. THE BURDEN CREATED BY PATIENTS WITH "WARNING SYMPTOMS"

The 10 G.P.s who participated during the full inclusion-period of 20 months registered 1,255 patients or about 75 patients per G.P. per year. This provided an estimate of the burden created by patients with the symptoms at issue in a practice consisting of about 2,200 people in the age-categories considered, i.e. men $\geq 20$ and women $\geq 25$ years of age. Under the protocol, no patient could be included twice and nor the number of recurrent patient-G.P. contacts nor their reasons are known. Therefore, the above rate is an underestimate of the real burden put on the G.P.

"Definite A.M.I." was present in only a small minority of the patients seen with "warning symptoms". In merely 93 or about 7% of the 1,343 registered contacts for such symptoms did the patient in fact have A.M.I. on the basis of the criteria used. This finding seems to underline the difficulty of diagnosing A.M.I. in general practice and, again, the need for some form of diagnostic service to the G.P.

### 5.4.5. EXTRAPOLATION OF RESULTS

Whether the present results may be extrapolated to other practices is a complex question since it involves issues of methodology, of protocol compliance and of the representativeness of the participating G.P.s. With respect to methods, the availability of diagnostic service to the G.P. may have influenced the results. Protocol compliance was found to be satisfactory if there was indeed no

apparent extra-cardiac cause for the patient's symptoms and refusal by the patient to cooperate was rare[12]. Therefore, we are of the opinion that the present results are representative for the participating G.P.s. But these G.P.s. were selected on the basis of their interests and willingness to participate and they can therefore not be considered as being representative for Dutch G.P.s in general. In conclusion, it is underlined that extrapolations to other practices, even within The Netherlands, which are based on the present results have to be made with caution.

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The study was supported by the Netherlands Heart Foundation. J. Lubsen was supported in part by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.)

## APPENDIX: SCORING CRITERIA FOR E.C.G.s, ENZYMES AND SYMPTOMS

### ELECTROCARDIOGRAMS

2 points ("typical"): Minnesota Code[13] (M.C.) 1-1 or 1-2 (major Q-wave abnormalities), M.C. 7-1 (complete left bundle branch block), injury current as described by the World Health Organization.[14]

1 point ("suspect"): M.C. 1-3 (minor Q-wave abnormalities), M.C. 5-1 or 5-2 (T-wave inversions), serial E.C.G. changes suspect for A.M.I.

### ENZYMES

2 points ("typical"): $\alpha$-H.B.D.H. $> 140$ and G.O.T. $> 30$ or C.P.K. $> 50$; G.O.T. $> 30$ and C.P.K. $> 50$; $\alpha$-H.B.D.H. $> 140$ on third day and G.O.T. $> 30$ or C.P.K. $> 50$ on first day.

1 point ("suspect"): G.O.T. $> 30$ or C.P.K. $> 50$ without elevated $\alpha$-H.B.D.H.; serial changes suspect for A.M.I. (cut-off values as used in the Academic Hospital Rotterdam-Dijkzigt, Rotterdam, The Netherlands).

### SYMPTOMS

2 points ("typical"): chest pain which had started or had increased acutely, had a retro-sternal localization, did not relate to exercise, lasted longer than 30 minutes and which was not described as "stabbing".

1 point ("suspect"): chest pain missing any one or two of the features mentioned for typical.

"Definite A.M.I." was diagnosed when the total score was four or more points, "possible A.M.I." was diagnosed when the total score was two or three points. Otherwise, A.M.I. was considered to have been absent.

REFERENCES

1. Armstrong, A., Duncan, B., Oliver, M.F., Julian, D.G., Donald, K.W., Fulton, M., Lutz, W. and Morrison, S.L., Natural history of acute coronary heart attacks, A common study. B. Heart J. 34: 67-80, 1972

2. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G. and Arntzenius, A.C., Acute coronary events in general practice, Objectives and design of the I.M.I.R. study. Hart Bull. 7: 91-98, 1976. This thesis, chapter 2

3. Lubsen, J., Van der Does, E., Pool, J., Acute coronary events in general practice, A diagnostic probability function for myocardial infarction. Submitted for publication as companion paper. This thesis, chapter 6

4. Lubsen, J., Van der Does, E., Pool, J., Acute coronary events in general practice, Incidence of acute myocardial infarction and sudden death. Hart Bull. 7: 107-113, 1976. This thesis, chapter 7

5. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G., Acute coronary events in general practice, Predictability of future events in patients with new or worsening symptoms. Submitted for publication. This thesis, chapter 4

6. World Health Organization, Regional Office for Europe, Myocardial infarction community registers. Public health in Europe 5, Copenhagen, W.H.O., 1976

7. Miettinen, O.S., Comment on Connover, J., Some reasons for not-using the Yates continuity correction on 2 x 2 tables. J.A.S.A. 69: 380-383, 1974

8. Armitage, P., Statistical methods in medical research, Oxford, Blackwell, 1971

9. Hurst, J.W., in Hurst J.W., Logue, R.B., Schlant, R.C., Wenger, N.K., (eds.) The heart, arteries and veins, New York, McGraw-Hill, 1974

10. Colling, A., Delipiani, A.W., Donaldson, R.W., MacCormack, P., Teesside coronary survey; An epidemiological study of acute attacks of myocardial infarction. B.M.J. 2: 1169-1172, 1976

11. Burch, G.E., Of home cardiac care. Am. Heart J. 93: 125-126, 1977

12. Van der Does, E., Lubsen, J., Pool, J., Van Strik, R., Van der Sijde, J. and Stroink, J., Acute coronary events in general practice. Early warning symptoms of acute myocardial infarction and sudden death. Hart Bull. 7: 99-106, 1976. This thesis, chapter 3

13. Rose, G.A., Blackburn, H., Cardiovascular survey methods. Geneva, World Health Organization, 1968

14. World Health Organization, Regional Office for Europe; Report of the Fifth Working group on ischaemic heart disease registers, Copenhagen, W.H.O., 1971

6. ACUTE CORONARY EVENTS IN GENERAL PRACTICE: A DIAGNOSTIC PROBABILITY FUNCTION FOR MYOCARDIAL INFARCTION

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SAMENVATTING

De uitkomsten van de Imminent Myocardial Infarction Rotterdam (I.M.I.R.)studie hebben aangetoond dat het op dit moment in de huisartsgeneeskunde moeilijk is de aan- of afwezigheid van een acuut myocardinfarct (A.M.I.) met zekerheid vast te stellen. Echter, er lijkt geen methode beschikbaar te zijn die het mogelijk maakt in een bepaald geval de diagnostische onzekerheid te quantificeren.

In deze bijdrage wordt een statistische aanpak beschreven van het diagnostiseren van A.M.I. zonder de hulp van electrocardiografie en serumenzymebepalingen. Op grond van de gegevens van 92 patiënten met een bewezen A.M.I. en van 1.211 patiënten zonder A.M.I., allen afkomstig uit de patiëntenpopulatie die door de huisarts wordt gezien met klachten die bij een acuut coronair lijden kunnen passen, werd een methode ontwikkeld voor het bepalen van de waarschijnlijkheid dat A.M.I. aanwezig is, gegeven een aantal door de huisarts makkelijk te observeren kenmerken van de patiënt. Gegevens over de leeftijd, het geslacht, pijn op de borst, het tijdstip van begin ervan, benevens de aard en de duur van de aanval, de aanwezigheid van een koude klamme huid, de bloeddruk, de hartfrequentie en de aanwezigheid van premature slagen worden geïntegreerd in één score met behulp van gewichtsfactoren die bepaald werden met gebruikmaking van Lineaire Discriminant Functie (L.D.F.) analyse. Vervolgens wordt de zo verkregen L.D.F.-score door toepassing van de regel van Bayes omgezet in een diagnostische waarschijnlijkheid.

Om de noodzaak tot rekenwerk bij de toepassing aan het bed overbodig te maken werd een op een rekenlineaal gelijkend instrument ontwikkeld.

SUMMARY

Results from the Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study have shown that it is at present difficult in general practice to diagnose with confidence the presence of acute myocardial infarction (A.M.I.) or its absence. However, no method seems available to quantify the diagnostic uncertainty in a particular case.

The present paper describes a statistical approach to diagnosing A.M.I. without laboratory assistance. On the basis of a series of 92 definite cases of A.M.I. and of 1,211 non-cases drawn from patients seen by a general practitioner (G.P.) for coronary-type symptoms, a procedure was developed for obtaining the probability that A.M.I. is present given a set of patient-characteristics which are readily observable by a G.P. Information about age, sex, chest pain and its onset, duration, character and severity, the presence of a cold clammy skin, the blood pressure, the heart rate and the presence of premature beats is integrated into a single score by the use of a set of weights, which were derived by Linear Discriminant Function (L.D.F.) analysis. Next, the resulting L.D.F.-score is converted into a diagnostic probability by an application of Bayes' rule.

To eliminate the need for arithmetic in bedside application, a slide-rule-type device was developed.

## 6.1. INTRODUCTION

As was discussed in a companion paper[1], results from the Imminent Myocardial Infarction Rotterdam (I.M.I.R.)study have indicated that at present it is difficult in general practice to diagnose with confidence the presence of acute myocardial infarction (A.M.I.) or its absence. Although the general practitioner (G.P.) will in general be aware of the existence of diagnostic uncertainties, no method seems currently available to him which allows the formal quantification of the degree of uncertainty in a particular case.

It was the objective of the present analysis to develop for the G.P. a method to quantify the probability that A.M.I. is present on the basis of data which are easily obtained by him and require no laboratory assistance. Recently, methods for deriving multivariate diagnostic or prognostic functions have become available. For instance, one such method was developed in the context of predicting the future occurrence of clinical coronary heart disease on the basis of information about risk factors[2,3,4]. In that particular application, information about cholesterol level, blood pressure, smoking habits and other characteristics is summarized into a single score by the use of a weighing procedure. On the basis of the score value, the probability is then obtained that a given individual will develop coronary heart disease. The present paper describes a similar approach for obtaining the probability that A.M.I. is present on the basis of

information about the patient's age, sex, symptoms and signs. The database used for its development originated from the I.M.I.R. study[5].

## 6.2. METHODS

A detailed description of the design and methodology of the I.M.I.R.-study has appeared elsewhere[5] and selected aspects are described in a companion paper[1].

### 6.2.1. ANALYSIS

Linear discriminant function (L.D.F.) analysis was used to derive a weighing procedure, which consisted of multiplying the weights with the values of the associated information variables and adding the results. It yielded a composite score which separated patients with "definite A.M.I." from patients with "no A.M.I.". Patients with "possible A.M.I." were excluded from this part of the analysis. In the L.D.F., continuous variables were inserted as such, attributes were represented by indicator variables coded as either zero or one. Based on transformed score means for cases of A.M.I. and for non-cases respectively and on its pooled variance, a function expressing the probability that A.M.I. is present given a value of the L.D.F.-score was obtained by an application of Bayes' rule and normal density theory. Details are given as Appendix. The performance of the resulting probability function was examined by dividing the entire patient group into strata of estimated probability and determining the actual proportion of cases of "definite A.M.I." present within each stratum. An alternative diagnostic procedure based on L.D.F.-analysis consisted of allocating the diagnosis A.M.I. to a patient when the L.D.F.-score which is obtained exceeded a chosen cut-off value. The performance of such a procedure was investigated by determining its sensitivity and specificity for different levels of the cut-off value.

## 6.3. RESULTS

### 6.3.1. FINAL DIAGNOSIS AT INCLUSION

In the present analysis, 1,340 patients were included. Of these, 92 (6.9%) were diagnosed as having "definite A.M.I." and another 37 (2.8%) as having "possible A.M.I." on the basis of the diagnostic criteria used.

Results of the scoring of symptoms[1], E.C.G.s and enzyme tests for the 92 cases of "definite A.M.I.", i.e. those patients for whom a total score of four or more points was obtained, are presented in table 6.1. In 49 of the 92 cases, both E.C.G.s and enzyme tests were "typical" for A.M.I. In these cases, the scoring of symptoms was therefore of no consequence for the final diagnosis. In fact, six cases with "typical" E.C.G.s and enzyme tests had the symptoms classified as "not suspect". In the remaining 43 cases of A.M.I. however, either E.C.G.s or enzymes were not classified as "typical". Consequently, the points scored for symptoms were required to establish the final diagnosis in these cases.

## 6.3.2. MULTIVARIATE ANALYSIS

In table 6.2., the results of L.D.F.-analysis of the 92 cases of "definite A.M.I." and the 1,211 non-cases are presented. For these two groups of patients respectively, the uni-variate distribution of the variables retained in the final L.D.F. are given also. In addition to age and sex, four variables describing symptoms and five describing signs are present. All weights differ from zero at the 5% level of statistical significance in a two-sided t-test. Two variables, "stabbing chest pain" and "pulse pressure", i.e. systolic minus diastolic blood pressure, had a negative weight on the coding used, which indicates that a stabbing pain and a higher pulse pressure are more likely in the absence of A.M.I. than in its presence. All other variables had a positive weight. In the case of a variable representing an attribute, A.M.I. is consequently more likely to be present when the attribute is present. The same conclusion holds with respect to relatively high values for the variables representing the continuous characteristics age and heart rate. By the application of the methods outlined in the Appendix, the following probability function was obtained:

$$\Pr.(\text{A.M.I.} \mid \text{L.D.F.-score}) = \frac{1}{1+\exp.\left[-4.2\ {}^{e}\log(\text{L.D.F.-score} - 0.9) + 9.8\right]}$$

where $\Pr.(\text{A.M.I.} \mid \text{L.D.F.-score})$ represents the probability of the presence of A.M.I. given the value of the L.D.F.-score.

The observed frequencies of cases of A.M.I. present within strata of calculated diagnostic probability are shown in table 6.3. Except within the stratum $\Pr.(\text{A.M.I.} \mid \text{L.D.F.-score}) > 80\%$, which contained only four patients, the proportions of cases of A.M.I.

observed within each stratum were well within their limits.

The sensitivity and specificity of a diagnostic procedure which allocates the diagnosis "A.M.I." if the L.D.F.-score exceeds a chosen value are plotted in fig. 6.1. for different choices of the cut-off value. For instance, diagnosing A.M.I. when the L.D.F.-score exceeded 9.0 had a sensitivity of 42% and a specificity of 96%.

## 6.4. DISCUSSION

The present study describes a particular probabilistic approach to the diagnosis of A.M.I. in a patient with symptoms of potential coronary origin. It is based on information which is readily obtainable by a G.P. and describes symptoms and signs of generally accepted relevance within the context of diagnosing A.M.I. on clinical grounds. Also, the criteria used to establish the final diagnosis are believed by us to resemble closely current clinical practice. Nevertheless, the application of statistical methods to such a diagnostic problem raises complex theoretical and practical issues, one being its general applicability.

First of all, it must be emphasized that application is proper only if the patient is seen by a G.P. either at home or in the office for symptoms which would have led to inclusion into the I.M.I.R. study. Although the inclusion criteria used in that study encompass, apart from new or worsening chest pain irrespective of its suspected cause, a range of other symptoms without apparent extra-cardiac cause, it was found that the majority (91%) of the patients included had in fact chest pain either as primary or secondary symptom. Furthermore, the G.P.s included only patients in whom no obvious extra-cardiac explanation for the symptoms was present[6]. Consequently, the type of patient to which the use of the present results is restricted may conveniently be described as "a patient seen by a G.P. for new or worsening chest pain without obvious extra-cardiac cause".

A diagnostic allocation procedure based on the present L.D.F. would not improve the diagnostic performance of the I.M.I.R.-G.P.s. In diagnosing A.M.I., they reached a sensitivity of 44% and a specificity of 97%[1]; diagnosing A.M.I. if the L.D.F.-score exceeds 9.0 would yield similar, but not better, sensitivity and specificity (fig. 6.1.). Nevertheless, there seem to be advantages associated with the use of the present diagnostic probability function.

The physician is forced to ask for at least those symptoms and to investigate those signs which have "proven" diagnostic relevance. Thus, the collection of redundant information is avoided. The gathered information is integrated by the use of a set of weights which derive from studying a relevant patient population and results in an objective probability statement rather than a subjective diagnosis based on the personal "assimilated experience"[7] of the physician. Also, the function does not provide assurances in a situation which precludes diagnostic certainty and it forces the physician to take the uncertainty into account. Finally, it could be argued that the concern is primarily with taking the proper actions in the management of the patient rather than with making a diagnosis. Possibly, an approach could be envisioned whereby such a diagnostic probability function would be used as a basis for determining which action is the most desirable one.

Acceptance of these methods by the medical profession will depend on a variety of factors. First, the problem for which a solution is offered should be recognized as relevant to current medical practice; second, the solution itself should have clear advantages over more traditional approaches and, third, the method proposed should be easy to use and understand. We are of the opinion that these requirements are met in large part by the present approach. The relevance of appropiate management of A.M.I. is difficult to deny in the face of the high community mortality and the conclusion of the I.M.I.R. study that the diagnostic performance of the G.P. with respect to this condition is unsatisfactory[1]. In the choice of information variables, the present approach is conventional. And finally, to provide for ease of use, a slide-rule-type device was developed[8] which eliminates the need of arithmetic in obtaining the diagnostic probability.

The present diagnostic function is the result of a particular study. The participating G.P.s were selected because of their special interest in cardiology and their compliance with the protocol was good[6]. Therefore, we are of the opinion, that the patient population studied is, as far as the I.M.I.R.-G.P.s are concerned, representative of patients seen in general practice with symptoms which raise in the G.P.'s mind at least the suspicion of A.M.I. As a consequence, the issue of the representativeness of the cases and non-cases, forming but subsets of the entire patient group, is a moot one,

provided that the diagnostic methods are accepted, Whether accurate probabilities will be obtained in different patients seen by different G.P.s is, even when the same criteria for establishing the final diagnosis are applied, still a matter of conjecture. An empirical evaluation in practice is currently under way and will involve G.P.s in various parts of The Netherlands. The results could, if necessary, lead to a readjustment of the way in which the L.D.F.-score is converted into a diagnostic probability. But no reassessment of the magnitude of the weights will be possible on the basis of the data which are collected.

We consider the present function as a first step in the application of exact methods to the problem of diagnosing A.M.I. in general practice. In the future, we anticipate the collection of a new database which will allow for further development and possible improvement in performance of the present function.

ACKNOWLEDGEMENTS

This analysis would not have been completed without the stimulating advice and continuing help and interest of O.S. Miettinen, M.D., Ph.D., Professor of Epidemiology and Biostatistics at the Harvard School of Public Health, Boston, U.S.A. Invaluable assistance in computing was given by R.K. Neff, director of the Health Sciences Computing Facility at the Harvard School of Public Health, and by Susan Gorter-Mayer of the Department of clinical information processing at the Thoraxcenter, Rotterdam, The Netherlands.

The I.M.I.R. study was supported by the Netherlands Heart Foundation. Dr. Lubsen was supported in part by the Netherlands Organization for the Advancement of Pure Science (Z.W.O.)

## APPENDIX: STATISTICAL METHODS

### COMPOSITE SCORE

Let $y = b_1.x_1 + b_2.x_2 + \ldots b_n.x_n$, where y represents the composite score, $b_1 \ldots b_n$ a set of n weights and $x_1 \ldots x_n$ a set of n information variables. The weights $b_1 \ldots b_n$ were estimated by linear discriminant function (L.D.F.) analysis[2], y is consequently referred to as "L.D.F.-score". The C.O.P.S./4 program[9] was used to compute the estimates and their standard errors.

### TRANSFORMATION OF L.D.F.-SCORE

Denote by $P_n$ the n-th percentile of the distribution of the L.D.F.-score for the entire group of patients. Let $z = {}^e\log(y + c)$. Since z increases for increasing y if $(y + c) > 0$, ${}^e\log(P_n + c)$ is the n-th percentile of the distribution of z. Denote the n-th percentile of z by $P'_n$. Then, we have $P'_n = {}^e\log(P_n + c)$.

A value of c was sought which ensures that $P'_{50} - P'_{20} = P'_{80} - P'_{50}$. This condition requires that:

$${}^e\log(P_{50} + c) - {}^e\log(P_{20} + c) = {}^e\log(P_{80} + c) - {}^e\log(P_{50} + c), \text{ or}$$

$$(P_{50} + c)/(P_{20} + c) = (P_{80} + c)/(P_{50} + c) \qquad (1)$$

From the data, $P_{20}$, $P_{50}$ and $P_{80}$ were estimated at 4.24, 5.40 and 6.97 respectively. Using these values, the solution of equation (1) yields c = -0.94. The cumulative distributions of ${}^e\log(y - 0.94)$ for cases of "definite A.M.I." and for "no A.M.I." respectively are shown in figure 6.2.

### DIAGNOSTIC PROBABILITY OF A.M.I.

The conditional probability of A.M.I. given a value z of the transformed score may, by an application of Bayes' rule[10], be written as:

$$Pr(A.M.I.|z) = \frac{p.Pr(z|A.M.I.)}{p.Pr(z|A.M.I.) + (1 - p).Pr(z|\overline{A.M.I.})}$$

In this equation, $Pr(A.M.I.|z)$ represents the conditional probability of A.M.I. given z, p the unconditional probability of A.M.I., and $Pr(z|A.M.I.)$ and $Pr(z|\overline{A.M.I.})$ the probability densities of the transformed score at z for cases of "definite A.M.I." and of "no A.M.I." respectively. Rearranging the above expression for $Pr(A.M.I.|z)$ yields:

$$Pr(A.M.I.|z) = \frac{1}{1 + \frac{1-p}{p}.R} \qquad (2); \text{ where } R = \frac{Pr(z|\overline{A.M.I.})}{Pr(z|A.M.I.)}$$

If it is assumed that z has a normal distribution with the same variance for cases of A.M.I. and for non-cases, the following expression is obtained for R, using an obvious notation:

$$R = \frac{\exp\left[-\frac{1}{2}\left(\frac{z - \bar{z}_{\overline{A.M.I.}}}{s}\right)^2\right]}{\exp\left[-\frac{1}{2}\left(\frac{z - \bar{z}_{A.M.I.}}{s}\right)^2\right]} \qquad (3)$$

The transformed score means $\bar{z}_{A.M.I.}$ and $\bar{z}_{\overline{A.M.I.}}$ were estimated at 2.017 and 1.456 respectively and their variances at 0.132 and 0.135. For $s^2$, the variance of z common to cases and non-cases of A.M.I., was taken the pooled variance, i.e. $\frac{1211.(0.135) + 92.(0.132)}{1211 + 92}$. Inserting these values of $\bar{z}_{A.M.I.}$, $\bar{z}_{\overline{A.M.I.}}$ and $s^2$ in equation (3) yields, after simplification: $R = \exp(-4.162z + 7.227)$. For p was taken the proportion of cases of "definite A.M.I." present in the entire patient population, i.e. 92/1340. Consequently, $(1-p)/p = 13.57$ or $\exp(2.608)$. Inserting the above expressions for R and for $(1-p)/p$ in equation (2) and writing z as ${}^{e}\log(L.D.F.\text{-score} - 0.94)$ yields the following conditional probability function for the presence of A.M.I. given a value of the L.D.F.-score:

$$Pr(A.M.I.|L.D.F.\text{-score}) = \frac{1}{1 + \exp\left[-4.162\,{}^{e}\log(L.D.F.\text{-score} - 0.94) + 9.835\right]}$$

COMMENTS

In the present study, the weights which are applied to the information variables in obtaining the score were derived with the help of L.D.F.-analysis. This is theoretically optimal only under the assumption that the variance-covariance matrices of the two groups considered are equal. Such a condition cannot be met even in principle when, as is the case here, indicator variables are used. Experience has shown however that L.D.F.-analysis yields satisfactory results even when the assumption mentioned above is not met.[11]

To ensure the justifiability of the assumptions which underlie the conversion of the L.D.F.-score into a diagnostic probability by an application of Bayes' rule and the normal density function, an empirical normalizing transformation was used. The fit of the function to the data is satisfactory, as is shown by the reasonable agreement between predicted and observed frequencies of "definite A.M.I." within strata of estimated probability (table 6.3.).

The present function was to take into account only information readily obtainable by the G.P. Symptoms therefore play an important role in it. But scoring of the same symptoms was also used in making the final diagnosis. In fact, in 43 of the 92 instances of "definite A.M.I." points scored for symptoms were needed to establish that diagnosis (table 6.1.). This may explain in part the reason for the appearance in the L.D.F. of attributes which are also mentioned in the scoring criteria for symptoms (see appendix to the companion paper[1]). This anomaly could have been avoided only if the final diagnosis had been made without taking symptoms into account. This however was considered unrealistic since it would not resemble current clinical practice. Furthermore, the anomaly mentioned is irrelevant provided one accepts the diagnostic criteria and the function merely as a means of estimating the probability that these particular criteria will be met in the patient under consideration. In this context, it is noted that the diagnostic criteria used are, although operationally different, similar to those employed in A.M.I. registration projects carried out under the auspices of the World Health Organization.[12]

REFERENCES

1. Van der Does, E., Lubsen, J., Pool, J., Acute coronary events in general practice. Diagnosis and misdiagnosis of myocardial infarction. Submitted for publication as companion paper. This thesis chapter 5

2. Cornfield, J., Discriminant functions. Review Int. Stat. Inst. 35 : 142-153, 1967

3. Cornfield, J., Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure : A discriminant function analysis. Fed. Proc. 21 : 58-61, 1962

4. Truett, J., Cornfield, J., Kannel, W., A multivariate analysis of the risk of coronary heart disease in Framingham. J. Chron. Dis. 20: 511-524, 1967

5. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G., Arntzenius, A. C., Acute coronary events in general practice. Objectives and design of the I.M.I.R. study. Hart Bull. 7 : 91-98, 1976. This thesis chapter 2

6. Van der Does, E., Lubsen, J., Pool, J., Van Strik, R., Van der Sijde, J., Stroink, J., Acute coronary events in general practice. Early warning symptoms of acute myocardial infarction and sudden death. Hart Bull. 7 : 99-106, 1976. This thesis chapter 3

7. Wintrobe, M.M., et al. (editors), Harrison's principles of internal medicine, New York, McGraw-Hill, 1974

8. Lubsen, J., Pool, J., Van der Does, E., A practical device for the application of a diagnostic or prognostic function. In press (Methods in information in medicine). This thesis chapter 8

9. Neff, R.K., COPS/4 User's guide, Boston, Health sciences computing facility, Harvard School of Public Health, 1974

10. Freund, J. E., Mathematical Statistics, Englewood Cliffs, Prentice Hall, 1971

11. Halperin, M., Blackwelder, W.C., Verter, J. I., Estimation of the

multivariate logistic risk function: A comparison of the discriminant function and maximum likelihood approaches. J. Chron. Dis. 24 : 125-128, 1971

12. World Health Organization, Regional Office for Europe. Myocardial Infarction community registers. Public health in Europe 5, Copenhagen 1976

7. ACUTE CORONARY EVENTS IN GENERAL PRACTICE: INCIDENCE OF ACUTE MYOCARDIAL INFARCTION AND SUDDEN DEATH

J. Lubsen*, E. van der Does** and J. Pool*

SAMENVATTING

Zorgvuldige schatting van het optreden (incidentie) van acute coronaire episodes (A.C.E.'s), d.w.z. van acuut myocardinfarct (A.M.I.) en plotse dood, in bepaalde bevolkingsgroepen is van belang, zowel om inzicht te krijgen in de omvang van volksgezondheidsproblemen veroorzaakt door A.C.E., als om de resultaten van interventieprogramma's nader te kunnen evalueren. De Imminent Myocardial Infarction Rotterdam (I.M.I.R.)studie was niet opgezet als registratieprojekt om de incidentie te schatten, maar om de prognostische waarde te bepalen van onstabiele klachten, mogelijk van cardiale herkomst, waarvoor de huisarts wordt geconsulteerd. Nauwkeurige schatting van de incidentie van A.C.E. is, door de in de I.M.I.R. studie gebruikte methoden, in principe mogelijk.

In tien van de deelnemende huisartsenpraktijken was de incidentie van A.C.E., uitgedrukt als aantal episodes per 1.000 personen per jaar, als volgt: voor mannen van 30-39: 1; 40-49: 5; 50-59: 7; 60-69: 16; 70-79: 17; 80-89: 39. Voor vrouwen onder de 50 jaar was de incidentie vrijwel 0, van 50-59: 3; 60-69: 6; 70-79: 12 en 80-89: 12. Van alle A.C.E.'s verliep 34% fataal binnen 24 uur (plotse dood). Nog eens 10% van de patiënten met een A.C.E. overleden binnen een maand. Van alle patiënten met A.C.E. hadden 27% al eerder een hartinfarct gehad.

Bij optimale medewerking van de deelnemende huisartsen zouden alleen hartinfarcten zijn gemist waarbij de klachten zo gering waren, dat de huisarts niet was geconsulteerd. De A.C.E.'s werden opgespoord door middel van vooraf bepaalde criteria, onafhankelijk van het vermoeden van de huisarts of een andere arts dat een acuut of dreigend infarct aanwezig was. Dit houdt in dat zelfs atypische A.C.E.'s werden opgespoord die bij een registratieschema gebaseerd op diagnostiek van huisarts en/of specialist zouden zijn gemist.

SUMMARY

Accurate assessment of the incidence rates of acute coronary events (A.C.E.s), i.e. of acute myocardial infarction (A.M.I.) and sudden cardiac death, is of interest in evaluating the magnitude

of the health problem created by A.C.E. and the effects of intervention programs. The Imminent Myocardial Infarction Rotterdam (I.M.I.R.) study was not primarily intended as a registration project for incidence rate assessment but rather as a means to assess the prognostic significance of unstable symptoms of suspected cardiac origin for which a general practitioner (G.P.) is consulted. Nevertheless, the methods employed allow, in principle, accurate assessment of A.C.E. incidence rates.

In 10 of the participating general practices, the incidence rates of A.C.E., expressed as the annual number of events per 1,000 population, were as follows. For men aged 30-39: 1; 40-49: 5; 50-59: 7; 60-69: 16; 70-79: 17; 80-89: 39. For women under 50, A.C.E. incidence was near zero. For women aged 50-59: 3; 60-69: 6; 70-79: 12; 80-89: 12. Of all A.C.E.s, 34% were fatal within 24 hours (sudden death). Another 10% resulted in death within one month. A positive history of myocardial infarction was given by 27% of the cases of A.C.E.

Given optimal cooperation of the G.P.s, only A.M.I. accompanied by such non-disturbing symptoms that no physician was consulted would have been missed. A.C.E.s were detected according to set criteria independent of whether a G.P. or some other physician suspected an acute or imminent coronary event. By the same token, even atypical cases of A.M.I., which could have been missed in a registration scheme dependent on notification, were detected.

## 7.1. INTRODUCTION

Not only to the epidemiologist but also to the medical community at large, measurements of the occurrence rates of disease have substantial interest. These describe the magnitude of a health problem; they serve as parameters for comparison of (sub-) populations and therefore as objects of inquiry in causal research and in evaluation of intervention programs. To be useful, such measures have to pertain to specific and recognizable disease entities occurring in well defined populations.

Since coronary atherosclerotic heart disease (C.A.H.D.)† in its various manifestations has drawn considerable attention as the single most important cause of death in many industrialized countries, the need for investigation into clinical precursors of acute myocardial infarction (A.M.I.) and early cardiac death

† For criteria, definitions and abbreviations see Appendix on page 29

and into the possibility of their prevention has been emphasized.[1-6] Part of the effort has been the establishment of registers to measure the occurrence of C.A.H.D. A working group of the World Health Organization[7] expressed the opinion that "the long-term purpose of the registers and associated activities must be to contribute to the prevention and control of ischaemic heart disease".

The I.M.I.R. study,[8-11] not intended primarily as a registration project, was designed to assess the prognostic significance with respect to future acute coronary events (A.C.E.s), i.e. A.M.I. and sudden cardiac death, of unstable symptoms of suspected cardiac origin for which a general practitioner (G.P.) is consulted. However, as the study registered cases of A.C.E. occurring in a population depending for health care on a group of participating G.P.s the question arose whether measurements of occurrence of A.C.E. could be obtained. The resolution of this question requires first of all consideration of the nature of the measurements of interest. The two most commonly used measurements are the prevalence rate and the incidence rate.[12] The prevalence rate is defined as the proportion of a population that suffers from a disease at a specific point in time. The incidence rate can be expressed as the proportion of the population at risk that acquires a disease within a specified period of time.

Unfortunately, estimation of the prevalence of C.A.H.D. was impossible within the framework of I.M.I.R. Incidence rates of A.C.E. could be estimated however and this created an opportunity to compare the rates found in I.M.I.R. with the results of other studies. In this publication, incidence rate estimates are given based on 179 A.C.E.s recorded during a period of 20 months within a population of about 23,500 people living in a large city in The Netherlands.

## 7.2. METHODS

The methodology of I.M.I.R. has been described in detail elsewhere.[8] In brief, all patient-G.P. contacts for recent or worsening chest pain and recent upper abdominal pains, dyspnea, palpitations, dizzyness, syncope or fatigue, for which no extracardiac cause was evident, were registered during 20 months and each patient was followed for 10 months under a common protocol in 14 general

practices in Rotterdam and suburbs. On inclusion into the study, a clinical history was taken and a simple physical examination done by the G.P. Males younger than 20 years of age and females younger than 25 were excluded.

Directly after inclusion, a standard 12-lead electrocardiogram (E.C.G.) was recorded and a blood-sample was taken by a technician for assessment of serum levels of glutamic oxaloacetic transaminase (S.G.O.T.), alphahydroxybutyric dehydrogenase ($\alpha$-H.B.D.H.) and creatinine phosphokinase (C.P.K.). During the follow-up period, E.C.G. and enzyme studies were repeated at fixed times as stipulated in the protocol. At the conclusion of follow-up, 10 months after inclusion, an E.C.G. was recorded, a final history was taken from the patient and supplementary data were requested from his G.P. All data were collected on standardized forms.

A diagnosis of "definite A.M.I.", "possible A.M.I." or "no A.M.I." was made at the time of inclusion according to preset clinically accepted criteria.[8] During follow-up, new or recurrent A.C.E.s were also detected according to preset criteria. A.M.I. was rated as "definite" or "possible", cause of death as "cardiac", "possible cardiac", "unknown" or "not-cardiac". Also, death was classified as "sudden" if death occurred within 24 hours after the onset of symptoms initiating the final clinical episode and as "probably sudden" if this was not definitely known to be the case but likely. All instances of "sudden" and "possible sudden" death occurring in patients belonging to participating practices but not previously included into the study, were registered also and similarly classified.

From October 1972 through May 1974, 1,387 patients were included in the study. Only the data from 10 general practices fully participating during this period are taken into account here. These practices included 1,298 patients.

The data necessary to determine the denominators, i.e. all persons registered with participating general practices, were derived from the administration of the health insurance system of the city of Rotterdam and through individual counting of persons who were not at all or otherwise insured. Denominators reflect the state on January 1, 1974.

The incidence rate estimates are based on the number of A.C.E.s occurring during a 20-month period.

As the protocol did not provide for possible re-inclusion of those patients who had completed their 10-month follow-up, some A.C.E.s which might have taken place in patients who had completed follow-up before inclusion was closed, could have been missed. In an effort to compensate for this, all A.C.E.s recorded during follow-up were counted in the numerator regardless of whether the date of occurrence was before or after the date that inclusion was closed (May 31, 1974). Incidence rates were expressed as number of events per 1,000 population per year.

## 7.3. RESULTS

For the purpose of this report, an A.C.E. detected at the moment of inclusion or during follow-up comprises the following:

Sudden death: "sudden death" or "probably sudden death" except when the cause of death was "not cardiac",

Lethal A.M.I.: "definite A.M.I." or "possible A.M.I." with subsequent death except when the cause was "not cardiac",

Non-lethal A.M.I.: "definite A.M.I." without subsequent cardiac or possible cardiac death within one month.

### 7.3.1. ACUTE CORONARY EVENTS AT INCLUSION

In 43 patients (30 male, 13 female) sudden death occurred without previous inclusion to the study alive. Their medical records showed that 33 (77%) cases did not have a history of a previous M.I.

Among 84 patients (55 male, 29 female) diagnosed as having an A.M.I. at the moment of inclusion, the one-month mortality rate was 17% (14 out of 84). In 65 patients (77%) this A.M.I. was the first one.

In males, one A.M.I. was detected in the age-category 20-29. Except for one case of sudden death, all A.C.E.s in females occurred in patients older than 50. In both sexes, the highest number of A.C.E. at inclusion was found in the age-category 60-69 (table 7.1.)

### 7.3.2. ACUTE CORONARY EVENTS DURING FOLLOW-UP

In patients with A.M.I. at inclusion, 5 recurrent A.C.E.s were detected after the first month of follow-up (table 7.1.). Of a total of 47 A.C.E.s (33 in males, 14 in females) occurring in patients without A.M.I. at inclusion, 16 were sudden deaths. Of the remaining 31 cases of A.M.I., 2 died during follow-up.

In 33 cases of A.C.E. (70%), history of previous M.I. was negative (table 7.2.).

### 7.3.3. INCIDENCE RATES OF A.C.E.

Rates found are much higher in men than in women and rise sharply with age. In women under 50 years of age, the incidence rate is near zero; in men aged 40-49 already 5 per 1,000 per year. In men aged 60-69 a rate of 16 was found, in women of the same age the rate was 6. The highest number of A.C.E.s occurred in the age-category 60-69 for men and 70-79 for women (table 7.3.).

### 7.3.4. LETHALITY

In men, the proportion of all A.C.E.s that are lethal rises with age. In our data, a lethality of 29% was observed for men aged 40-49. This figure rises to 87% for men aged 80-89 ($p = 0.02$, chi-square test with 4 degrees of freedom). The data indicate that this rise is due in part to an increase of the proportion of A.C.E.s that are sudden deaths and to an increase of the proportion that is lethal but not sudden. In women, the paucity of the data does not warrant any conclusions about such trends.

The lethality within 24 hours was high. In men, 39% of all cases of A.C.E. died within 24 hours; in women this proportion was 24% This difference was not statistically significant, $p = 0.09$, according to a two-sided modified Fisher-exact test[13] (table 7.3.).

### 7.3.5. HISTORY OF M.I. AND PREVIOUS INCLUSION INTO THE STUDY

Of the total number of A.C.E.s recorded (121 in men, 58 in women), the proportion that had a positive history of previous M.I. was 29% in men and 22% in women (table 7.3.)

The proportion of patients sustaining an A.C.E. without foregoing inclusion to the study was 127/(127 + 47) or 73% (tables 7.1. and 7.2.). This proportion did not depend significantly on sex and history of M.I.

## 7.4. DISCUSSION

### 7.4.1. ACCURACY OF RATE ESTIMATES

The accuracy of an incidence rate estimate depends on the methods employed in ascertaining the cases making up the numerator and on the

precision with which the denominator, i.e. the size of the population from which the cases originate, is known.

The denominators used here derive from precise information about the number of people registered with a G.P. Mutations in a practice are infrequent and occur both ways, the denominators can therefore be considered stable over the time-period that the study was carried out. Over-estimation of rates through under-estimation of denominator-size could however occur if people not registered with a G.P. would nevertheless consult him in emergencies such as an A.C.E. This would be rare in Holland. The majority of the population is covered by a partly obligatory health insurance system; registration with a G.P. is required upon entry. People not covered by this system are almost without exception registered with a G.P.

The numerators raise questions about verification and completeness of ascertainment of cases during any given period of time, here 20 months.

The I.M.I.R.-G.P.s had to include a patient if his/her symptoms met the inclusion criteria, and not because an acute imminent coronary event was suspected. Given optimal awareness by the G.P., cases of A.C.E. would be missed only if the patient failed to consult him for symptoms meeting the inclusion criteria either in the prodromal or the acute phase of an A.C.E. Due to the broad range of symptoms described in the inclusion criteria, this would happen only if the A.C.E. was "silent" or the accompanying symptoms were of insufficient severity to induce consultation of a G.P. It seems unlikely that this would be the case in any but a minor portion of occurring A.C.E.s, if it occurs at all.

Optimal cooperation of the G.P.s was encouraged in many ways. The strongest incentive was the immediate diagnostic support offered. Training, regular meetings and checks on protocol compliance and data completeness were also helpful. We were however unable to monitor incoming death certificates and hospital admissions in the area. The possibility remains that cases were missed because they were seen by a locum tenens of a participating G.P. and therefore not reported to the study. Consequently, absolute certainty that no instances of early death or A.M.I. with direct hospital admission were missed could not be obtained.

Subsequent to inclusion, A.C.E.s were detected using predetermined criteria.

Those for A.M.I. closely follow current clinical practice, only definite cases of A.M.I. are included in numerators. There is little reason to doubt that the cases of sudden death indeed died within 24 hours after onset of symptoms. Classification of the timelag was left to the G.P., who had direct access to family information if he did not witness the event himself. Classification of the cause of death had to rely on information about the clinical history in the majority of cases as only 13% of all deaths were autopsied. In lethal cases of documented A.M.I., misclassification of the cause of death is not of much concern. In many instances of early death however no clinical history will be available. Studies of Kuller[1] indicate that the majority of sudden deaths without obvious extracardiac cause are due to C.A.H.D. In this report, therefore, only deaths of non-cardiac causes were excluded from the numerators but deaths of "unknown" causes were included. This is believed to be the closest approximation possible from these data to the real incidence of sudden death due to C.A.H.D.

The numerators used are considered to represent all A.C.E.s occurring during the 20-month period that inclusion to the study was open. All A.C.E.s detected are counted, notwithstanding the fact that some of them occurred after the 20-month inclusion period. On the other hand, some A.C.E.s occurring in patients after their completion of the 10-month follow-up are missed, as no patient could be included twice. Both effects approximately compensate each other (fig. 7.1.).

### 7.4.2. COMPARISON WITH OTHER STUDIES

Bekker conducted in Nijmegen, The Netherlands, a C.A.H.D.-registration project under the auspices of the World Health Organization.[14] Armstrong et al. published incidence rates derived from a natural history study in Edinburgh, Scotland, which was intended also as a pilot registration project.[15] Compared to these, rates observed for men in I.M.I.R. are slightly lower than the remarkably similar rates reported by Bekker and by Armstrong except for men aged 50-59 for whom I.M.I.R. observed a much lower rate. For women, the findings of I.M.I.R., Bekker and Armstrong are essentially the same (table 7.4.).

De Haas conducted a survey of incident cases of first A.C.E. in The Hague and its suburbs in The Netherlands.[18]

For the same age-categories used by him, I.M.I.R. observed slightly lower rates of first A.C.E. for men and slightly higher ones for women (table 7.5.).

In estimating incidence rates of first A.C.E., the denominators should in principle pertain to people without a history of A.M.I. This would require sex and age specific data about the prevalence rate of a positive history of A.M.I. As the design of the study did not provide for such information, incidence rates of first A.C.E. could not be obtained. The effect of correction will however be small, probably of the order of 5%. For The Netherlands, few prevalence data are available. May found in a survey in a rural part of The Netherlands a positive history of A.M.I. in about 2% of the population.[19] Abnormal Q-waves in the E.C.G. indicating the presence of a history of A.M.I. was however found in a higher fraction, about 5%, of the population. The findings of De Soto-Hartgrink in a population of civil servants were of the same order of magnitude.[22] In the age-category 40-65, 2% of men and 0.5% of women had a history of myocardial infarction. Abnormal Q-waves were found in 1.5-5% of men and 1.5-2.5% of women.

On the assumption that atypical cases which might have been missed would be detected, it was expected that I.M.I.R. rates would be higher than those reported elsewhere. This was not substantiated. For the data provided for by Bekker,[14] a possible explanation is that the author included "possible A.M.I." in his numerators also. In the present study, rather stringent criteria for A.M.I. were applied and only definite cases were included. For the data provided for by Armstrong et al.[15], a possible explanation might be that C.A.H.D. rates are higher in England than in Holland.[16] A comparison with the rates published by De Haas[18] is hampered by the fact that exact information about the diagnostic classification methods was not available. Also, it must be borne in mind that the population under surveillance by I.M.I.R. might not be similar with respect to C.A.H.D. rates as the ones of Bekker and De Haas. Regional differences found in Holland are of the order of 25% difference between highest and lowest rates.[20]

Finally, a note on nomenclature and diagnostic classification, may be in order. All authors quoted here included cases of sudden death in the numerator and reported incidence rates of "A.M.I." A recent report on the Seattle resuscitation experience by Cobb et

al.[21] indicates that the pathophysiological mechanisms behind a case of C.A.H.D. dying instantaneously might be very different from the ones behind an initially non-lethal A.M.I. The nomer "acute coronary event" is therefore prefered over "acute myocardial infarction".

### 7.4.3. I.M.I.R. AS A REGISTRATION PROJECT

The W.H.O. working group on ischaemic heart disease registers was of the following opinion: "Ideally, all suspected cases of myocardial infarction should be registered, including any patient with a suggestive history ..... Doubtful case histories and findings could be adequately assessed without full registration."[7]

The evaluation of doubtful case histories and findings was provided for by the design of I.M.I.R. A further advantage was that the detection of A.C.E.s did not depend in any way on the diagnostic skills of a physician but relied on the application of preset criteria on independently and in a standardized way collected information about the patient's symptoms, signs, history and the results of diagnostic tests. An argument can therefore be made that the methods employed by I.M.I.R. are superior with respect to registration of incident A.C.E.s in comparison to the ones used by studies reported so far.

I.M.I.R. methods are probably more reliable than dependence on notification by G.P.s and/or hospitals of incident A.C.E.s. As reported elsewhere,[11] the I.M.I.R. study showed that the sensitivity of the unassisted G.P. diagnosis "A.M.I." based on history and clinical findings alone is poor. Also, not all proven A.M.I.s were referred to a hospital by the G.P. cooperating in I.M.I.R. Rates based on hospital admissions and death certificates alone would therefore underestimate the rates. Adding registration of cases of A.M.I. kept at home by the G.P. would not solve this problem unless the G.P. has better diagnostic tools than seems to be the case at present.

## 7.5. CONCLUSIONS

The methods employed in the I.M.I.R. study enabled the estimation of incidence rates of acute coronary events (A.M.I. and sudden death) in a population registered with a group of general practitioners. In the absence of absolute certainty that no cases were

missed, the rates observed must be viewed as lower limits of the real incidence. Except for men aged 50-59, where a lower rate was found, rates observed were essentially equal to those reported from Nijmegen, The Netherlands[14] and Edinburgh, Scotland.[16]

Under Dutch circumstances and with some modifications in terms of concomitant surveillance of hospital admissions and death certificates, the design of I.M.I.R. is well suited for a registration scheme of acute coronary events and offers definite advantages with respect to the ascertainment of cases with an atypical course. However, cause of death classification in instances of early death requires an autopsy in the context of such a scheme.

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The study was supported by the Netherlands Heart Foundation. J. Lubsen was supported in part by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.)

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REFERENCES


1. Kuller, L., Sudden death in arteriosclerotic heart disease; the case for preventive medicine. Amer. J. Cardiol 24: 617-628, 1969

2. Chiang, B.N., Perlman, L.V., Ostrander, L.D., Epstein, F.H., Relationship of premature systoles to coronary heart disease and sudden death in the Tecumseh epidemiologic study. Ann. Int. Med. 70: 1159-1165, 1969

3. World Health Organization. Regional Office for Europe. The prodromal symptoms of myocardial infarction and sudden death. Report of a working group, Copenhagen, 1971

4. Fulton, M., Duncan, B., Lutz, W., Morrison, S.L., Donald, K.W., Kerr, F., Kirby, B.J., Julian, D.G., Natural history of unstable angina. Lancet 1: 860-865, 1972

5. Bondurant, S., Problems of the pre-hospital phase of acute myocardial infarction. Amer. J. Cardiol 24: 612-616, 1969

6. Kannel, W.B., Feinleib, M., Natural history of angina pectoris in the Framingham study. Amer. J. Cardiol 29: 154-163, 1972

7. World Health Organization. Regional Office for Europe. Ischaemic heart disease registers. Report of a working group, Copenhagen, 1971

8. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G., Arntzenius, A.C., Acute coronary events in general practice. Objectives and design of the I.M.I.R.-study. Hart Bull. 7: 91-98, 1976. This thesis, chapter 2

9. Van der Does, E., Lubsen, J., Pool, J., van Strik, R., van der Sijde, J., Stroink, J., Acute coronary events in general practice. Early warning symptoms of acute myocardial infarction and sudden death. Hart Bull. 7: 99-106, 1976. This thesis, chapter 3

10. Lubsen, J., Pool, J., van der Does, E., Acute coronary events in general practice. Acute risk of myocardial infarction or sudden death in a symptomatic patient. Hart Bull. 7: 114-117, 1976. See also this thesis, chapter 4

11. Van der Does, E., Lubsen, J., Pool, J., Gorter, S., Acute coronary events in general practice. Diagnostic power of the general practitioner without laboratory assistance. Hart Bull. 7: 118-121, 1976
See also this thesis, chapter 5

12. Friedman, G.D., Primer of epidemiology. McGraw Hill Book Comp. Ltd., London, Toronto, 1974

13. Miettinen, O.S., Comment on Conover, J., Some reasons for not using the Yates continuity correction on 2 x 2 contingency tables. J.A.S.A. 69: 380-383, 1974

14. Bekker, B.V., Interim verslag resultaten W.H.O. registratieprojekt ischaemische hartziekten Nijmegen, Nijmegen, 1972

15. Armstrong, A., Duncan, B., Oliver, M.F., Julian, D.G., Donald, K.W., Fulton, M., Lutz, W., Morrison, S.L., Natural history of acute coronary heart attacks; a community study. Brit. Heart J. 34: 67-80, 1972

16. World Health Organization. Epidemiological and vital statistics report 20, no. 2, 1967

17. Armitage, P., Statistical methods in medical research. Blackwell Scientific Publications, Oxford, 1971

18. De Haas, J.H., Eerste myocardinfarct in Groot-Den Haag; een retrospectieve epidemiologische survey. Hart Bull. 6: 36-49, 1975

19. May, J.F., Epidemiological cardiology, ischaemic heart disease study Vlagtwedde 1970. Thesis, Groningen, 1974

20. Centraal Bureau voor de Statistiek. Hart- en vaatziekten, een statistische verkenning. Staatsuitgeverij, Den Haag, 1972

21. Cobb, L.A., Baum, R.S., Alvarez, H., Schaffer, W.A., Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. Circulation 52, suppl. III: 223-228, 1975

22. De Soto-Hartgrink, M.K., Epidemiologie van ischaemische hartaandoeningen. Thesis, Leiden, 1968

8. A PRACTICAL DEVICE FOR THE APPLICATION OF A DIAGNOSTIC OR PROGNOSTIC FUNCTION†

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SAMENVATTING

De toepassing van een diagnostische of prognostische Multipele Logistische Functie (M.L.F.) in de medische praktijk kan, afhankelijk van de complexiteit van het model, een aanzienlijke hoeveelheid rekenwerk vergen. Verschillende methoden om zulk rekenwerk overbodig te maken, zoals tabellen of nomogrammen, zijn voorgesteld.
Een alternatieve methode voor het overbodig maken van het benodigde rekenwerk wordt hier beschreven. De methode is gebaseerd op het principe van de gebruikelijke rekenlineaal. Als voorbeeld wordt het ontwerp beschreven van een schuiflineaal voor de evaluatie van een diagnostisch model van het acute myocardinfarct. De schuiflineaalmethode laat de evaluatie van logistische modellen toe met gecompliceerde lineaire combinaties in de exponent. De benodigde schuiflinealen kunnen tegen lage kosten worden geproduceerd.

SUMMARY

The application of a diagnostic or prognostic Multiple Logistic Function (M.L.F.) in medical practice may, depending on the complexity of the model, require considerable arithmetic. Various methods for the elimination of arithmetic, such as sets of tables or nomograms have been proposed. An alternative method of eliminating the necessary arithmetic is described here. It is based on the principle of the familiar slide-rule. As an example, the design of a slide-rule for the evaluation of a diagnostic model for acute myocardial infarction is described. The slide-rule method allows for the evaluation of logistic models with complex linear combinations in the exponent. Adequate devices can be produced at low cost.

† Supported in part by the Netherlands Heart Foundation, The Netherlands Organization for the Advancement of Pure Science Z.W.O. and Boehringer Ingelheim B.V., Haarlem, The Netherlands.

## 8.1. INTRODUCTION

The multiple logistic function (M.L.F.) has found application in estimating the probability that a person with particular characteristics has, or will develop, a certain disease. For instance, Truett et al.[1] have described its application to the estimation of the risk of coronary heart disease given information on seven risk indicators. The M.L.F. for disease probability has the following form:

$$P(D|x_1, x_2 \ldots x_n) = \frac{1}{1 + e^{-\left\{b_o + \sum_{i=i}^{i=n} b_i . x_i\right\}}} \qquad (1)$$

where $x_i$ is the i-th information variable; $P(D|x_1 \ldots x_n)$ is the conditional probability that disease is present (or will occur) given $x_1 \ldots x_n$ and $b_o \ldots b_n$ are constant. Methods for estimating the constants in the M.L.F. are available. Truett er al.[1] used the linear discriminant function (L.D.F.) approach as proposed by Cornfield[2]; Walker and Duncan[3] have described a more general maximum likelihood method. Consequently, a M.L.F. predicting or diagnosing a certain disease may be obtained by analyzing a suitable data base.

Applying the result in practice is hampered by the required arithmetic. First, $\Sigma b_i . x_i$ is to be calculated, after which $P(D|x_1 \ldots x_n)$ may be obtained by inserting the result in equation 1. It seems that widespread use of M.L.F.s in every-day medical practice can be expected only if the need for the execution of arithmetic is eliminated. Various methods of achieving this goal have been proposed.

The "Coronary Risk Handbook", published by the American Heart Association[4], presents a set of tables for the estimation of coronary heart disease risk as determined by sex, age, rate of cigarette smoking, blood pressure, serum cholesterol, glucose tolerance and electrocardiogram. Wilhelmsen et al.[5] have described sex and age specific nomograms for the same purpose, with serum cholesterol, cigarette smoking and systolic blood pressure as prognostic indicators. The present paper describes an alternative method of eliminating the need for all arithmetic in evaluating a M.L.F. The method is based on the same principle as the familiar slide-rule. As an example of a practical application, the structure and use of such a device, designed for the evaluation of a multiple logistic model for diagnosing acute myocardial infarction (A.M.I.), is described.

## 8.2. PRINCIPLE

Like any slide-rule, the device consists of a slide moving between two fixed parts, and an indicator which can be moved along the ruler. For the purpose of explaining its application to the evaluation of a M.L.F., a simple version, taking into account an indicator variable $x_1$ and a continuous variable $x_2$, is depicted schematically in fig. 8.1. Let $x_1$ be coded as 0 = characteristic absent, 1 = characteristic present and let $x_1$ have, on this coding, a coefficient of $b_1$. Furthermore, let $x_2$ have a coefficient of $b_2$. On the upper fixed part of the ruler, a zero-point is defined. On the slide, $x_1$ is represented by a line segment with a length representing the absolute value of $b_1$ while the scale of $x_2$ is calibrated in such a way that a unit interval represents $b_2$. If a coefficient is positive, the scale or the line segment representing the variable is drawn with the 0-end to the left. If the coefficient is negative, the scale or line segment is drawn with the 0-end to the right. The value of $\Sigma b_i.x_i$ is obtained as follows.
First, the indicator is adjusted to the zero-point on the upper fixed part, and the slide is moved so as to align the "$x_1 = 0$" end of the line segment representing $b_1$ with the indicator. Next, move the indicator to the "$x_1 = 1$" end if the characteristic is present or, alternatively, leave the indicator in its position if the characteristic is absent. Now, move the slide so as to align the zero-end of the $x_2$-scale with the current position of the indicator. Then, adjust the indicator to the value observed for $x_2$. The distance between the position of the indicator so obtained and the zero-point on the upper fixed part is proportional to $\Sigma b_i.x_i$. Since, for any particular value of a in equation 1, there is a one-to-one correspondence between the value of $P(D|\ x_1, x_2)$ and the value of $\Sigma b_i.x_i$, the scale on the lower fixed part can be calibrated in units of $P(D|\ x_1, x_2)$, which allows the user to read off $P(D|x_1, x_2)$ directly.

## 8.3. EXAMPLE OF APPLICATION

The Imminent Myocardial Infarction Rotterdam (I.M.I.R.) study[6] registered instances of patient-general practitioner contact for new or worsening symptoms of possible cardiac origin. Among 1,340 such instances, 92 cases of A.M.I. were diagnosed on the basis of history, electrocardiograms (E.C.G.s) and enzyme tests. A diagnostic function was sought which would take into account exclusively clinical infor-

mation readily obtainable by a general practitioner and require no reference to an E.C.G. or to enzyme tests. To derive a scoring function on which a probability diagnosis of A.M.I. could be based, L.D.F. analysis was used. The variables retained in the final L.D.F. and their coefficients are given in table 8.1. After an empirical logarithmic transformation of the L.D.F.-score to obtain approximate Normality and equality of variance of the transformed L.D.F.-score distributions for cases and for non-cases respectively, the application of Normal theory leads to the following multiple logistic model for the conditional probability that A.M.I. is present:

$$P(A.M.I.\,|\,\Sigma b_i.x_i) = \frac{1}{1 + e^{a.\{\log_e(\Sigma b_i.x_i + c)\} + d}} \qquad (2)$$

In this equation, $\Sigma b_i.x_i$ represents the L.D.F.-score, which is obtained by multiplying the L.D.F.-coefficients of table 8.1. with the values of the respective information variables and summing the results. The constant c is part of the empirical logarithmic transformation, as its value was taken -0.94. Using this value of c and the coefficients of table 8.1., the transformed score means for cases of A.M.I. and for non-cases respectively were estimated from the I.M.I.R. data base, as was its pooled variance. The constant a involves these estimates, its value was determined at -4.162. Apart from the same estimates of transformed score means and its pooled variance, the constant d involves also the prior probability of the presence of A.M.I.; its value was determined at 9.835

According to the principle described in the previous section, a slide-rule was designed to accumulate $\Sigma b_i.x_i$ and apply equation 2 to the result. As is shown in fig. 8.2., two age scales, one for females and one for males, were positioned on the upper fixed part of the ruler, thereby eliminating the need for defining a zero-point on that part. The age scales were calibrated in units spaced apart proportionally to the coefficient of age. With respect to the scale for females, the scale for males was shifted over a distance proportional to the coefficient of sex to the left since that coefficient had a positive sign. All other variables were positioned on the slide. Indicator variables were phrased as questions with "yes" or "no" answers, corresponding to a coding yes = 1, no = 0. The symbols, representing these answers, were spaced apart proportionally to the res-

pective coefficients. The scales representing the two remaining continuous variables were calibrated in units with a length proportional to their coefficients. Scales or line segments representing variables with a positive coefficient were drawn with the 0-end to the left; if the coefficient was negative, the scales were drawn with the 0-end to the right. Since the value of $\pm b_i . x_i$ transforms directly into the conditional probability that A.M.I. is present, the scale on the lower fixed part, which gives that probability as a percentage, could be calibrated accordingly.

## 8.4. DISCUSSION

By careful recording and statistical analysis of medical data, M.L.F.s for diagnostic and/or prognostic purposes can be developed and be made available for use by the medical practitioner. For instance, Kannel et al.[7] have advocated the use of a M.L.F. for the determination of general cardiovascular risk, developed on the basis of data from the Framingham study, in the detection of high risk individuals by screening programs. Such an application implies the evaluation of a particular M.L.F. for each of a large number of individuals. Within the framework of a special screening clinic, the use of a computer for this purpose could be justifiable, especially if a computer is used for data-management also. The individual medical practitioner will however in general not have such facilities available either in the office or at the patient's bedside. Clearly, other alternatives have to be provided in such situations.

Preliminary experience with the slide-rule method described here has shown that the method is acceptable to the medical practitioner since its use is easy to understand, it is quick to apply and it requires no mathematical or statistical background. Whether such a method will ultimately find acceptance seems to be less dependent on its ease of use than on the clinical relevance of the problem for which it is designed.

The slide-rule seems to offer advantage over other methods of eliminating the need for arithmetic in evaluating a M.L.F., such as tables or nomograms. Rather complex models may be accomodated by the slide-rule. The number of variables taken into account is not as severely restricted as by the other methods mentioned, transformations of variables can be build into the calibration of the scales and the

use of product terms to take interactions into account is possible by the use of logarithmic scales.

As to costs, it is our experience that slide-rules for these purposes can be produced cheaply since simple construction not involving great machining accuracy suffices. For instance, the slide-rule shown in fig. 8.2. could be produced in a quantity of 5,000 for the equivalent of $ 1.20 apiece.

It is underlined that the slide-rule shown in figure 8.2 is presented here merely as an example of the application of the method for evaluating a M.L.F. described. The diagnostic model for A.M.I. on which it is based and the slide-rule method for its application at the bedside are currently under evaluation.

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In press (Methods of Information in Medicine)

REFERENCES

1. Truett, J., Cornfield, J., Kannel, W., A multivariate analysis of the risk of coronary heart disease in Framingham. J. Chron. Dis. 20: 511-524, 1967

2. Cornfield, J., Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure: a discriminant function analysis, Fedn. Proc. 21: 58-61, 1962

3. Walker, S.H., Duncan D.B., Estimation of the probability of an event as a function of several independent variables, Biometrika 54: 167-179, 1967

4. American Heart Association: Coronary risk handbook: estimating risk of coronary heart disease in daily practice. New York, 1973

5. Wilhelmsen, L., Multifactorial risk, M.S.D.-symposium "Epidemiologie en Preventie van Cardiovasculaire aandoeningen", De Doelen, Rotterdam, 1976

6. Van der Does, E., Lubsen, J., Pool, J., Hugenholtz, P.G., Arntzenius, A.C., Acute coronary events in general practice: objectives and design of the I.M.I.R. study, Hart Bull. 7: 91-98, 1976. This thesis, chapter 2

7. Kannel, W.B., McGee, D., Gordon, T., A general cardiovascular risk profile: The Framingham study, Amer. J. Cardiol. 38: 46-51, 1976

# 9. THE I.M.I.R. STUDY, A SUMMARY OF THE RESULTS

J. Lubsen and E. van der Does

In the preceding chapters, the results of the I.M.I.R. study were presented and discussed in detail. The objective of the present chapter is to summarize the results. It is devided into two parts. The first part covers results considered relevant to the objectives of the study as described in chapter 2 on page 16 . The second part summarizes findings which have no direct connection to the objectives and it contains also some data which have not been presented before. The present chapter serves as a basis for the two chapters of general discussion which follow.

## 9.1. MAIN RESULTS

Relative to the occurrence in general practice of acute coronary events, i.e. acute myocardial infarction or sudden cardiac death, the general practitioner frequently saw patients with potential coronary-type symptoms. Of the patients included under the I.M.I.R.-inclusion criteria, the majority (90%) had chest pain either as primary or as secondary symptom. In 71%, chest pain was the primary symptom, palpitations (7%) and dyspnea (6%) were the next most frequent primary symptoms. Otherwise, symptomatology was multifarious. Of the patients with chest pain, half had "atypical", i.e. not exercise induced pain of recent onset, another 26% had "atypical" pain which had recently worsened and only 23% had unstable angina pectoris according to questionnaire-based criteria. As secondary symptom, mood changes, dyspnea and palpitations were the most frequent; on the average, three different symptoms were recorded per patient. The participating general practitioners included 34 patients per year per 1,000 practice-size in the age-categories considered, i.e. men of at least 20 and women of at least 25 years. This figure was somewhat higher for men than for women and it rose with increasing age (chapter 3).

During the period that inclusion was open, 43 instances of sudden cardiac death were registered in patients not previously included alive. Among the 1,344 patients included alive, 93 (7%) cases of "definite" acute myocardial infarction and 37 (3%) cases of "possible" acute myocardial infarction were present at the moment of

inclusion while the remaining 1,214 patients did not have acute myocardial infarction at the time. Of these, 83 (7%) sustained an acute coronary event during 10 months of follow-up, of which 44 took place during the first month. Nineteen new acute coronary events were classified as "sudden cardiac death", 34 as "definite" acute myocardial infarction and the remaining 30 as "possible" acute myocardial infarction. Of the 83 new events, 53 (64%) were predicted at inclusion by the general practitioner since the inclusion diagnosis was "imminent myocardial infarction" in these instances. However, a large number of false-positive diagnosis "imminent myocardial infarction" was made since 310 (26%) of the 1,214 patients free of acute myocardial infarction at inclusion were so diagnosed by the general practitioner. Unstable, i.e. recent or worsening, exercise induced angina was present in 21% (252/1,214) of the patients free of acute myocardial infarction. For this sub-group, a 13% (33/252) 10-month rate of acute coronary event was observed. Patients with other, i.e. non-anginal, chest pain and patients with other symptoms than chest pain had a similar prognosis, 5% (42/841) and 6% (7/117) 10-month rates of acute coronary event respectively were observed for these sub-groups. Multivariate analysis showed that in patients with potential coronary-type symptoms who were free of acute myocardial infarction and who were seen by a general practitioner, the following characteristics were independently associated with the short-term occurrence of an acute coronary event: age, male sex, Q- and T-wave abnormalities in the electrocardiagram, unstable angina, hypertension, diabetes and râles. On the basis of a composite score which incorporated these characteristics, a sub-group of patients could be identified for which a 31% 10-month rate of acute coronary event was observed (chapter 4).

Of these 93 cases of "definite" acute myocardial infarction present at inclusion, 41 (44%) were recognized as such by the general practitioner since his inclusion diagnosis was "acute myocardial infarction". Of the 52 cases of "definite" acute myocardial infarction which were not initially recognized by the general practitioner, 31 were diagnosed by him as "imminent myocardial infarction" and the remaining 21 unrecognized cases received some other diagnosis. Of 1,214 patients free of acute myocardial infarction at the moment of

inclusion, 40 (3%) were nevertheless initially diagnosed as "acute myocardial infarction" by the general practitioner (chapter 5).

## 9.2. OTHER RESULTS

Of the 14 general practices who participated, 10 did so during the whole study period. The total population covered by these 10 practices consisted of 11,160 men of at least 20 years of age and 10,926 women of at least 25. The population covered was slightly older than the Dutch population and contained somewhat more men; the differences were small however. The median practice size was 2,277 people in the age-categories considered and its range was 1,516 - 2,736. The total number of inclusions per practice had a median of 6.0% of the practice-size in the age-categories considered and a range of 2.3% - 10.0% (chapter 3).

During a two-month period, a mail inquiry was held in all patients seen for non-administrative reasons in 9 practices. It appeared that of the 98 patients, detected by the inquiry and a subsequent interview with the general practitioner, who should have been included during the period that the investigation was done, 44 (45%) had indeed been included. Of the "missed" patients, 85% had chest pain and an "evident extra-cardiac cause" or "pain unrelated to the heart" was the general practitioner's justification for non-inclusion in most of these patients. Also, in a few instances the general practitioner had "forgotten" to include the patient or the patient had refused cooperation. However, all patients with unstable angina detected by the investigation had indeed been included by the general practitioner. In the remaining 15% of the "missed" patients, symptoms other than chest pain fulfilling the inclusion criteria had been present and inclusion was omitted for unspecified reasons (chapter 3).

For each of the categories of the general practitioner's inclusion diagnosis, i.e. "acute myocardial infarction", "imminent myocardial infarction", "other somatic disease", "psycho-social disorder" and "no provisional diagnosis", the number of inclusions per 1,000 practice-size in the age-categories considered varied considerably between the practices (fig. 8.1.). These differences could not be explained on the basis of differences in age and sex composition of the respective practices.

The presence of chest pain was not a prerequisite for the general practitioner to make a "coronary" initial diagnosis of acute or

imminent myocardial infarction since 8% of the patients diagnosed as having acute myocardial infarction and 4% of those diagnosed as having imminent myocardial infarction did not have chest pain either as primary or as secondary symptom. Of the patients who received initially a "non-coronary" general practitioner's diagnosis, i.e. other somatic disease or psycho-social disorder or no provisional diagnosis, 11% did not have chest pain. In the sub-group of patients having a "non-coronary" general practitioner's diagnosis, a "stabbing" quality of the chest pain was twice as frequent as in patients having a "coronary" general practitioner's diagnosis but within the latter sub-group of patients, the quality of the pain did not discriminate between acute myocardial infarction or imminent myocardial infarction as the general practitioner's diagnosis. In patients who did not have chest pain as the primary symptom and were diagnosed by the general practitioner as having acute myocardial infarction, dyspnea was the most frequent primary symptom (chapter 5).

Abnormal findings at the physical examination were infrequent in patients receiving a "non-coronary" general practitioner's diagnosis and in patients who were diagnosed as having imminent myocardial infarction. On the other hand, abnormal findings were frequent in patients initially diagnosed by the general practitioner as having acute myocardial infarction (chapter 5).

The presence of abnormal findings was associated with a false-positive initial general practitioner's diagnosis in patients who in fact did not have acute myocardial infarction. Similarly, the absence of any abnormal findings was associated with initial non-recognition of this condition by the general practitioner if it was in fact present (chapter 5).

Of the patients who were initially diagnosed by the general practitioner as having acute myocardial infarction, 56% were immediately referred to a hospital. Such a referral was associated with the presence of abnormal findings at the physical examination. Of the patients referred, 61% had in fact acute myocardial infarction. In the non-referred patients this percentage was significantly lower (29%, chapter 5).

In chapter 6, a diagnostic model for acute myocardial infarction is presented which is based on information readily obtainable by a general practitioner. For its development, the I.M.I.R. data-base was used.

Information about the patient's age and sex; the presence of chest pain and its onset, duration and quality; a cold and clammy skin, the heart rate and the blood pressure is integrated into a single score by means of a set of weighing coefficients, which were derived by linear discriminant function analysis. By an application of Bayes' rule, the score value which is obtained may be converted into the probability that acute myocardial infarction is present given the information which is represented in the model. An allocation procedure for the diagnosis "acute myocardial infarction", which is based on the present model, would not surpass the unassisted I.M.I.R. general practitioner in diagnostic accuracy. But the model allows for the quantification of the degree of certainty which can be attached to a diagnosis "acute myocardial infarction" made in primary care. Application of the model is restricted to patients seen by a general practitioner for symptoms which would have led to inclusion into the I.M.I.R. study. A method to eliminate the arithmetic needed in practical application of such models is presented in chapter 8.

Although the I.M.I.R. study was not intended as a registration project, the methods employed allow in principle accurate assessment of incidence rates of symptomatic acute coronary events. In 10 of the participating practices, the incidence rates of acute coronary event, expressed as the annual number of events per 1,000 population, were as follows. For men aged 30-39: 1; 40-49: 5; 50-59: 7; 60-69: 16; 70-79: 17; 80-89: 39. For women under 50, the incidence of acute coronary event was neglegible; for women aged 50-59: 3; 60-69: 6; 70-79: 12 and 80-89: 12. Of all acute coronary events, 34% were fatal within 24 hours (sudden death). Another 10% resulted in death within one month. A positive history of myocardial infarction was present in 27% of the cases of acute coronary event (chapter 7).

# 9. DE I.M.I.R. STUDIE, EEN SAMENVATTING VAN DE RESULTATEN

J. Lubsen en E. van der Does

In de voorafgaande hoofdstukken werden de resultaten van de I.M.I.R. studie gepresenteerd en in detail besproken. Het doel van dit hoofdstuk is om de resultaten samen te vatten. Het is daartoe in twee paragrafen verdeeld. De eerste paragraaf omvat de resultaten die belangrijk worden geacht met betrekking tot de doelstellingen van de studie, zoals beschreven in hoofdstuk 2 (pagina 16). De tweede paragraaf geeft een samenvatting van de resultaten, die niet direkt in verband staan met deze doelstellingen. Deze paragraaf bevat tevens enkele bevindingen, die nog niet eerder zijn gepresenteerd. Het voorliggende hoofdstuk dient als uitgangspunt voor de twee hierop volgende diskussiehoofdstukken.

## 9.1. RESULTATEN IN DIREKTE RELATIE TOT DE DOELSTELLING VAN DE STUDIE

In verhouding tot het voorkomen van acute coronaire episoden, d.w.z. acuut myocard infarct of plotse cardiale dood zag de huisarts veel patiënten met symptomen van mogelijk coronaire origine.

Van de patiënten die voldeden aan de I.M.I.R. toelatingscriteria had 90% pijn op de borst in een of andere vorm, hetzij als hoofdklacht, hetzij als bijklacht. Als hoofdklacht kwam borstpijn het meeste voor (71%), terwijl hartkloppingen met 7% en kortademigheid met 6% daarna de meest voorkomende hoofdklachten waren. Verder waren de klachten van uiteenlopende aard. Van de patiënten met pijn op de borst had de helft "atypische", d.w.z. niet door inspanning geïnduceerde, recent ontstane pijn. Nog eens 23% had acuut verergerde "atypische" pijn en slechts 23% had onstabiele angina pectoris volgens de op de vragenlijst gebaseerde criteria.

Als bijklachten kwamen recent ontstane stemmingsveranderingen, alsmede hartkloppingen, het meeste voor. Gemiddeld waren er drie verschillende klachten per patiënt. Door de deelnemende huisartsen werden gemiddeld 34 mensen per 1.000 praktijkomvang in de leeftijdscategorieën mannen van tenminste 20 en vrouwen van tenminste 25 jaar, tot de studie toegelaten. Dit getal was wat hoger voor mannen dan voor vrouwen en steeg bij toename van de leeftijd. Gedurende de toelatingsperiode tot de studie, werden 43 gevallen van plotse dood geregistreerd bij patiënten die niet eerder tijdens hun leven tot de studie

waren toegelaten. Op het moment van toelating was bij 93 (7%) van 1.344 in leven tot de studie toegelaten patiënten sprake van een "bewezen" acuut myocard infarct, terwijl bij 37 (3%) van de patiënten een "mogelijk" acuut myocard infarct aanwezig bleek. Bij de overige 1.214 patiënten was geen acuut myocard infarct aanwezig op het moment van toelating. Van deze 1.214 personen maakten 83 (7%) tijdens de 10 maanden durende vervolgperiode een acuut coronaire episode door; bij 44 gebeurde dit tijdens de eerste maand. Negentien nieuwe acute coronaire episodes werden als plotse dood geregistreerd; 34 als "bewezen" acuut myocard infarct en de overige 30 als "mogelijk" acuut myocard infarct. Van deze 83 acute coronaire episodes waren 53 (64%) door de huisarts voorspeld aangezien de toelatingsdiagnose in deze gevallen dreigend myocard infarct was. Hier tegenover staat dat het aantal fout-positieve diagnoses dreigend myocard infarct groot was, aangezien 310 (26%) van de 1.214 patiënten zonder aantoonbaar myocard infarct bij toelating tot de studie als dreigend myocard infarct werden aangemerkt. Onstabiele, d.w.z. acuut of recent verergerde, bij inspanning optredende angina pectoris was bij 21% (252/1.214) van de patiënten aanwezig. In deze groep met onstabiele angina pectoris maakte 13% (33/252) binnen 10 maanden een acute coronaire episode door. Patiënten met andere vormen van borstpijn en patiënten met andere klachten dan borstpijn hadden een overeenkomstige prognose, respectievelijk 5% (42/841) en 6% (7/117) maakten binnen 10 maanden een acute coronaire episode door. Multivariate analyse toonde aan dat bij patiënten met mogelijke coronaire klachten die geen aantoonbaar acuut myocard infarct hadden en die hun huisarts consulteerden, de volgende kenmerken onafhankelijk geassocieerd waren met een op korte termijn optredende acute coronaire episode: leeftijd, mannelijk geslacht, Q- en T-golf afwijkingen in het electrocardiogram, onstabiele angina pectoris, hypertensie, diabetes en vochtige rhonchi. Op basis van een samengestelde score waarin deze kenmerken vertegenwoordigd waren, kon een subgroep van patiënten worden geïdentificeerd, waarvan 31% binnen 10 maanden een acute coronaire episode kreeg (hoofdstuk 4). Van de 93 patiënten bij wie een "bewezen" acuut myocard infarct aanwezig was op het moment van toelating, werden 41 (44%) als zodanig door de huisarts herkend, aangezien zijn toelatingsdiagnose acuut myocard infarct was. Van de overige 52 gevallen van "bewezen" acuut myocard infarct die door de huisarts aanvankelijk niet werden herkend, werden 31 door hem

als een dreigend myocard infarct aangeduid en de overige 21 niet herkende gevallen kregen verschillende andere diagnoses. Van de 1.214 patiënten die op het moment van toelating geen acuut myocard infarct hadden, werd desondanks bij 40 mensen (3%) door de huisarts aanvankelijk de diagnose acuut myocard infarct wèl gesteld (hoofdstuk 5).

## 9.2. OVERIGE RESULTATEN

Van de 14 deelnemende huisartspraktijken namen er 10 tijdens de gehele studieperiode deel. Deze 10 praktijken omvatten in totaal 11.160 mannen van tenminste 20 jaar en 10.926 vrouwen van tenminste 25 jaar. De praktijkpopulatie was iets ouder dan de Nederlandse bevolking en omvatte iets meer mannen; de verschillen waren echter klein. De mediaan van de praktijkgrootte lag bij 2.277 mensen in de betrokken leeftijdscategorieën met als uitersten respectievelijk 1.516 en 2.736 personen. Het totaal aantal tot de studie toegelaten personen per praktijk had een mediaan van 6.0% van de praktijkgrootte in de betrokken leeftijdscategorieën met als uitersten respectievelijk 2.3% en 10.0% (hoofdstuk 3). Gedurende twee maanden werd een schriftelijke enquête gehouden in 9 praktijken onder alle patiënten die om niet administratieve redenen door de arts waren gezien. Het bleek dat van de 98 patiënten die op grond van de enquête en een daarop volgend vraaggesprek met de huisarts tijdens de onderzoekperiode tot de studie toegelaten hadden moeten worden, er 44 (45%) inderdaad waren toegelaten. Van de "gemiste" patiënten had 85% pijn op borst en was, naar de mening van de huisarts, een "duidelijke extra-cardiale oorzaak" of een "pijn van niet-cardiale oorsprong" de reden geweest om deze patiënten niet toe te laten tot de studie. Ook had de huisarts in enkele gevallen "vergeten" de patiënt toe te laten of had de patiënt medewerking geweigerd. Echter waren alle patiënten met onstabiele angina pectoris, door dit onderzoek ontdekt, wel door de huisarts toegelaten. Bij de overige 15% van de "gemiste" patiënten waren geen borstklachten, maar andere klachten die aan de toelatingscriteria voldeden, aanwezig. Toelating tot de studie werd nagelaten om niet nader omschreven redenen (hoofdstuk 3). In elk van de 5 diagnostische categorieën, die door de huisarts gebruikt konden worden, d.w.z. acuut myocard infarct, dreigend myocard infarct, andere somatische aandoeningen, psycho-sociale dysfunktie en geen voorlopige diagnose waren er aanzienlijke verschillen tussen de praktijken wat betreft het aantal tot de studie

toegelaten patiënten in de betrokken leeftijdscategorieën (fig. 8.1.). Deze verschillen konden niet worden verklaard op basis van de samenstelling van de respectievelijke praktijken wat betreft leeftijd en geslacht. De aanwezigheid van borstpijn was geen vereiste voor de huisarts om in eerste instantie een "coronaire" diagnose (acuut of dreigend myocard infarct) te stellen, aangezien 8% van de patiënten, bij wie een acuut myocard infarct was gediagnostiseerd en 4% bij wie een dreigend myocard infarct was gediagnostiseerd geen pijn op de borst, noch als hoofd-, noch als bijklacht hadden. Van de patiënten die van de huisarts een "niet coronaire" diagnose (andere somatische aandoening, psycho-sociale aandoening of geen voorlopige diagnose) kregen had 11% geen pijn op de borst. In de groep met een "niet coronaire" diagnose, kwam een stekend karakter van de borstpijn tweemaal zo vaak voor als in de groep met "coronaire" diagnose. In deze laatste groep was er geen samenhang tussen het karakter van de pijn en de huisartsdiagnose acuut myocard infarct of dreigend myocard infarct. Bij patiënten die geen pijn op de borst als hoofdklacht hadden en bij wie door de huisarts de diagnose acuut myocard infarct werd gesteld, was kortademigheid de meest voorkomende hoofdklacht (hoofdstuk 5). Abnormale bevindingen bij lichamelijk onderzoek kwamen weinig voor bij zowel patiënten die een "niet coronaire" huisarts-diagnose kregen als bij degenen die als dreigend myocard infarct werden aangeduid. Anderzijds kwamen afwijkingen vaak voor bij patiënten bij wie de huisarts in eerste instantie een acuut myocard infarct had gediagnostiseerd. De aanwezigheid van abnormale bevindingen was geassocïeerd met een aanvankelijk fout-positieve diagnose acuut myocard infarct van de huisarts. Evenzo was de afwezigheid van abnormale bevindingen geassocieerd met het aanvankelijk niet herkennen van een aanwezig acuut myocard infarct (hoofdstuk 5). Van de patiënten, bij wie de huisarts in eerste instantie de diagnose acuut myocard infarct stelde, werd 56% direkt naar een ziekenhuis verwezen. Onder deze patiënten waren er relatief veel met abnormale bevindingen bij lichamelijk onderzoek. Van deze 56% direkt verwezen patiënten had 61% in werkelijkheid een acuut myocard infarct. Bij de niet direkt verwezen patiënten was het percentage acute myocard infarcten, significant lager: 29% (hoofdstuk 5).

In hoofdstuk 6 wordt een diagnostisch model voor een acuut myocard infarct beschreven, dat is gebaseerd op gegevens die door een huisarts

gemakkelijk zijn te verkrijgen. Voor de ontwikkeling hiervan werd gebruik gemaakt van gegevens, welke door de I.M.I.R. studie zijn verzameld. Gegevens over leeftijd en geslacht van de patiënt, de aanwezigheid van pijn op de borst, de tijdsduur sinds het begin van de pijn, de duur van de aanval, het karakter ervan, de aanwezigheid van een koude klamme huid, de hartfrequentie en de bloeddruk werden met behulp van Linear Discriminant Functie-analyse bepaalde gewichten toegekend en geïntegreerd tot een enkelvoudige score. Door middel van het toepassen van de regel van Bayes, kan de verkregen waarde van de score worden vertaald in de waarschijnlijkheid dat een acuut myocard infarct aanwezig is op grond van de gegevens die in het model zijn begrepen. Het gebruik van dit model in een procedure voor het toekennen van de diagnose acuut myocard infarct zal geen grotere diagnostische nauwkeurigheid opleveren dan bereikt door de "I.M.I.R.-huisarten" zonder hulp van electrocardiografie en serumenzymbepalingen. Wel verschaft het model een quantificering van de mate van waarschijnlijkheid waarmee de diagnose acuut myocard infarct kan worden gesteld tijdens het eerste arts-patiënt kontakt. Toepassing van het model moet beperkt blijven tot die patiënten, die door hun huisarts worden gezien in verband met klachten die tot toelating in de I.M.I.R. studie zouden hebben geleid. Een methode om het voor praktische toepassing noodzakelijke rekenwerk te elimineren, wordt beschreven in hoofdstuk 8. Hoewel de I.M.I.R. studie niet als registratie projekt was bedoeld, maken de toegepaste methoden een nauwkeurige bepaling van de incidentie van acute coronaire episodes in principe mogelijk.

In 10 van de deelnemende praktijken was de incidentie van acute coronaire episodes uitgedrukt in het aantal jaarlijks voorkomende episodes per 1.000 ingeschrevenen als volgt: mannen van 30-39: 1; 40-49: 5; 50-59: 7; 60-69: 16; 70-79: 17; 80-89: 39. Bij vrouwen jonger dan 50 jaar was de incidentie van acute coronaire episodes te verwaarlozen. Van 50-59 was deze: 3; 60-69: 6; 70-79: 12; 80-89: 12. Van alle acute coronaire episodes verliep 35% dodelijk binnen 24 uur (plotse dood), nog eens 10% verliep dodelijk binnen 1 maand. In 25% van de gevallen van acute coronaire episodes werd al eerder van een myocard infarct in de ziektegeschiedenis melding gemaakt. (hoofdstuk 7).

# 10. GENERAL DISCUSSION: THE GENERAL PRACTITIONER'S PERSPECTIVE

E. van der Does

It is one of the objectives of the present chapter to reflect upon the results of the I.M.I.R. study from the general practitioner's point of view. Also, the I.M.I.R. study and its results are to be placed within the context of other cardiovascular research thought to be relevant. Furthermore, some practical aspects are discussed of undertaking a study like I.M.I.R., which required, among others, the active cooperation of already heavily burdened general practitioners (G.P.s) and their adherence to a study protocol. Finally, some recommendations are made which are based on the findings of, and the experience gained from, I.M.I.R. Within the structure of this thesis, some repitition of material covered elsewhere was unavoidable.

## 10.1. HAVE THE OBJECTIVES BEEN MET?

### 10.1.1. THE MAIN OBJECTIVE

In chapter 2 it was stated that (page 16 ): "The main goal was the recognition of those patients who were at high risk to sustain an acute coronary event (A.C.E.) in the near future in a population which consulted a general practitioner for a set of specified symptoms. Such recognition was to be based on information on history, symptoms and signs of the patient obtained by the G.P. and on an expanded history, electrocardiographic and biochemical findings, gathered by technicians.

There is no final answer to the question whether the I.M.I.R. study was successful in achieving its main goal. Partly, this is due to the presence in the description of the main goal of some undefined terms. In particular, it was left undefined what risk was considered "high" or what future "near" and the question asked can not be answered without attaching a meaning to these terms. Their meaning depends on one's perception of the purpose of the recognition of "high risk patients". For instance, one way of perceiving that purpose could be the provision of indications for hospitalization of individuals in whom the presence of "high risk" is established. The impending event may then actually take place in an environment where complications such as ventricular fibrillation or shock can be treated effectively when they occur. However, to justify such a policy

in patients so "recognized" and hospitalized as a consequence thereof, the risk of A.C.E. over a short period of time would obviously have to be very high since otherwise the costs involved would surpass the benefits to be expected. On the other hand, the purpose of the recognition could be to set indications for further diagnostic investigation and/or the initiation of some treatment which aims at lowering the risk or at diminishing the impact of the event if it occurs. Although by no means exclusive alternatives, these two ways of perceiving the purpose of the recognition of high risk patients and thereby of the meaning of the undefined terms in the redaction of the main goal of the I.M.I.R. study, are particularly relevant to the G.P. For, in general, he is the one who is consulted first when symptoms arise or increase and he has to decide which actions have to be taken. And in deciding on actions, he basically has but three options: immediate referral to a hospital, referral to a consulting physician or to an out-patient clinic and treating the patient himself. Therefore, the question whether the I.M.I.R. study has achieved the main goal as stated will be discussed against the background of the above possible perceptions of the purpose of "the recognition of those patients who were at high risk to sustain an A.C.E. in the near future".

In the I.M.I.R. study, a patient was included if the G.P. was consulted at the initiative of the patient for symptoms which were recognized by the G.P. as fulfilling the inclusion criteria. Among the patients included by this mechanism, a number of cases of "definite" or "possible" acute myocardial infarction (A.M.I.) were found to be present on the basis of electrocardiograms (E.C.G.s) and enzyme studies. But after exclusions of such cases, a group of symptomatic patients free of A.M.I. remained who had a 10-month A.C.E.-rate of 7% (83/1,214, table 4.1.). Such a rate is considerably higher than the rate which would obtain among the general population. In a sense therefore, the application of the inclusion criteria by the I.M.I.R. G.P.s together with subsequent exclusion of A.M.I. in itself implied the "recognition" of patients at an elevated risk of sustaining an A.C.E. However, the description of the type of patient which was in fact "recognized" in this way is quite unspecific. The majority, 90%, had chest pain of some kind but otherwise the symptomatology of included patients was highly variable, as was described in chapter 3. Furthermore, if no further separation according to the magnitude of the risk were possible in the group of patients so recognized, the

practical applicability of such recognition would be limited and certainly the admission to a hospital of all these patients would, to say the least, be impractical.

The question of the possibility to predict an early A.C.E. in patients who were included in the I.M.I.R. study and consequently shown to be free of A.M.I. at the moment of inclusion, was extensively discussed in chapter 4. Only the salient points are reiterated here. At inclusion of a patient into the study, the G.P. had to indicate whether the patient had, in his opinion, "imminent myocardial infarction" (I.M.I.), or in other words, was at "high risk" to sustain an A.C.E. in the "near future". As pointed out before, the protocol did not provide clarification of what risk was to be considered "high" and what future "near"; nor were criteria or guidelines given for making the diagnosis "I.M.I.". Partly for these reasons, it is impossible to describe exactly what a case of "I.M.I." constituted in the minds of the participating G.P.s. A profile of symptoms and signs found in patients diagnosed as "I.M.I." may be found in chapter 5 but we were unable to deduce from the data a posteriori a syndrome of symptoms and signs which characterized this diagnostic category. Whatever the entity "I.M.I." as diagnosed by the I.M.I.R.-G.P. represented, the G.P. was, on the basis of this diagnosis, to a certain extent able to distinguish between "high" and "low" risk patients. Patients who were free of A.M.I. at inclusion and were diagnosed as "I.M.I." had an 8% (26/310) one-month and a 17% (53/310) 10-month A.C.E.-risk. This last figure is about six times higher than the risk of patients diagnosed either as having "other somatic disease" (O.S.D.), "psycho-social disorder" (P.S.D.) or "no provisional diagnosis" (N.P.D.), who had a 3% (23/864) 10-month A.C.E.-risk (table 4.2.). Most likely, an 8% one-month A.C.E.-risk, although considerable, is not high enough to warrant the hospitalization of all patients diagnosed by a G.P. as having "I.M.I.". On the other hand, the risk of patients so diagnosed is certainly high enough to warrant further diagnostic investigation and possible therapeutic intervention. Even-so, the practical value of these findings is limited since we do not know how, and why, "I.M.I." was diagnosed in the patients studied. The I.M.I.R.-G.P.s were not really representative of Dutch G.P.s in general since they had shown a special interest in this type of problem. Other G.P.s, when asked to diagnose "I.M.I." without any further guidelines and without a study which imposes a certain

behaviour, might do either better or worse.

Unstable angina has received much attention as a prodromal symptom of A.C.E.[1] In the present study, patients free of A.M.I. who had unstable angina according to our criteria (see chapter 4), had an 8% (20/252) one-month and a 13% (33/252) 10-month A.C.E.-risk. For all other patients taken together, the 10-month A.C.E.-risk was 5% (49/958) or only about one-third of the risk associated with the presence of unstable angina (table 4.3.). Consequently, the presence of unstable angina identified a sub-group which was indeed at elevated risk, but less so than the group diagnosed by the G.P. as having "I.M.I.". However, again, the mere presence of unstable angina in itself does not constitute such high risk that medical intervention should be guided by an inordinate fear for an immediate life-threatening situation.

In the context of unstable angina and its implications for A.C.E.-risk, one finding of the I.M.I.R. study seems of particular practical interest to G.P.s. Of 43 patients free of A.M.I. who sustained an A.C.E. during one month of follow-up, less than half, 20, had unstable angina at inclusion (table 4.3.). As was pointed out in chapter 4, this finding together with the fact that a number of A.C.E.s were already present at inclusion, indicated that patients who eventually sustain an A.C.E. are infrequently seen for unstable angina shortly before the event takes place. Therefore, the absence of unstable angina can not be taken by the G.P. as necessarily meaning that no short-term risk of A.C.E. exists. In dealing with the problem of impending coronary events, the G.P.can not confine his attention only to patients who present to him with unstable angina.

In chapter 4, the estimation of A.C.E.-risk on the basis of a composite risk-score was discussed in detail and only a brief comment is made here. First of all, it is underlined again that its application is limited to patients seen in general practice for symptoms which would have led to inclusion into the I.M.I.R. study and in whom the presence of A.M.I. was excluded. But when these two conditions are met, the procedure yields a risk-score, which is based on well defined patient-information and which relates to the patient's risk of sustaining an A.C.E. in the coming 10 months. Consequently then, the risk-score does provide, with limitations, for the recognition in general practice of the patient who is at high risk to sustain an A.C.E. in the near future, as was the main goal of the I.M.I.R. study.

The limitations are that the risk-score procedure at best identifies patients who have a 31% estimated risk to sustain an A.C.E. in a future of 10 months. Although high, such risk does not seem to justify drastic action such as, for instance, hospitalization as a precautionary measure. On the other hand, such risk represents a considerable threat which justify optimal diagnostic procedures and treatment. The risk-score procedure does not just identify patients at an arbitrary "high" risk on the basis of a set of defined criteria. Rather, it provides also for risk-estimates between the extremes of 31% and near zero, leaving the user to decide whether the risk-estimate obtained in a particular instance justifies the anticipated action. The score-value does not predict when the event, if it occurs, is going to take place during the 10-month period for which the risk-estimate applied. For, in the present study, high score-values were, although associated with high risk, not in particular associated with events which occurred, for instance, early during follow-up.

In conclusion, then, we are of the opinion that the main goal of the I.M.I.R. study was met to a large extent. First of all, we have shown in a prospective study that a number of patients who are eventually to sustain an A.C.E. do indeed consult a G.P. comparatively shortly before the event occurs for symptoms of potential coronary origin. But the patients who are to sustain an A.C.E. soon represent only a minor fraction of all patients who consult a G.P. for similar symptoms. Their "classical" identifiers, such as a G.P.-diagnosis "I.M.I." or the presence of unstable angina, have only limited value in their recognition. Although the analysis did not yield a syndrome of symptoms and signs which is easily recognized by the G.P. and is specific for an impending coronary event, the risk-score procedure does provide the G.P. with a means of estimating on the basis of the history and an E.C.G. the risk that an A.C.E. will occur in the next 10 months in a patient who consults him for potentially coronary-type symptoms and in whom an A.M.I. was excluded. No predictors of A.C.E. were incorporated in the risk-score procedure which have not been implicated in other studies but, to our knowledge, it is the first time that a composite risk-score is presented for the recognition of high-risk patients in the community by general practitioners. However, the procedure presupposes the availability of an E.C.G.

10.1.2. THE SECONDARY OBJECTIVE

A patient who is eligible for inclusion into the I.M.I.R. study because he consulted the G.P. for, say, recent chest pain may thereby at times present a diagnostic problem to the G.P., particularly so with respect to the possibility that an A.M.I. is present. Because of the fact that E.C.G. and enzyme studies were done directly when the patient was included into the study, a unique diagnostic service was made available to participating G.P.s since abnormal findings, when present, were immediately conveyed to him. The service was available also outside normal working hours and patients who were considered unfit to come to the I.M.I.R. center were visited by a technician at their homes.

In chapter 2 a second goal was described as "the evaluation of the diagnostic support provided by the program to the participating G.P." (see page 16 ). How that evaluation was to take place was left unclear. However, some observations on the apparent value of the support can be made. In our opinion, the most important one was the unexpected finding that the accuracy of the unassisted G.P.-diagnosis "A.M.I." was no better than it appeared to be from our data. As was presented in chapter 5, less than half, 44%, of the cases of "definite A.M.I." present at inclusion were in fact recognized as such by the G.P. at the moment when he made his inclusion examination. The majority of the unrecognized cases were diagnosed as "I.M.I.", which indicates that at least the cardiac origin of the problem was recognized. But in 21 of the 93 cases, the G.P. made some other diagnosis than either "M.I." or "I.M.I.". For instance,"psycho-social disorder" was the diagnosis made in 5 cases of "definite A.M.I.". On the other hand, in 40 patients the diagnosis "A.M.I." of the G.P. was not supported by the results of E.C.G. and enzyme studies (table 5.1.). The fact that these figures represent a low diagnostic accuracy should by no means be taken to indicate that the diagnostic skills of the participating G.P.s were inadequate. On the contrary, as was discussed in chapter 5, there is every reason to believe that the low diagnostic accuracy is simply a reflection of the fact that the symptoms and signs which are caused by A.M.I. may be very unspecific, rendering it difficult to diagnose the presence of A.M.I. on the basis of symptoms and signs alone, as is customarily expected from the G.P. But these figures do form the basis for our conjecture that the diagnostic service provided by I.M.I.R. served a very useful purpose.

The availability of such service most likely does not affect the policy of the G.P. with respect to hospitalization of the "typical" case of A.M.I. But for patients kept at home, a diagnostic service will enable the G.P. to diagnose A.M.I. with accuracy, which will help him to give the proper treatment if necessary or to reassure the patient and himself if the presence of A.M.I. is excluded. Even in this last instance, the effort made by the service is by no means wasted. The possibility to reassure is in itself important enough and, also, the E.C.G. recording which was made may contain important prognostic information which could bear on the management of the patient.

To illustrate the foregoing, a case-history taken from the I.M.I.R. patient files is described here. It is the case of Mr. A., a 55-year old crane-driver. He consulted the G.P. in the morning during the normal surgery hours because he had experienced the evening before an episode of chest discomfort while watching television. He described the discomfort as "a heavy pressure" and indicated its location as behind the mid and lower sternum. He felt quite sick, was sweating and a little bit dizzy and staggered to the balcony to get some fresh air, where his wife had wetted his pulses and forehead. He recovered quickly and had therefore seen no reason to call a doctor; he slept well afterwards and went off to work as usual the next morning. But on his way he felt some pain again and therefore decided to see the G.P. first "just to make sure". Sitting in the surgery, Mr. A. appears in good health and is ascribing the pain of yesterday evening to the duodenal ulcer which was discovered five years ago. The physical examination revealed no abnormalities except a blood pressure of 150 mmHg systolic and 100 mmHg diastolic. Because of the nature of his complaints, there was no doubt in the G.P.'s mind that Mr. A. was to be included into the I.M.I.R. study. But, the inclusion diagnosis posed a problem. The present symptoms could be caused either by the duodenal ulcer or by an A.M.I.; also, a myocardial infarction could be impending. The last possibility was, for the time being, considered by the G.P. as the most likely one. Mr. A. went to the I.M.I.R. center immediately after he was seen by the G.P. An E.C.G. was recorded there and a blood sample taken. No elevated serum enzyme levels were present but the E.C.G. showed inverted T-waves. These results reassured the G.P. with respect to his fears about the possible presence of A.M.I. but the T-wave inversion was

nevertheless taken by him as indicating that Mr. A.'s heart was not in good condition. He saw Mr. A. back three days later and explained the situation. Since the bloodpressure was still high, antihypertensive treatment was begun. The clinical course of Mr. A. during follow-up was uneventful; no A.C.E. developed although he had an occasional attack of angina.

Three comments might be added to the case-history above. First of all, Mr. A. did indeed pose a difficult diagnostic problem to the G.P. Although he thought it very well possible that the patient had A.M.I. he decided not to send him to hospital because Mr. A. appeared to be in good clinical condition, the episode of pain had taken place already hours ago and he did not want to upset the patient. Without the diagnostic service inherent in his participation in the I.M.I.R. study, he would however probably have referred Mr. A. to a cardiologist, who could not have seen him immediately given the present shortage of specialists. The diagnostic service made such a referral at this point in time unnecessary and the results of the diagnostic investigations were known to the G.P. the same day. Second, this case-history underlines in our opinion that diagnostic service consisting of only the recording and reading of an E.C.G. does not suffice. For, the presence of T-wave inversions and the absence of an injury current is not incompatible with the presence of A.M.I. The in this case normal results of enzyme level determinations were therefore an essential element to the G.P. in deciding on his actions. Third, it is of interest to note here that Mr. A. belonged to a high-risk group on the basis of the composite risk-score. On the basis of the G.P.'s findings and the results of the E.C.G., that score may be determined by using the weights given in table 4.4. Mr. A.'s age of 55 years contributes 55 x 0.03 or 1.65, male sex adds 1.1, T-wave inversion 3.6, unstable angina (Mr. A. felt pain when he came to the G.P.'s surgery which was apparently induced by exercise) 1.0 and hypertension 0.5, to yield a total score of 7.85, which puts Mr. A. in the 31% category of 10-month A.C.E.-risk according to fig. 4.1. Of course, the G.P. was unable to make such a calculation at the moment he saw Mr. A. But even if the procedure itself had at that time been known to him, it could not have been used without the E.C.G. recording which was provided by the diagnostic service. Although his risk was high according to that procedure, Mr. A. did not sustain an A.C.E. during follow-up.

This however is in the nature of the concept of risk; a 10-month A.C.E.-risk of 31% only conveys that about one in three patients having such a risk will actually sustain an A.C.E, but not in whom of the three patients the event is going to take place. Nevertheless, the possibility to determine such risks could prove of value and provide another argument to justify the institution of diagnostic service.

Apart from the diagnostic aspect reflected upon above, only one other aspect of the service inherent in the I.M.I.R. study was evaluated, namely the effect on the number of referrals to consulting physicians. The assumption was put forward that the number of referrals made while the I.M.I.R. study was in progress would be lower than usual. To test this hypothesis, we compared data on referrals made by participating G.P.'s during the period that inclusion into the study was open with similar data for the same calender period just before the study was begun. No decrease in the total number of referrals occurred during the study and, in fact, the number of referrals made to a cardiologist or internist increased slightly during that period. No attempt was made to ascertain the reason for this finding but we speculate that it was due to increased attention on cardiovascular pathology of the participating G.P.s, who were of the opinion that the referrals made were easier to justify in the presence of the diagnostic service.

In conclusion, with respect to the secondary objective, two aspects of the diagnostic service inherent in the I.M.I.R. study were evaluated. First, the limited diagnostic accuracy attained by the participating G.P.s suggested that a diagnostic service, which consists of the recording and the reading of an E.C.G. and of taking a blood sample for enzyme studies, serves a useful purpose since, without such means at his disposal, the G.P. seems to be unable to diagnose or to exclude with confidence the presence of A.M.I. in patients kept at home. Second, a slight increase in the number of referrals to cardiologists or internists could result from such a service. Other aspects, such as the effect on the patient-management other than referral and on the quality of medical care, were beyond evaluation with the means at our disposal. It would be no easy task to evaluate such aspects. Subjectively however, the I.M.I.R.-G.P.s not only saw substantial utility in the service but also considered it an incentive to take on the burden inherent in their participation.

## 10.2. I.M.I.R. AS RELATED TO SIMILAR INVESTIGATIONS

As a community-based follow-up study of patients seen by a G.P. for a wide range of symptoms, the design of the I.M.I.R. study seems to have been different from most other investigations and not many direct comparisons can be made. As explained in chapter 4, the characteristics which were found of importance in predicting early A.C.E.s in the future have been found in numerous other studies. Of these, especially "unstable angina" has been studied extensively. Most studies however were concerned with hospitalized patients and did not attempt to investigate the problem at the community level. Cairns et al.[1] have recently reviewed the literature. These authors observed that "a variety of terms has been used in an attempt to describe this group of manifestations" and that "the reports concerning these clinical states are difficult to evaluate and compare because of the inconsistent nomenclature and patient selection". Conti et al.[2] have advocated the use of the term "unstable angina" to describe the entity which Cairns et al.[1] call "the spectrum of symptomatic manifestations of ischaemic heart disease" which "lies between the well defined diagnosis of stable angina pectoris on the one hand and acute myocardial infarction on the other". Three groups are distinguished by Conti et al.[2] (1) Angina on effort of recent onset (past 4 weeks). (2) Angina on effort with a changing pattern, i.e. increasing frequency and/or severity of pre-existing stable angina. (3) Angina at rest, i.e. no stress is required to provoke an episode of ischaemic cardiac pain. Another frequently used term is "intermediate coronary syndrome" (I.C.S.) or "pre-infarction syndrome". On the basis of Vakil's description[3], this syndrome represents a subgroup of group 3 unstable angina patients according to the classification of Conti et al.[2] and is characterised by "prolonged chest pain of cardiac origin", with a "character between that of angina pectoris and acute myocardial infarction", "usually arising at rest", "almost invariably accompanied by electrocardiographic manifestations of myocardial ischaemia" and "terminating either in recovery or an attack of acute myocardial infarction". From these descriptions of "unstable angina" and of "I.C.S.", it seems no surprise that highly different short-term A.C.E.-rates have been reported, depending on the (sub-)groups of patients studied and possibly also on such factors as the treatment given. For instance, Vakil[4] observed a 41%

(146/360) three-month A.C.E.-rate in patients admitted to a hospital because of I.C.S. Lie et al.[5] published a follow-up study of 100 hospitalized patients with unstable angina according to the description of Conti et al.[2] Since only 9 of these patients had a normal E.C.G. at admission, these patients were probably for the greater part suffering from I.C.S. according to Vakil's description.[3] However, Lie et al.[5] observed a 16% (16/100) one-month rate of A.C.E. although the longer-term prognosis was good, which possibly suggests that these patients had a better prognosis than those studied by Vakil.[4] Unfortunately, the difference in length of follow-up precludes a direct comparison. From the only other community study which seems to have been done apart from I.M.I.R., Duncan et al.[6] reported a similar A.C.E.-rate as Lie et al.[5], although for a longer follow-up period. In that study, which was carried out in Edinburgh, Scotland, males under 70 years suffering from unstable angina were followed for six months; a 16% (39/251) A.C.E.-rate was reported for that period.[6] The Edinburgh study[6] was concerned with both "new" and "worsening" angina. The diagnosis was made by a cardiologist; 171 of the 251 patients had S.-T. depression or T-wave changes on the E.C.G. and only 28 patients had a completely normal E.C.G. Eighty-seven patients were admitted to hospital but their prognosis did not differ significantly from the non-hospitalized patients; nor did the prognosis depend significantly on whether the angina was "new" or "worsening". One may ask why the A.C.E.-rate reported by Duncan et al.[6] should be so much lower than the one reported by Vakil[4]; undoubtedly, the major factor must have been the way in which the patients were selected. In the I.M.I.R. study, an even lower A.C.E.-rate was observed for patients with either "new" or "worsening" angina than in the Edinburgh study.[6] In I.M.I.R., these patients had a 13% (33/252, table 4.3.) 10-month A.C.E.-rate. In comparing these two studies, it must however be remembered that I.M.I.R. studied also women, who have a lower A.C.E.-risk, and that in I.M.I.R. the diagnosis "unstable angina" was based on a questionnaire rather than on the physician's impression, as was the case in the Edinburgh study.[6] On the other hand, for I.M.I.R. patients who had a composite risk score in its highest decile, a 31% 10-month A.C.E.-rate was observed (table 4.4. and fig. 4.1.), which is more in the neighbourhood of,but still lower than, the rate reported by Vakil.[4]

Although the results mentioned here seem at first sight conflicting, they reflect different aspects from the same coin. One conclusion is evident: patients suffering from unstable angina are a heterogeneous group in reference to their prognosis, which is worse when more abnormalities are present and/or when the symptoms are more severe.

Apart from information on the prognosis of unstable angina, I.M.I.R. supplied also information on other aspects of the prodromata of A.C.E.s. Patients who were sustaining an A.C.E. at the moment of inclusion did not have prodromal symptoms of such nature or severity that they consulted a G.P. and were consequently included into the study before the event occurred. Since 77% of these patients did not have a history of a previous M.I., it is evident that many patients who sustain an A.C.E. do not have prodromal symptoms for which a physician is consulted or even a history of a previous event. For non-anginal new or worsening symptoms without apparent extra-cardiac cause, there was a 5% (49/958, table 4.3.) 10-month A.C.E.-rate while A.C.E.s were only infrequently heralded by typical unstable angina present at the moment of inclusion (chapter 4). Taking the I.M.I.R. findings together with the results mentioned above[4, 5, 6], the following picture of the prodromal clinical manifestations of A.C.E. is tentatively put forward (fig. 10.1.). In the disease process which leads from health to an acute coronary event, the following major clinical manifestations may be distinguished: non-anginal unstable symptoms without apparent extra-cardiac cause, stable angina, unstable angina and intermediate coronary syndrome. While this suggests a gradual progressive series of events, in the disease process itself there is no fixed sequence; the symptoms and all other characteristics may vary, thereby leading at times to a highly variable and unpredictable classification of the patient. Also, from the state of perfect health or from one of the intermediate states, a patient may sustain an A.C.E. without necessarily having shown any other manifestation first. Non-anginal unstable symptoms without apparent extra-cardiac cause have in this context a low short-term A.C.E.-risk (I.M.I.R.: 5% in 10 months), which risk increases in patients with unstable angina (I.M.I.R.: 13% in 10 months; Duncan et al.[6]: 16% in 6 months) and is still higher when the patient is suffering from I.C.S. (I.M.I.R.: 31% in 10 months for patients in the highest decile of the composite risk score; Vakil[4]: 41% in 3 months; Lie et al.[5]:

16% in 1 month). The risk of stable angina is probably of the same order as the risk of unstable non-anginal symptoms without apparent extra-cardiac cause; from the Framingham study, Kannel et al.[7] have reported that 25% of men with "angina pectoris" sustain an A.C.E. within 5 years after onset of symptoms. This would represent approximately a 6% one-year A.C.E.-rate†). The risk reported for women was half this. In fig. 10.1., the densities of the arrows indicate the magnitudes of these risks.

It is to be emphasized that the clinical manifestations of fig. 10.1. represent in part ill-defined clinical syndromes. In daily practice, it will often be difficult to classify a patient accurately on the basis of the symptoms and other characteristics. The practical value of such classification as a means of determining risk in the individual patient is therefore limited. A more desirable approach would therefore be the use of appropriate prognostic functions. From the Framingham study, such a function was derived for application to apparently healthy individuals.[8] I.M.I.R. provided one for use in patients seen by a G.P. for symptoms which may presage an early future A.C.E. (chapter 4); the practical implications for the G.P. are discussed in paragraph 10.4.

Another interesting finding from the I.M.I.R. study was the unexpectedly low diagnostic accuracy of the G.P. in recognizing A.M.I. These findings are difficult to compare with those of other studies because of the way in which patients were selected. For patients hospitalized because the G.P. suspected the presence of A.M.I., Schilperoort[9] reported that this condition was indeed present in 85% (55/65) of such patients. In I.M.I.R., this percentage was 61% (30/49, see paragraph 5.3.1.). There is no apparent explanation for the difference between these two findings, both are based on small numbers of patients however. With respect to the diagnostic accuracy attained by G.P.s in non-hospitalized patients, no other information than the one supplied by I.M.I.R. seems to be available.

## 10.3. PRACTICAL ASPECTS OF THE G.P.'s INVOLVEMENT

To many people "time", and lack of it, is one of the important life determining factors. "Whole person" medical care in an average general practice of 2,500-3,000 people is a demanding task which leaves little time and opportunity for research activities.

† $(1 - 0.25)^{1/5} = 0.94$

It took the G.P. about 20 minutes to complete the I.M.I.R. inclusion procedure. Two or more patients subsequently presenting themselves during surgery hours with "I.M.I.R. symptoms" could take a considerable amount of time and cause a major deviation from the appointment schedule, thereby burdening both the doctor and his other patients. This would be felt especially if the patient's symptoms, although meeting the inclusion criteria, were thought to be not related to the heart. In such an instance, the G.P. might consider the extra work "useless" and omit inclusion. Nervousness of the patient, who might be unduly alarmed by the I.M.I.R. investigations, could then contribute to the G.P.'s decision not to include.

The G.P. got something in return for his efforts however. Inherent in his participation was the diagnostic service providing the doctor within a matter of hours with an E.C.G. read by a cardiologist and, generally the next day, with the results of enzyme tests. This allowed the G.P. to reconsider his provisional diagnosis and management in 52 initially unrecognized cases of A.M.I. and in 40 patients who were diagnosed initially as having this condition but in whom this diagnosis was not confirmed by the diagnostic investigations provided by the service (chapter 5). Thereby, if this was not already known to him, he must have become aware of the fact that the "classical" clinical picture is not always present in patients with A.M.I. and that diagnosing this condition can therefore be difficult. Since the G.P. had to fill out on the inclusion form his provisional diagnosis and also whether he had judged immediate hospitalization necessary or not, another consequence of his participation was that he put his diagnostic power and important aspects of his management in discussion. The front page testifies to this; such a "picture of doubt" was no rare appearance on the I.M.I.R. forms and shows the difficulties at times encountered in making a diagnosis.

Apart from his willingness to put his diagnostic power under investigation, the I.M.I.R.-G.P. also had to submit during a certain period to the special investigation of his compliance to the rules of the study itself. This was the implication of the inquiry into the reasons for the contact held in a probability sample of all patient-doctor contacts (see chapter 3). That so many aspects of his behaviour came under such overt scrutiny is, as far as we know, unique for I.M.I.R. A certain strain on the participating G.P.s must have been

the result and behaviour must have been influenced by it, although we do not know to what extent. But I.M.I.R. certainly did not leave its objects of inquiry, i.e. the G.P.s, unscathed.

More efforts were required from the G.P. than those connected with the inclusion procedure. The mail-inquiry form used in the special investigation mentioned above was kept as short and simple as possible. Nevertheless, many patients phoned their doctor to ask what the meaning was and whether is was proper for them to take part in such an inquiry. This again took time, as did the completion of the questionnaires received by the G.P. for every patient who had completed follow-up. And then there were monthly meetings to attend.

Many G.P.s are not familiar with participating in research projects. A study should be carefully introduced to them and its purpose made clear so that they understand the "what" and the "why". The amount of extra work required from the G.P. should be kept as low and as simple as possible. Some compensation, such as for instance the diagnostic service provided by I.M.I.R., can be an important incentive to take part. While the study is in progress, close contact should be maintained with all participants. Regular meetings should be held to discuss problems which may arise and to monitor progress of the study, preferably on the basis of interim analysis of incoming data. In I.M.I.R., the monthly meetings brought G.P.s, clinicians and other disciplines together, which provided mutual understanding and learning and changed the "pupil-teacher" attitude of G.P.s so often present when they meet clinicians.

Much effort was made to meet these requirements for successful research cooperation with G.P.s. Possibly, the fact that by and large all G.P.s maintained cooperation until the end of the study is a measure of success of these efforts.

## 10.4. RECOMMENDATIONS FOR PATIENT-MANAGEMENT IN GENERAL PRACTICE

In paragraph 10.2., a comprehensive picture of the prodromal clinical manifestations of A.C.E. was presented on the basis of the evidence provided both by I.M.I.R. and by other related investigations. That picture led to the conclusion that it is in general practice impossible to recognize accurately instances of impending coronary event on clinical grounds since symptoms and/or signs which precede an A.C.E. are either absent or variable and unspecific. As discussed in chapter 5, the same conclusion holds also with respect to

the recognition of instances of A.M.I. on clinical grounds since, again, the symptoms and signs are often variable and unspecific. The G.P. can not hope to detect asymptomatic instances of acute or impending coronary event. However, both in view of the possibility that A.M.I. is present and in view of the possible existence of an elevated short-term A.C.E.-risk, the G.P. should carefully examine all patients consulting him for:

- recent or worsening angina pectoris,
- recent or worsening non-anginal chest pain or, dyspnea, dizzyness and/or syncope unless there is an obvious extra-cardiac cause.

This recommendation is based on the fact that more than 95% of the patients included in I.M.I.R. had one or more of the symptoms mentioned either as primary or as secondary complaint. The doctor should follow this policy disregarding his opinion about the possible cause of the symptoms. Since patients do not always tell all their symptoms unless questioned, the importance of taking a good history is underlined, as is the importance of a simple physical examination since certain signs have diagnostic or prognostic importance (see chapters 4 and 6). Furthermore, an electrocardiogram should always be made since it contains, again, both diagnostic and prognostic information. Also, enzyme tests should be done since it is not possible to diagnose with confidence the presence or absence of A.M.I. without such information. A.C.E.s are rare in men under 30 and in women under 40. Although such limits are always arbitrary, it seems justifiable to follow the policy outlined here rigorously only in patients above these age limits.

The management policy outlined above can be implemented only if the G.P. has at his disposal the possibility to obtain an expertly interpreted E.C.G. and serum enzyme level assessments at short notice. This should be the task of a specially set up support organization serving all G.P.s within a certain area. The G.P. should also be able to interpret the results and integrate these with other patient information. Postgraduate training in the interpretation of the results of such diagnostic investigations and in management of cardiovascular diseases in general should be provided.

## 10.5. RECOMMENDATIONS FOR FURTHER RESEARCH AND DEVELOPMENT

In our opinion, the results of the I.M.I.R. study suggest in particular the following areas for further research and developement:

1. The prognostic (chapter 4) and diagnostic models (chapter 6) are the results of a particular study done in cooperation with well motivated and interested G.P.s. First of all, the accuracy of the models in the hands of other G.P.s working under different conditions should be evaluated. Also, an attempt should be made to improve the power of the respective models by the inclusion of more information.
2. Little is known about the management of A.M.I. by G.P.s in the Netherlands. The I.M.I.R. study showed that not all patients diagnosed as having A.M.I. are sent to hospital (see section 5.3.2) but the study was not designed to investigate the relative merits of home and hospital care of patients with A.M.I. Therefore, the management of such patients should be studied as to when to hospitalize and as to therapy in case of home care. In particular, the question should be studied whether it is possible to base certain management decisions on a diagnostic model such as the one presented in chapter 6.
3. A prognostic model as presented in chapter 4 could form the basis for the recognition in general practice of patients who are at high risk to sustain an A.C.E. early in the future. However, systematic application of such a method is useful only if intervention can be offered to the patient so detected. Therefore, the question how to intervene in patients at high short term A.C.E.-risk should be studied. A prognostic model could form the basis for the selection of patients to be entered into trials of the efficency of short and long term treatment. Also, the possibility to induce behavioural changes in high risk patients and the benefits of such changes should be investigated.
4. The I.M.I.R. study provided the participating G.P. with a certain kind of diagnostic service. As discussed in section 10.1.2., there are reasons to believe that such service is useful. How diagnostic service to first-line medicine in reference to cardiovascular diseases can best be given, what it should offer, how it should fit within existing local health care facilities and its cost effectiveness should be subject to further investigation.

5. Although the I.M.I.R. inclusion criteria covered a wide range of symptoms, less than half of the total number of A.C.E.s which were detected, were included into the study before the event occurred. The reasons for this should be studied. Questions which deserve attention are: What is the natural history of patients who do not have the kind of symptoms studied by I.M.I.R. shortly before they sustain an A.C.E.? Why do patients not always tell their symptoms to the G.P. when they consult him and why is the G.P. not always consulted when symptoms are experienced? In particular, long-term natural history studies are indicated of patients who are known to have cardiovascular disease such as hypertension, angina pectoris or status post-M.I. since case-history studies have shown that patients who sustain an A.C.E. often have a history of cardiovascular disease.

REFERENCES

1. Cairns, J.A., Fantus, I.G., Klassen, G.A., Unstable angina pectoris. Am. Heart J. 92 : 373-386, 1976

2. Conti, C.R., Brawley, R.K., Griffith, L.S.C., Pitt, B., Humphries, J.O., Gott, V., Ross, R., Unstable angina pectoris: Morbidity and mortality in 57 consecutive patients evaluated angiographically. Am. J. Card. 32 : 745-751, 1973

3. Vakil, R.J., Intermediate coronary syndrome. Circulation 24 : 557-571, 1961

4. Vakil, R.J., Preinfarction syndrome, management and follow-up. Am. J. Card. 14 : 55-63, 1964

5. Lie, K.I., Wellens, H.J.J., Durrer, D., Een prospectieve studie van het dreigend hartinfarct. Ned. T. Geneesk. 118 : 1218-1220, 1974

6. Duncan, B., Fulton, M., ?orrison, S.L., Lutz, W., Donald, K.W., Kerr, F., Kirby, B.J., Julian, D.G., Oliver, M.F., Prognosis of new and worsening angina. B.M.J. 1 : 981-985, 1976

7. Kannel, W.B., Feinleib, M., Natural history of angina pectoris in the Framingham study, prognosis and survival. Am. J. Card. 29 : 154-163, 1972

8. Kannel, W.B., McGee, D., Gordon, T., A general cardiovascular risk profile: the Framingham study. Am. J. Card. 38 : 46-51, 1976

9. Schilperoort, J., De toepasbaarheid van electrocardiografische diagnostiek in de huisartsenpraktijk. Thesis, Utrecht, 1977

# 11. GENERAL DISCUSSION: THE EPIDEMIOLOGIST'S PERSPECTIVE

J.Lubsen

## 11.1. INTRODUCTION

In the team of investigators who carry out an epidemiologic study, the epidemiologist is usually responsible for the design and the methods used, for quality control and for data-analysis. In chapter 2, the methods of the I.M.I.R.-study were described and an introduction from the point of view of the methodology was given in chapter 1. To the results as presented in chapters 3 to 8, only topical comments were added. But no comprehensive *post bellum auxilium* (Erasmus) discussion of the methods used was offered. In our opinion, such a discussion is definitely indicated. In principle, the design of a follow-up study is straightforward: individuals with certain characteristics are ascertained and followed for a certain period of time to establish whether disease develops of not. The I.M.I.R.-study had such a design for reasons which have been explained in section 1.2.2., i.e. direct estimability of A.C.E.-risk in relation to symptoms and signs present before an A.C.E. occurs. The attainment of internal validity was the major concern in designing I.M.I.R., in setting-up its procedures and during its execution. Since any study plan is based on expectations about the amount of cooperation and efforts the participants are willing to give and about certain aspects of the phenomena studied, these expectations should be evaluated when the data are in. Did the participants perform as was required? What are the consequences as to the inferential validity of the results if deviations from the protocol were detected? These questions can only be addressed with hindsight. But they must be asked and they are therefore dealt with in sections 11.2.1-11.2.5. It is underlined that it is easy to point at Achilles' heel when the battle is over. The objective of study design and execution must always be the eventual prevention of omissions rather than the detection of their occurrence.

Section 11.3. contains an appraisal of the results. First of all, the question is dealth with whether the main goal of I.M.I.R. was achieved. A discussion follows of what was learnt from I.M.I.R. and of the implications of the learning. Finally, a few general remarks on research in general practice are made in section 11.4. before some specific recommendations for future work are given.

## 11.2. AN APPRAISAL OF THE METHODOLOGY OF I.M.I.R.

### 11.2.1. THE ROLE OF THE GENERAL PRACTITIONERS

One of the central issues in an epidemiological study is subject enrollment. In I.M.I.R., this was the responsibility of the participating G.P.s, who were asked to include patients on the basis of the inclusion criteria as specified in the protocol.As discussed in section 2.4.1., these criteria covered intentionally a wide range of symptoms. In retrospect, it seems that the range was probably too wide. In particular, this applies to the criterion "recent pain or discomfort in the chest". The intention was that the G.P. would take this criterion strictly and include *all* patients with recent chest pain irrespective of its suspected cause, the reason being to reduce the chance of missing a case of acute or imminent M.I. through a mis-judgement about the cause of the pain.In reference to the other symptom criteria however, the G.P. was asked to make a judgement about the cause before deciding on inclusion since "unexplained", i.e. without apparent extra-cardiac cause, was added to the respective non-chest pain criteria (see section 2.3.2.). Although the reasons for including all chest pain were thoroughly explained to the G.P.s, the results of the special investigation into their inclusion policy described in section 3.3.4. have shown that, as a rule, the G.P.s did not include patients with chest pain when there was an evident extra-cardiac cause for the symptoms. Possibly, part of the explanation is that there was still confusion in the G.P.'s mind about the scope of application in practice of the restriction "unexplained". More likely, it was simply unrealistic to ask from the G.P. to include a patient with chest pain into a study concerned with coronary heart disease when the G.P. was, rightly or wrongly, convinced that the patient in question did not have heart disease.For, asking the G.P. to include such patients could imply that he was asked to do something which, in his opinion, served no useful purpose, took time and caused him and his patient unnecessary trouble. Whatever the explanation, the results of the investigation into the actual inclusion policy of the G.P.s described in section 3.3.4. showed unequivocally that, contrary to the inclusion criteria, patients with chest pain were not included if there was an evident extra-cardiac cause for the pain. Inasmuch as the inclusion criteria seemed not clear enough, the design is to be blamed. It would have been better

if the proviso "unexplained" had applied to all symptom criteria. Furthermore, some more clarification of what was meant with "unexplained" than "without apparent extra-cardiac cause" should have been given. Instead of adding such a proviso to the symptom criteria, and leaving the interpretation to the G.P., it would probably have been preferable to define a set of exclusion criteria. These should have consisted of the commonly occurring non-cardiac diseases seen in general practice which may cause the symptoms mentioned in the inclusion criteria and, in case of the presence of any of these diseases in the opinion of the G.P., non-inclusion should have been the rule. It is possible that some patients who actually had (sub) acute coronary heart disease would have been missed under such criteria. The advantage would have been however, that the kind of patient includable into the study would have been more clearly defined.

Tight control of the quality of execution is essential in epidemiological studies. However, such control was almost impossible to carry out in reference to the inclusion policy of the G.P., which policy was made on the basis of the inclusion criteria in offices and during home visits spread over the Rotterdam area. The special investigation into the inclusion policy during two months (see section 3.2.2.) was very cumbersome, covered only a sample of all patient-G.P. contacts and could certainly not have been carried out during the whole study period. Nevertheless, certain aspects of the inclusion policy should have been subject to verification. As pointed out in section 1.2.3., the application of the inclusion criteria would be tantamount to the inclusion of patients with a symptomatic myocardial infarction and patients in whom the presence of this conditions was suspected by the G.P. The completeness of inclusion of such patients if they were hospitalized, should have been checked by monitoring the hospital admissions in the Rotterdam area. Similarly, the completeness of the reporting of instances of sudden death should have been checked by monitoring death records. Finally, attention should have been paid to patients belonging to one of the participating practices seen for "I.M.I.R.-symptoms" during periods that the patient's own G.P. was replaced by a locum tenens.

One other aspect of the cooperation with G.P.s in I.M.I.R. must be mentioned here. For an inclusion, the G.P. was "rewarded" by a quick

diagnostic service consisting of an E.C.G. read by a cardiologist and of serum enzyme tests (see section 2.3.3.). This service was an important incentive for the G.P. to take part in the study. But it could have distorted his inclusion policy since, at least in principle, the G.P. might have had the tendency to include especially those patients in whom the information provided by the service seemed most useful to him, thereby introducing a selection bias which would have been very difficult to detect. One solution to this problem could have been to keep the diagnostic service and the inclusion of patients apart. By providing diagnostic service if, and only if, desired by the G.P. but without other limitations and by keeping inclusion into the study conditional on the patient's symptoms,this goal could have been achieved.

In conclusion then, it must be said that notwithstanding the extra training given to them, some difficulties concerning the cooperation with G.P.s in I.M.I.R. have been identified. Probably because the inclusion criteria were too unrestrictive with respect to chest pain, these criteria were in general not taken literally by the G.P.s. It would have been almost impossible to carry out direct quality control on the inclusion policy of the G.P. but certain aspects of it, such as hospitalization and reporting of sudden death, could in principle have been subject to direct verification. Also, in the interest of avoiding bias the design should have kept "diagnostic service" and "inclusion of patients" separate issues to the greatest possible extent. It should not be concluded from these remarks that the G.P.s themselves are to blame in any way for the problems mentioned in this section; they have done what was in their power to comply with the rules of the study.Rather, it might be questioned whether the design was practical as far as their role was concerned and whether the extra training given to them was sufficient. This last issue is extremely difficult to evaluate however. The special investigation described in section 3.2.2. has provided an insight into how the inclusion of patients by the G.P. worked in practice. The consequences of the problems mentioned here for the validity of the results are discussed below in section 11.2.5.

### 11.2.2. THE CONTENT OF THE DATA-BASE

Another central feature of epidemiological studies is the data-base which is to be collected uniformly on all subjects entered in the study. In the context of I.M.I.R., the data-base had two main functions: (i) to describe the patient's symptoms, signs and other characteristics which were thought to be of possible interest in the search for predictors of

a future A.C.E.; and (ii) to supply the information necessary to establish the occurrence or non-occurrence of an A.C.E. either at inclusion or during follow-up. A great deal of effort and thought went into the design of the set of forms to be used for the collection of all relevant patient data; its final version is reproduced on page 44-89 of "Tables and Figures".

It may be unavoidable that omissions and obscurities in the design of the data-base emerge during the execution of a study as complex and of such duration as I.M.I.R. Some omissions in the data collected during follow-up were corrected during its course by designing the two additional questionnaires reproduced on page 92-101 of "Tables and Figures". Furthermore, Minnesota coding of E.C.G.s was introduced and, consequently, a modification of the conclusion based on E.C.G. and enzymes (see page 90 and 91 of "Tables and Figures"). Apart from these additions, the I.M.I.R. forms were left unchanged after the modifications which were made on the basis of experience gained from the pilot study. Although there was discussion about possible further changes later on, this was resisted in the interest of keeping procedures simple and the data-base uniform.

During analysis, more omissions tend to emerge, in particular because often the attention turns to questions which the study was not specifically designed to answer. This happened to I.M.I.R. also. For instance, the study was not intended to investigate the problem of diagnosing A.M.I. in general practice.The diagnostic model for A.M.I. presented in chapter 6 could therefore possibly have been more powerful if the information available on the patient's symptoms and signs had been more detailed. Furthermore, questions related to the G.P.'s diagnostic accuracy and to the management of patients diagnosed by him as having A.M.I. could have been analysed more comprehensively had such detail been present. For instance, since it is not known whether the patient still had pain at the moment he was seen, information on a presumably important determinant of both diagnosis and management was missing.Also, the question on the G.P.'s own diagnosis at inclusion (item 111 of the I.M.I.R. forms, see page 57 of "Tables and Figures")was too superficial. It was not requested from the G.P. to state how recent he thought the infarction was when A.M.I. was his diagnosis. Nor was it possible to give more than one diagnosis or to express diagnostic uncertainties. Finally, there was no specific question on the cause to which the patient's current symptoms at inclusion were attributed. It is a matter of conjecture

whether the analysis with respect to some of the problems associated with the diagnosis and management of A.M.I. could have been more informative had the data-base been more specifically designed to probe into these problems. Nor is the design of the data-base really at fault since these questions were not the main object of inquiry,which was short-term A.C.E.-risk in patients seen by G.P.s for "I.M.I.R.-symptoms". Whether the results in reference to the main objective have suffered also from some of the omissions mentioned above seems doubtful, especially since so little of the information on symptoms which was available, was retained in the final prognostic function. From the purely scientific point of view it is regrettable however that no serum cholesterol determinations were done since it would be of interest to know whether cholesterol level is an independant risk indicator when added to the prognostic function discussed in chapter 4. But it is emphasized that in designing the content of the data-base, conflicting interests emerge. On the one hand, there is hardly an end to the number of items of possible relevance which can be included in a questionnaire or added to the investigations which are done. On the other, there are feasibility aspects like costs and the amount of effort which can be asked from both patients and other participants, in particular from G.P.s who have to fit such work within their normal duties. Notwithstanding these restraints, a cholesterol determination would not have been much of an extra burden since a blood sample was taken directly after inclusion for serum enzyme determinations. Also, the questionnaire on symptoms could have been more informative without adding too much to the work required from the G.P. since a number of items which were filled out by the G.P. could have been dealt with by the I.M.I.R. assistant.

Another deficiency which can be pointed at in retrospect and which is closely related to the content of the data-base, has to do with the spacing of the follow-up examinations. It was expected that most A.C.E.s which occur during follow-up would do so within, say, the first month after inclusion. This did not prove to be the case. Of the total of 83 A.C.E.s detected in patients free of A.M.I. at inclusion, only 44 occurred in the first month of follow-up while the remainder were spread over the last nine (see table 4.2.). The I.M.I.R. follow-up scheme had the drawback that, for such late events, very little information was collected on the progression of the patient's condition between the moment of inclusion and the moment the A.C.E. occured. Future studies will have to take the I.M.I.R. experience in this respect into account and will

have to use quite different follow-up schemes.

In conclusion then, the data-base lacked some presumably important items of information. Also,the follow-up scheme was such that no information could be collected on the progression of the patient's condition in case an A.C.E. occurred after the first month of follow-up. Again, to what extent these deficiencies affect the validity of the results will be discussed below in section 11.2.5. At any rate it can be stated that much is to be learned about the ideal design of this type of study.

### 11.2.3. THE I.M.I.R.-CENTER

To perform the multiple activities other than those of the G.P. which were associated with the execution of the I.M.I.R. study, a special organizational unit was set up within the department of cardiology (Thoraxcenter) of the Erasmus University, Rotterdam, the Netherlands. It is this unit which is referred to as the "I.M.I.R.-center". Its functions and organization were described in sections 2.3.3 and 2.3.5.

The workload of the I.M.I.R.-center has been considerable.The 1,343 patients admitted to the study required together the recording and Minnesota coding of about 6,700 standard 12-lead E.C.G.s.About 4,000 blood-samples were drawn for serum enzyme tests and about 800 patients were connected to a portable taperecorder for an 8-hour E.C.G. Apart from these investigations, a considerable amount of administrative work was required to keep track of all the follow-up examinations,to inform the G.P.s of the results of investigations done and to collect medical information from other physicians in the Rotterdam area who saw I.M.I.R.-patients. Also, the center had to keep the file of so called "summary cards" up to date, a file which contained central elements of information on every included patient and which was used for interim analyses by computer. Furthermore, the center was responsible for the coding and other work associated with getting all the data on the final data-tape, which consisted of 6 standard 80 column punch card images per included patient.

In retrospect, it can be said that the I.M.I.R.-center staff performed these tasks with devotion. Loss to follow-up and lack of patient-cooperation was no problem whatsoever. Possibly, the presence of a real or supposed health impairment, leading not only to symptoms but also inducing a visit to a G.P., had a positive influence on patient cooperation. A lot of effort was made to ensure the completeness of the data and a good quality of the diagnostic investigations. Although these ef-

forts were generally successful,problems were encountered in certain areas. In patients who were immediately hopitalized after inclusion, the additional questionnaire could not always be completed. Since this questionnaire covered smoking habits and physical activity, these items were not included in the analysis. Eight-hour E.C.G. recordings were also impossible in hospitalized patients. Furthermore, the equipment used proved to be unreliable in our hands. Therefore, the information derived from these recordings was not included in the present analysis. But apart from these problems,the data-base was reasonably complete and only small numbers of patiens had to be excluded from certain parts of the analysis because of insufficient information.

It has not always been easy to keep the I.M.I.R.-center functioning properly and maintain the quality standards required. The problems were largely of an organizational character and, especially in the earlier phase of the study due to ill-defined tasks and responsibilities of the various members of the center's staff. There is a very sound basis for setting up a special unit to execute a study like I.M.I.R.Although the diagnostic investigations could have been handled by the Thoraxcenter's out-patient clinic, it would have been difficult to maintain the standards required and the organization tight. Investigations done within the framework of epidemiological studies need to be of even higher quality than required in a clinical setting. In that setting, the investigations are generally done only to study the condition of a single patient and its time course. In epidemiological studies however, these are used also as a basis for comparing patients with each other. Furthermore, the timing of the investigations tends to be more critical.Therefore, the staff responsible for performing this effort needs special training. The importance of this and of excellent organization of the unit responsible for the execution of an epidemiological study can not be overemphasized. These issues were perceived in time during the execution of the I.M.I.R.-study; otherwise, the study could not have been completed.

### 11.2.4. METHODS OF ANALYSIS

In the derivation of composite scores as a basis for the prediction of future A.C.E.s (see chapter 4) and for a diagnostic probability function for A.M.I. (see chapter 6), linear discriminant function (L.D.F.) analysis was used. As mentioned before in chapter 6, the use of L.D.F.-

analysis is theoretically optimal only if the underlying assumption of equal variance-covariance structure and Normality of the groups considered, is met. Nevertheless, L.D.F.-analysis has found wide-spread application[1-4] even if this assumption is not met, as is in particular the case when indicator variables are used.Halperin et al.[5] have investigated the effects of deviations from the assumption underlying L.D.F.-analysis by comparing its results with those obtained by the theoretically optimal maximum likelihood ( M.L.) method of estimating the coefficients in a multiple logistic function, as proposed by Walker and Duncan[6]. Halperin et al.[5] came to the conclusion that L.D.F.-based estimates of the coefficients may be biased, and possibly seriously so. Also, significance tests may be misleading. On the other hand, they found empirically good agreement between the two methods in the instances studied. Notwithstanding this last conclusion, there is no doubt that M.L.-estimation would have to be preferred in both instances in which L.D.F-analysis was used. The M.L.-method is however computationally much more complex than the L.D.F.-method and was not available to us when the the I.M.I.R. analyses were done.

Another problem is caused by the fact that several tens of variables were tried in each of the L.D.F.-analyses. Such a procedure might yield misleading results if selection of variables for inclusion in the final model is based on the statistical significance of their coefficients only. In the face of both this and the bias problem mentioned above, certain precautions were taken in applying L.D.F.-analysis. A variable was included in the final model only if two requirements were met: (i) the coefficients had to differ from zero at the 5% level of significance, and (ii) the variable selected and the sign of its coefficient had to be in accordance with current understanding of the problem at hand. Using such requirements, it seems no surprise that the analysis presented in chapter 4, yielded only hitherto known predictors of future A.C.E.s, and that in the diagnostic function shown in chapter 6, only symptoms and signs were represented which have established relevance in the context of diagnosing A.M.I. Nor was the discovery of "new" factors the prime objective of these analyses. Instead, the development of prognostic and diagnostic procedures applicable in primary care was the aim. By the same token, the separate variable coefficients were not the object of inquiry, as may be the case in causal research, and the interest was only in the use of composite

scores in such procedures. In doing so, care was taken not to violate theoretical assumptions other than the one underlying L.D.F.-analysis. No other assumptions have to be made in the methods used in chapter 4 to determine the magnitude of the short-term A.C.E.-risk as a function of the L.D.F.-score. In chapter 6 an empirical normalizing transformation suggested by Miettinen[7] was used in an effort to satisfy the assumptions made in the conversion of the L.D.F.-score into a diagnostic probability by an application of Bayes' rule and Normal density theory. Because of the precautions taken, it seems reasonable to believe that the results obtained by L.D.F.-analysis are qualitatively trustworthy in the sense that it is unlikely that violations of theoretical assumptions led to erroneous selection of variables. But the probabilities obtained by the methods presented need further evaluation notwithstanding the care taken not to violate assumptions which underlie the conversion of scores into probabilities. For, these conversions are based on prior probabilities and score distributions which were derived in a particular study and by possibly biased coefficient estimation procedures. By the same token, the values of the coefficients need further evaluation.

Apart from L.D.F.-analysis,customary statistical methods were used with, possibly, the use of a modification of Fisher's exact test in fourfold tables being an exception.For this modification, which was proposed by Miettinen[8], there seems to be ample theoretical justification and its application is a simple matter even for large tables when a programmable pocket calculator, such as Hewlett-Packard's model H.P.-67, is used.

### 11.2.5 VALIDITY OF THE RESULTS

#### INTERNAL VALIDITY

In section 1.2.3, internal validity was defined as the dimension of validity which has to do with the validity of the inferential conclusions made in reference to the subjects actually studied. It is the design of a study as laid down in the protocol together with the quality of execution which determines eventually whether internal validity is achieved. However, in case of the I.M.I.R.-study, there is no uniform answer to the question whether internal validity was achieved. For, the answer must depend on what is taken to be as the "subjects actually studied". As far as the main goal of the study is

concerned, these are the "patients consulting a G.P. for a set of specified symptoms" (see section 2.2.).But the study also provided data in reference to general practices, such as the consultation rate for "I.M.I.R.-symptoms" (chapter 3) or the incidence of A.C.E.s (chapter 7).

In reference to the main goal, i.e. the determination of A.C.E. risk in patients consulting a G.P. for a set of specified symptoms, internal validity assumes the absence of a selection bias with respect to the eventual occurrence of an A.C.E. together with completeness of follow-up and proper procedures for data collection and establishment of the occurrence or non-occurrence of an A.C.E. during follow-up. Among these issues, the absence of selection bias seems to be the most critical one because of the problems encountered with the inclusion policy of the G.P. (see section 11.2.1.); the other conditions for internal validity were met. The special investigation into the inclusion policy (see section 3.3.4.) showed that the G.P. as a rule did not include a patient if there was a very evident extra-cardiac cause for the symptoms.It is noted in passing that this conclusion is based only on the results of this special investigation; it was not possible to determine to what extent patients with such a cause for their symptoms were included since it was one of the omissions in the data-base that the suspected cause of the symptoms was not specifically ascertained. Furthermore, the special investigation into the inclusion policy showed that patients were sometimes missed for reasons unrelated to the suspected cause of the symptoms. The findings of that investigation do limit the applicability of the risk-estimation results to patients without an evident extra-cardiac cause for their symptoms. But since there is no reason to assume that a selection bias in reference to the eventual A.C.E.-outcome was present in the inclusion policy of the G.P., the risk-estimation results of chapter 4 can be considered internally valid in reference to the classes of symptoms mentioned there. The same conclusion should hold in reference to the composite risk score and the risk-estimation procedure based on that score. It applies also to the results presented in chapter 5 and 6 in reference to the problem of diagnosing A.M.I. in general practice since, again, no evidence of selection bias, this time in reference to the presence of an A.M.I., was found.

For results having the general practices as the "subjects actually studied", the conclusion is different. Here, internal validity can not be assumed since completeness of inclusion was not achieved (see section 3.3.4.). Therefore, the results presented in chapter 3 in reference to the consultation rate of patients with I.M.I.R. symptoms in general practice and those presented in chapter 7 in reference to the incidence of A.C.E.s must be taken as the lower limits of the real occurrence of these phenomena. It is emphasized however that these phenomena were not the primary object of inquiry of the study.

EXTERNAL VALIDITY

The generalizability of the results of I.M.I.R., i.e. their external validity as defined in section 1.2.3., raises a complex conceptual issue. Generally in research, the interest is not with, say, patients at large but with a distinct sub-category of patients.Thus, to quote Miettinen[9] :" the design goal as to generalizability is to provide for ( ) learning about a single homogeneous category or about the pattern over such categories". It is emphasized that generalizability in these terms differs from the sample-to-population inference which is based on a probability sample of the population and which is so familiar from statistics. Such statistical generalizability moves only from the actual study to a potential larger study in which the whole population is investigated rather than a sample only. Instead, scientific generalizability, which is the concern here, "moves from the domain of experience ( ) to the domain of theory",i.e. "from this experience to this *kind* of experience" [9].

Theory consists of hypotheses about the nature of phenomena and the scientific generalizability of a study may be viewed in terms of the generation of hypotheses about its objects of inquiry. Viewed in these terms,the question whether scientific generalizability was achieved translates into the question whether the results can be regarded as credible hypotheses. For instance, the composite risk score procedure presented in chapter 4 can be seen as a hypothesis about the relationship between 10-month A.C.E.-risk and patient characteristics for patients seen in general practice for "I.M.I.R. symptoms". Its scientific generalizability then, has to do with the question to what extent this hypothesis is credible. Such credibility requires first of all internal validity of the study. As argued above, internal validity is assumed to have been achieved in reference to the results

presented in the chapters 4,5 and 6. But the study should also be of sufficient size for all of the sub-categories of interest so that enough information is generated to base hypotheses on. In our opinion, it is the amount of information collected by the I.M.I.R.-study which is the prime concern as far as the scientific generalizability of its results is concerned.The analytic techniques used in chapters 4 and 6 contrast the distribution of entry characteristics of future cases of A.C.E. with the one of non-cases (chapter 4) or the one of present cases of A.M.I. with the one of non-cases (chapter 6). In either instance, there was ample information about the distribution of the entry characteristics of non-cases. But the case series included in the analyses were small in both instances: 82 cases of A.C.E. which occurred during follow-up (chapter 4) and 92 cases of A.M.I. which were present at inclusion (chapter 6). It does not seem possible to evaluate formally the amount of information collected. In particular, it is not possible to obtain as a measure of the amount of information formal confidence limits on the prognostic and diagnostic probabilities obtained by the methods presented in chapters 4 and 6. As far as their internal validity is concerned, these results are credible hypotheses. But otherwise, only their application to a similar "kind of experience" can support or disprove their external validity. In closing, it is noted that the external validity of results in reference to the general practices must be viewed as poor. Not only is their internal validity questionable, as was discussed above. But also a small number of general practices took part who were so selected as to preclude any generalization to "this kind of practice". Nevertheless, these results are given because they provide an indication of what can be expected to happen in other practices.

## 11.3. AN APPRAISAL OF THE RESULTS

### 11.3.1. HAS THE MAIN GOAL BEEN ACHIEVED?

In section 2.2. the main goal of the I.M.I.R.-study was described as "the recognition of those patients who were at high risk to sustain an A.C.E. in the near future". The relevant findings in reference to the main objective were described and discussed extensively in chapter 4.

There is no unequivocal answer to the question whether the main ob-

jective of I.M.I.R. was met. The data seem virtually to reject the possibility that an important part of all A.C.E.s are preceded by a typical "pre-infarction syndrome" which can be recognized by a G.P. without diagnostic assistance. By the same token, the data also reject the possibility that at present community mortality from A.C.E. can be decreased by the hospitalization of patients who have been recognized by the G.P. to be at such high A.C.E.-risk that such action is justified on that basis. On the other hand, the results presented in chapter 4 provide the G.P. with some clues on what has to be looked for in a patient who consults him for I.M.I.R.-complaints. The presence of unstable angina, Q- and/or T-wave abnormalities in the E.C.G., hypertension, diabetes and râles are all ominous signs which are independently associated with an early A.C.E. in the future and which are easily observed by a G.P. if he has access to an E.C.G. Furthermore, the above information, together with the patient's age and sex, may be integrated into a single score on the basis of which an estimate of the patient's 10-month A.C.E.-risk may be obtained. The possibility to obtain such an estimate is the basis of "the recognition of those patients who are at high risk" and it depends on one's perception of what risk is considered to be "high" whether one accepts the results of I.M.I.R. as meeting the main goal. That perception will primarily depend on the action taken in patients recognized to be at high risk. It was mentioned already that the I.M.I.R. results do not provide the criteria for the selection of patients with impending M.I. for hospitalization. But the risk-estimation procedure presented in chapter 4 does allow for considerable separation between high and low risk patients. We are therefore of the opinion that the main goal of the study was met since learning was provided about both the possibilities and the limitations of recognizing patients at high risk of an A.C.E. in the early future in general practice.

### 11.3.2. WHAT EXACTLY CAN BE LEARNT FROM I.M.I.R.?

At considerable effort and expense, the study employed fulltime the equivalent of 6 I.M.I.R. assistants, 2 student-assistants and 3 research fellows and was supported by the Netherlands Heart Foundation with 602,000.-- Dutch guilders, I.M.I.R. provided information on certain aspects of the occurrence of A.C.E.s in general practice. These figures are recalled here because inevitably, the amount of

learning provided must be judged against the background of the expenditures which were incurred. What, then, was the return in terms of learning which was obtained?

One could summarize the results by stating that at present in general practice, it is difficult if not impossible to determine on the basis of syptoms and signs which patient is in danger to sustain an A.C.E. soon or to make a reliable diagnosis of A.M.I. when this condition is in fact present. The impossibility to distinguish which patient is in danger on the basis of a recognizable syndrome of symtoms and signs was hinted at in the previous section while discussing whether the main goal was achieved. Only the addition of an E.C.G. to the information which can be obtained by the G.P. makes, to a certain extent, recognition possible of the patients in danger. In reference to actual A.M.I., data presented in chapters 5 and 6 show that its clinical manifestations as seen in general practice were highly variable and, in retrospect, it did not surprise that the accuracy of the G.P.'s initial diagnosis "A.M.I." was no better than it appeared to be from the data presented in table 5.1.

If nothing more could be said about the achievements of the I.M.I.R.-study, there would be reasons for disappointment. What then, were the important "positive" findings which provided both new understanding and may serve as starting points for future research and development?

First of all, it is underlined that I.M.I.R. showed that patients who eventually sustain an A.C.E. were indeed seen by a G.P. in the prodromal phase of the event. By the methods of I.M.I.R., 83 patients were "caught" who were eventually to sustain an A.C.E. within 10 months after they consulted a G.P. for "I.M.I.R. symptoms". These 83 represented an important fraction of all A.C.E.s detected (83/256 or 32%, table 4.1.). Nevertheless, this fraction was smaller than expected at the outset of the study on the basis of case-history studies. Also, they belonged to a large group of patients seen for "I.M.I.R. symptoms" by the G.P., to which group also belonged a number of patients who had already an A.M.I. when seen. However, these can be recognized if proper diagnostic procedures are used. What remained then, was a group of patients who had a 7% (83/1,214, table 4.1.) 10-month rate of A.C.E. but were free of A.M.I. at the moment they consulted the G.P. Among these, there were a number of patients with more specific symptoms, i.e. had unstable angina. The 10-month rate of A.C.E. among these patients was about twice as high as the overall rate (33/252 or 13%, table 4.3.)

and further separation is possible on the basis of the composite risk score (see table 4.4. and figure 4.1.). Obviously then, these findings imply that it is possible to detect patients in general practice who are in urgent need of secondary preventive treatment, an implication which is discussed further in the subsequent section 11.3.3.

A second objective of the study stated in section 2.2. was the evaluation of the diagnostic service which was provided by I.M.I.R. to its participating G.P.s. In reference to this objective, the main finding was the limited diagnostic accuracy achieved by the G.P. in recognizing instances of A.M.I. In patients seen for "I.M.I.R. symtoms", the sensitivity of the G.P.'s initial diagnosis "A.M.I." was 44% and the specificity 97% (see section 5.4.1.). Overdiagnosis of A.M.I. is a phenomenon known from coronary care experience but the low sensitivity was both a new and an unexpected finding, which was also the impetus to carry out the analyses presented in chapters 5 and 6. It is noted that these are based on data from an unselected group of patients sustaining A.M.I. since patients were included in the I.M.I.R.-study when the symptoms met the inclusion criteria and not because the presence of A.M.I. was suspected. Therefore, the present findings on the symptomatology of A.M.I. can not be compared to findings based on, for instance, patients who were hospitalized. The analysis of chapter 5 probed into the reasons for the limited diagnostic accuracy. No unequivocal explanation was found but misdiagnosis was clearly related to the absence of signs in patients who actually had A.M.I. and to the presence of signs in patients who in fact did not have A.M.I. In chapter 6, the development of a diagnostic model for A.M.I. was discussed which can be applied in general practice without recourse to diagnostic investigations like an E.C.G. or enzyme tests. By L.D.F.-analysis,eleven variables describing patient-characteristics which have independent relevance in diagnosing A.M.I. were identified. But the amount of separation achieved was not very impressive since a procedure for allocating the diagnosis A.M.I. which is based on the L.D.F.-score did not achieve greater sensitivity and specificity than that attained by the G.P.(see figure 6.1.). On the basis of these results, it may be concluded that accurate diagnosis is impossible on the basis of the kind of data which were taken into account in the analysis since otherwise the separation achieved would have been greater. As pointed out in section 11.2.2., the

I.M.I.R.-study was not designed to investigate ways of diagnosing A.M.I. in general practice and the group of cases on which the present results are based is quite small. In principle, it can not be excluded therefore that better separation could be achieved on only the basis of the information which can be obtained by the G.P. On the other hand, diagnostic uncertainty will always given the limited facilities available to G.P.s and it is for this reason that the use of the L.D.F.-score as a basis for quantifying that uncertainty seems more attractive than its use as a basis for a diagnostic allocation procedure; how such quantification may be achieved was discussed also in chapter 6.

What has been mentioned so far constitutes in our opinion the main body of what was learnt from the I.M.I.-study. Learning is provided only by results which can be viewed as credible hypotheses, i.e. are internally valid and scientifically generalizable. It was argued in section 11.2.5. that the findings presented in chapters 4,5 and 6 have these qualities; the present section therefore contains only material taken from these chapters.

It is no easy task to judge research from a "cost-benefit" point of view. One criterion should be the question to what extent the information obtained is new. To our knowledge, no community study comparable to I.M.I.R. has been done before. Duncan et al.[10] studied only unstable angina in a similar way. The results of I.M.I.R. in reference to unstable angina corroborated their findings. But above that, I.M.I.R. provided new information on a much wider range of symptoms possibly related to an impending coronary event. Also, the diagnostic accuracy of the G.P.'s diagnosis "A.M.I." seems not to have been studied earlier nor as far as we know, has the development of a diagnostic model for that condition applicable to primary care. Another criterion for judging research is the implication which the results could have. These are discussed in the next section. This section starts with a brief summary of the expenditures spent on I.M.I.R. However, any judgement as to whether the results were worth the effort is to a major extent subjective. It is our firm belief that, in terms of learning, the results were worth the effort. It is up to the reader to make a judgement of his own.

## 11.3.3. IMPLICATIONS OF THE RESULTS

The acute sequelae of coronary atherosclerotic heart disease (C.A.H.D.) are mostly irreversible and frequently even fatal. Furthermore, A.C.E.s are the single most important cause of death in the Netherlands[11] as in many other western countries. It is also generally accepted that prevention must be the ultimate solution to the problem posed by C.A.H.D. Here, a distinction must be made between primary and secondary prevention. Primary prevention refers to activities which aim to evade the atherosclerotic lesions themselves while secondary prevention aims to avoid the clinical sequelae of those lesions, such as angina, A.M.I. or sudden cardiac death. There is no universal agreement yet as to what role the G.P. has in primary prevention of C.A.H.D.[12] Within the prevailing health care system in the Netherlands however, secondary prevention must be considered to be very much a challenge to and a task of the G.P. What then, are the implications of the results of I.M.I.R. in the context of the G.P.'s role in secondary prevention?

Customarily, a G.P. does not actively search for patients, although exeptions to this rule begin to emerge especially in reference to prevention. Evenso, the usual course of things at present is, that the G.P. is consulted on the patient's initiative when an impairment of health or well-being is perceived. One natural starting point for secondary prevention, therefore, is such a spontaneous visit. If all A.C.E.s did occur without prodromal symptoms (see also figure 2.1.) no such visits would take place before the event actually occurs. If such visits do occur, its reasons must be recognizable by the G.P. as being possibly related to an impending A.C.E. since, if this were not the case, it would not be a useful starting point for secondary prevention. That spontaneous visits do in fact frequently precede an A.C.E. was already known from case-history studies. In the I.M.I.R.-study, spontaneous visits of a special type, i.e. for "I.M.I.R.-symptoms", therefore were taken as the starting point. As indicated already in section 11.3.1., the study showed, in our opinion at least, that, notwithstanding the impossibility to predict precisely which patient seen for "I.M.I.R. symptoms" is in fact in danger (cf. section 11.3.1.), visits for such symptoms do form a useful starting point for secondary prevention. This view is based on the following considerations.

First, there has to be something to prevent. On the basis of I.M.I.R., we estimate that about 30% of all A.C.E.s are preceded by a patient-G.P. contact for"I.M.I.R.-symptoms" up to 10 months before the event occurs

(see table 4.1.). Consequently, the upper limit of what can in theory be prevented by taking "I.M.I.R.-symptoms" as a starting point represents a considerable fraction of all A.C.E.s.

Second, preventive measures have to be balanced against the probability that the event they seek to prevent would occur in the absence of prevention and against the reduction of that probability which is achieved. For any given type of prevention therefore, there exists a level of risk above which the patient should be in order to justify a particular type of preventive action. I.M.I.R. showed not only that the overall A.C.E.-risk of patients seen for "I.M.I.R.-symptoms" is considerable but also that it is possible to discern various levels of risk among such patients on the basis of the information taken into account in the composite risk score.

Thirdly however, what kind of secondary prevention is indicated for which risk-based subgroup of patients seen by the G.P. for "I.M.I.R.-symptoms", remains to be established. Eventually, proposed types of secondary prevention have to be put to a test in practice. In our opinion, it is in this context that the results of I.M.I.R. are most relevant. For, I.M.I.R. showed how to ascertain in general practice high risk patients who are in need of secondary prevention and are therefore candidates for inclusion into trials of secondary prevention. Possibly promising approaches begin to emerge. Most of the work that has been done or is under way focusses on the prevention of recurrent A.C.E.s in survivors of myocardial infarction. For instance, Vedin et al.[13] came to the conclusion that a particular bèta-blocking agent reduces morbidity and mortality in such patients. Also, the use of anti-arrhythmic drugs has been strongly advocated by Lown et al.[14] and their effectiveness in post-M.I. patients is currently under investigation. Finally, there is the contention that drugs which affect platelet function might be useful[15,16]. An earlier study of Elwood et al.[17] on the effect of acetyl salycilic acid on mortality in post-M.I. patients was inconclusive but a case-referent study by the Boston Collaborative Drug Surveillance Group[18] showed a negative association between a history of Aspirin use and non-fatal A.M.I. Further work also on other agents which affect platelet function is under way and promising preliminary results have already reached the press. But final results are still awaited. It is underlined however that most work is done in survivors of M.I.

Whether results achieved in such patients apply also in the kind of patients studied by I.M.I.R. remains to be seen.

Closely related to secondary prevention is the management of A.C.E. when it occurs. In discussing prevention, we have not made a distinction between "sudden cardiac death" and "A.M.I." Although these two entities presumably have different patho-physiologic mechanisms, they seem to be indistinguishable from the point of view of *prediction*. But from the management point of view, both entities have very different implications.

In reference, to "sudden cardiac death", the problems of management seem almost insurmountable. In the patient struck, resuscitation is possible only within a couple of minutes, otherwise death is inevitable. Succesful resuscitation is therefore possible only under ideal circumstances. For instance, some promising results have been reported by Cobb et al[19]. But these were achieved at great cost and effort. In a recent study from Rotterdam, the Netherlands, Hart[20], came to the conclusion that a well-run but otherwise conventional ambulance service can not be expected to make an appreciable inroad on the problem. He came to the conclusion that training programs should be started which teach resuscitation techniques to people who have because of their occupation contact with large groups of people, such as policemen,streetcar drivers, etc. As far as the G.P. is concerned, he does not seem to be in a position to be of much help to the patient struck by sudden collapse. Possibly, he might have a role in teaching resuscitation techniques to the family of cardiac patients.

The G.P. has however an important role in the management of A.M.I. when the patient survives the first moments. The need for accurate diagnosis of the condition by the G.P. can hardly be denied since he has, again, a central position in deciding on which action has to be taken. In particular, the decision to either hospitalize or to keep the patient at home is essentially his in most instances. In our opinion, the finding that the G.P.'s initial diagnosis "A.M.I." has low accuracy, provides ample justification for the institution of some form of diagnostic service to G.P.s.

I.M.I.R. showed that,relative to the occurrence of actual A.M.I. large numbers of patients are seen by the G.P. with symptoms possibly suggesting its presence. It can be argued that proper management of these patients is of more concern than accurate diagnosis. Possibly,

rules for management based on quantification of the degree of (un) certainty that A.M.I. is present can be developed with the help of decision theory. It was with this goal in mind that the model for the quantification of the probability that A.M.I. is present (chapter 6) was developed. The theoretical basis to develop decision models seems to be available and its application to therapeutic decision problems in medicine has been attempted[21,22]. Admittedly, the development of such a model for the management of A.M.I. in general practice seems to be a distant goal. On the other hand, there is no doubt that diagnostic models such as the one presented in chapter 6 for A.M.I. are really useful to the G.P. only when the diagnostic probability obtained implies a certain action. In our opinion, the results of I.M.I.R. in reference to the G.P.'s diagnostic accuracy imply the need to develop such models. For, diagnostic service which consists of an E.C.G. and enzyme tests will have very limited value in deciding on hospitalization of the acutely ill since such decisions have to be taken quickly and on the spot.

Another implication of the low diagnostic accuracy of the G.P. in reference to the recognition of A.M.I. is that registration of occurring cases must be inaccurate if it is based on notification by the G.P. Since the G.P. treats some instances of A.M.I. at home, registration of hospital discharge diagnoses is insufficient also. Consequently, registration projects of A.M.I. such as the ones organized by the W.H.O.[23], underestimate the real incidence if they do not incorporate diagnostic evaluation with E.C.G. and enzyme tests of patients with recent or recently increased symptoms of potential cardiac origin.

What has been said so far constitutes the, in our opinion, most important implications of the findings of I.M.I.R. In summary, they are secondary preventive therapy for patients seen for "I.M.I.R. - symptoms", the need for diagnostic service and the development of decision models for the management of patients suspected of having A.M.I. As is so often the case in research, the results of I.M.I.R. seem to pose more questions than to offer answers. However, to a certain extent, such a notion is delusive and underrates the importance of the study. For, I.M.I.R. provided at the very least the understanding which is necessary to formulate the new goals for further research and development which were discussed above.

## 11.4 RESEARCH IN GENERAL PRACTICE

### 11.4.1. INDICATIONS

The fact that the G.P. has an important role in the health care system which prevails in the Netherlands has been stressed before several times. The G.P. is a family doctor and the first line of defense against disease. He has a large influence on the type of care a particular patient receives and acts as the central point of entry into the various components of the health care system. If the annual income is below a certain level, membership of the health insurance system known as "sickfunds" is obligatory. This system requires from all members registration with a G.P. Generally, the population otherwise insured registers with a G.P. also.

Classically, the G.P. received his training from the basic scientists and clinicians associated with the medical schools and academic hospitals. It was generally assumed that the training received there in the various specialties would serve the future G.P. also. Only recently have his special training needs been recognized, the first university department of general practice was founded in 1967 at the University of Utrecht. As a consequence, the special research needs of general practice have remained largely unrecognized also. Just as is the case in clinical medicine however, research is necessary in general practice to develop the knowledge on which patient care is based. Not all knowledge derived from clinical research is directly applicable in general practice. Furthermore, there are problems which are unique to general practice. The G.P. has much less recourse to diagnostic investigations in comparison to the clinician. Also, he is usually working in an isolated position with little possibility for deliberation before decisions are taken. Working under such circumstances, he is nevertheless expected to have a broad medical knowledge and the ability to bring to light the problems of his patients, whether they are either medical or social or both. It appears therefore, that general practice has its special needs. The question rises what the indications for research in that field are and also to what extent the special position of the G.P. can, and should, be exploited in research.

One of the differences, although not an absolute one, between general practice and clinical medicine is that the first discipline

is primarily problem oriented while the latter is primarily disease oriented. In general practice, the symptoms and complaints which the patient has are both the reasons for the patient-doctor contact and the starting point for the G.P. In our opinion this provides one of the major indications for research in general practice. The object of inquiry should thus be defined in terms of symptoms, or problems in general, for which patients consult their G.P. and the research should both attempt to unravel their etiology and to guide the actions, such as diagnosis and management, which are required. It is noted in passing that the I.M.I.R. study is an example of the kind of problem-oriented research in general practice which is meant here."I.M.I.R.-symptoms" were the starting point and the study investigated their association with present and future A.C.E.s

A corollary of the above is that causal research of diseases should not be done in general practice unless the concern is with a disease which is usually treated by the G.P. at home. Especially causes of rare diseases are better studied at the institutions to which cases are referred. However,general practice can sometimes be a good source of a reference series in a case-referent study.

For certain kinds of research, the position of the G.P. in the Netherlands can conveniently be exploited. For instance, research which needs the determination of population denominators, this is the case when rates are of interest, should be based on general practices as the unit of information. For, the denominators are inherent in the number of people registered with the G.P. and the numerators, i.e. the absolute occurrence of the phenomena studied, can, at least in principle, be determined with precision. Also, health care evaluation should exploit the central position of general practice.Some other types of research should,on the other hand,avoid the necessity to involve the G.P. For instance, treatment effects are much more conveniently studied in the clinic or out-patient clinic where the treatment finds regular application. Only if the effectiveness of the treatment in the hands of the G.P. is in doubt should a study be done in general practice.

There is relatively little experience with research in general practice and, to our knowledge, no national policy nor a set of priorities has been defined in reference to such research. What has been

said so far is only of a very general nature. Recommendations with respect to research in the field of cardio-vascular diseases which are based on these remarks and on the results of I.M.I.R. are given in section 11.4.3.

### 11.4.2. PRACTICAL ASPECTS

Especially in academic hospitals,research and patient care traditionally go hand-in-hand and many a clinician is interested, and takes active part, in research activities. On the other hand, the G.P. is usually literally a "practitioner" who has little active interest himself in research. Consequently, there is not much of a research tradition in general practice and the investigator who wants to do research in this field is to encounter some problems of his own. First of all, he has to raise interest of the participating G.P.s in his research objectives. This aspect should not be underestimated. It requires, among other things, that the participating G.P. can identify himself with the objectives, which is more easily achieved if the G.P. had already independently recognized the need to study the proposed question. Second, the investigator will find out that there is considerable variability in the way G.P.s practice. Some have scheduled office hours, others do not. Some regularly call in certain patients for control, others do not. Some refer patients to specialists easily while others attempt to treat as many patients as they can themselves. Some are excellent record keepers, others do hardly keep any records. This means that the investigator can not rely on the availability of historical information and that existing record keeping is rarely of any use.At the very least therefore, uniform data-collection procedures have to be set up. Third, the investigator will have to appreciate not only the fact that G.P.s generally find it difficult to fit the extra work required by the research within their normal daily routine but also the fact that there is great variability in the daily burden which makes it sometimes very difficult for the G.P. to perform extra work. Therefore, the extra work required by the G.P. should be kept to a minimum. If the G.P. has an assistant, as much work as possible should be left to the assistant. If the assistant is too busy to take on the burden, or if no assistant is available, the investigator should provide extra assistance. The major implications of all this are, in our opinion, the following.

(i) One should cooperate only with the most cooperative and most motivated G.P.s who can be found. If there is doubt as to whether the results apply also to the average G.P., then that should be subject to a special study. (ii) The importance of a good protocol describing all the procedures and activities required in detail can not be overestimated. (iii) During execution, the organization of the study should be excellent and close contact should be kept with all participants. (iv) All aspects of the execution should be subject to rigorous quality control.

In conclusion then, the practical difficulties associated with research in general practice are considerable. It is no surprise therefore that the costs in terms of time and money can be large and that failure always lies in ambush around the corner , if not right under the water's surface.

### 11.4.3. RECOMMENDATIONS IN REFERENCE TO CARDIO-VASCULAR DISEASES

We finally turn to the recommendations which may be given for future research and development in general practice in the field of cardio-vascular diseases. The recommendations made below are primarily based on the implications of the results of I.M.I.R. (see section 11.3.3.).

1. As discussed in section 11.3.3., secondary preventive measures should be undertaken in patients seen by G.P.s for "I.M.I.R.-symptoms" who are free of A.M.I. at the moment they are seen. It is in this context that the TRACE-study (Town of Rotterdam Acute Coronary Events) was proposed[24]. Briefly, the design of that study is as follows. Every patient seen for "I.M.I.R.-symptoms" by participating G.P.s is to receive further diagnostic investigation by standard 12-lead E.C.G. and enzyme tests to establish the absence or presence of A.M.I. If no A.M.I. is present, the patient is treated for existing pathology according to a "treatment algorithm" which is based on current concepts in secondary prevention and consists of a combination of treatment with drugs and hygienic measures. Although the G.P. remains ultimately responsible for the treatment, a special support center is set up to monitor the administration of treatment and its results. Forty G.P.s are to be invited to participate. Data on the occurrence of A.C.E.s in their practices are to be compared with similar data for forty matched control practices drawn from "sickfund" administrations.

At the moment these lines were written, TRACE had not received the necessary support. Possibly, the design is to be reconsidered. Nevertheless, it is urgently recommended to carry out a project in secondary prevention along similar lines.

2. It was pointed out in section 11.3.3. that about 30% of the patients who eventually sustain an A.C.E. were estimated to have been seen up to 10-months before the event occurred for "I.M.I.R.-symptoms". The natural history of the remaining 70% should be investigated, especially in reference to their contacts with G.P.s which could serve as "starting points" for secondary prevention. The TRACE-study[16] is to investigate the natural history in the sense indicated here.
3. As mentioned before in section 11.3.3., the problems associated with the recognition and management of A.M.I. should be studied. The following aspects seem to be of particular importance: (i) What kind of diagnostic service should be given and how? (ii) Which patient can safely be treated at home? (iii) Is it possible and advantageous to base management decisions on a diagnostic model derived from I.M.I.R. (chapter 6) or a similar model? No particular study has yet been proposed in this field.

As mentioned before, these recommendations embody the topics which are, in our opinion, suggested by I.M.I.R. In essence all of them have to do with secondary prevention of C.A.H.D., i.e. with the prevention of the irreversible and dramatic sequelae of the coronary atherosclerotic lesions. Even if we knew how to prevent these lesions themselves, secondary prevention would be with us for a few more decades. Nevertheless, prevention of the lesions, i.e. primary prevention, remains the most basic approach to the problem[25]. This is mentioned here because the G.P. will have to take a major interest in primary prevention. There is therefore an urgent need to develop primary prevention algorithms applicable to general practice.

REFERENCES


1. Cornfield, J. Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure: a discriminant function analysis. Fed. Proc. 21:58-61,1962

2. Truett, J., Cornfield, J. and Kannel, W. B., A multivariate analysis of the risk of coronary heart disease in Framingham. J. Chron. Dis. 20:511-524,1967

3. Norris, R.M., Caughey, D.E., Deeming, L.W., Mercer, C.J. and Scott, P.J., Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. Lancet 2:485-488,1970

4. Cohn, P.F., Gorlin, R., Vokonas, P.S. and Williams, R.A., A quantitative clinical index for the diagnosis of symptomatic coronary artery disease. N.E.J.M. 296:901-907,1972

5. Halperin, M., Blackwelder, W.C. and Verter, J.I., Estimation of the multivariate logistic risk function: a comparison of the discriminant function and maximun likelihood approaches. J. Chron. Dis. 24:125-158,1971

6. Walker, S.H. and Duncan, D.B., Estimation of the probability of an event as a function of several independent variables. Biometrika 54:167-179,1967

7. Miettinen, O.S., Personal communication. Boston, 1975

8. Miettinen, O.S., Comment on Conover, W.J.: Some reasons for not using the Yates continuity correction on 2x2 contingency tables. J.A.S.A. 69:380-382, 1974

9. Miettinen, O.S., Principles of epidemiologic research: an introductory course. Harvard School of Public Health, Boston, U.S.A., 1977

10. Duncan, B., Fulton, M., Morrison, S.L., Lutz, W., Donald, K.W., Kerr, F., Kirby, B.J., Julian, D.G. and Oliver, M.F., Prognosis of new and worsening angina pectoris. B.M.J. 1:981-985, 1976

11. Centraal Bureau voor de Statistiek, Hart- en vaatziekten: een statistische verkenning. Voorburg, 1976

12. Arntzenius, A.C., Preventie van coronaire hartziekten. Hart Bulletin 7:26-29, 1976

13. Vedin, A., Wilhelmsson, C. and Werkö, L., Chronic alprenolol treatment of patients with acute myocardial infarction after discharge from hospital. Acta Med. Scand. 575, Suppl., 1975

14. Lown, B. and Wolf, M., Approaches to sudden death from coronary heart disease. Circulation 44:130-142, 1971

15. Editorial, B.M.J. 1:408, 1974

16. Verstraete, M., Are agents affecting platelet functions clinically useful? A review. Am. J. Med. 61:879-914, 1976

17. Elwood, P.C., Cochrane, A.L., Burr, M.L., Sweetnam, P.M., Williams, G., Welsby, E., Hughes, S.J. and Renton, R., A randomized controlled trial of acetyl salycilic acid in the secondary prevention of mortality from myocardial infarction. B.M.J. 1:436-440,1974

18. Boston Collaborative Drug Surveillance Group, Regular aspirin intake and acute myocardial infarction. B.M.J. 1:440-443, 1974

19. Cobb, L.A., Baum, R.S., Alvarez III, H., Schaffer, W.A., Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. Circulation 51/52, Suppl. III:223-228, 1975

20. Hart, N.H., Hartbewaking in de prehospitale fase. Thesis, Rotterdam, 1978

21. Decision making and medical care: can information science help? (De Dombal, F.T. and Grémy, F., eds.). Proceedings of the I.F.I.P. working conference on decision making and medical care. North-Holland Publ. Comp., Amsterdam, 1976

22. Editorial. J. Roy. Coll. Phycns. Lond. 9:191-192,1975.

23. World Health Organization, regional office for Europe, Myocardial Infarction community registers. Public Health in Europe 5, Copenhagen, W.H.O., 1976

24. Pool, J. et al., Grant application to the Prevention Fund, Rotterdam, 1977

25. De Haas, J.H., Het huwelijk van preventieve cardiologie en pediatrie; naar een rationele bestrijding van coronaire hartziekten. Hart Bulletin 8:133-136, 1977

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