4TH EUROPEAN PUBLIC HEALTH CONFERENCE 2011

First announcement:

Public Health and Welfare

– Welfare Development and Health

- Prognosis of stable angina pectoris
- Guide for the care of patients with stable angina pectoris
- What to do with patients with stable angina pectoris in daily practice? (Instead of a conclusion)

In writing of the book participated 45 authors. Most of them are from Sarajevo, and a few from Tuzla, Travnik, Zenica and Bihac, as well as six authors from abroad - five from Switzerland and one from the USA. The authors of these articles are:

Mehmed Kulić, Amela Kulenović, Amna Pleho, Edin Omerbašić, Amir Omerbašić, Jasmina Fočo-Solak, Suzana Tihić-Kapidžić, Adela Ćimić, Enisa Hodžić, Snežana Brđanović, Nermina Bešlić, Stephane Zaza (Genève), Jasmina Alibegović (Zürich), Edoardo De Benedetti (Genève), Phillip Urban (Genève), Hermann Hauser (Genève), Muris Ibralić, Azra Durak-Nalbantić, Muhamed Sarić (New Jersey-USA), Amela Džubur, Alen Džubur, Šekib Sokolović, Hilmo Čaluk, Jasmin Čaluk, Zina Lazović, Zlatko Midžić, Ermina Mujačić, Anes Šošević, Belma Pojskić, Slavenka Štraus, Belma Aščić-Buturović, Bakir Kapetanović, Adnan Saračević, Nermin Granov, Hidajeta Begić, Sanko Pandur, Senad Zukanović, Amela Kečo, Zaim Jatić, Milan Mioković, Meliha Pozderac-Memija, Zorica Hondo, Samir Mehmedagić, Elnur Tahirović, Behija Berberović.

The book is richly illustrated with images, drawings, diagrams, tables, photographs, x-rays and electrocardiographic recordings and other findings. At the end of each article is given a rich list of domestic and foreign references in these areas.

Although in the writing of monographs participated 45 authors, it was written by a single methodology so that large differences between individual chapters are not visible.

The book is written in simple and clear manner so that it is accessible and readily acceptable to readers. The goal of all authors was to inform the reader of the book with various methods of testing the function of the heart and coronary blood vessels, and obtaining all necessary findings in patients with stable angina pectoris, diagnosis, clinical treatment, treatment, prevention and rehabilitation of these patients. We can say that the authors fully succeeded in this. The book can be warmly recommended to medical students, trainees in graduate studies in cardiology and angiology, general practitioners and specialist physicians in internal medicine and cardio-surgery. For medical students, doctors and post-graduate students – residents it will help in faster and easier way to cope with voluminous material in cardiovascular pathology.

And finally it is necessary to congratulate the authors and give them recognition for successful work and effort, but also to all users of the book which will be in a huge number and will draw from it a new modern theoretical and practical knowledge about the widespread, serious and more frequent heart disease, especially coronary heart disease and its pronounced form - stable angina pectoris.

The book is promoted on January 22, 2010 in the premises of Collegium Artisticum in Sarajevo. Promoters were Professor Vjekoslav Gerc and Assistant Professor Mirsad Kacila.

Professor Mirko Grujić

MSM, 2011; 23(3): 186-187

BOOK REVIEW

STABLE ANGINA PECTORIS

Author: Mehmed Kulić and colleagues: Publisher: Institute for Medical Investigation and Development of Clinical Center, University of Sarajevo; 379 pages; ISBN 978-9958-631-60-3; Sarajevo, 2009.

Cardiovascular diseases are increasing worldwide and also in our country. They become super problem of our national pathology, especially as they increasingly affect young people in the period of most productive age. In particular is increasing ischemic heart disease or coronary heart disease which contributed to the fact that in our country began the intense work on the study of this disease. Coronary heart disease is a consequence of coronary insufficiency, or coronary artery disease as a consequence, myocardial ischemia, which can be manifested mainly in three clinical forms: atherosclerotic coronary sclerosis with myocardiopathy, such as angina pectoris or myocardial infarction. The most common form of expression is angina pectoris, characterized by chest pain and to its stable form is devoted this monograph. Angina pectoris is actually a subjective manifestation of acute myocardial ischemia, which manifests itself in the form of retrosternal pain of different severity. Pain in the heart area is an impressive sign for the doctor in practical terms has to deal with on a daily basis which is very difficult and responsible task. It is therefore particularly important that the doctor and practitioner internist are informed about all the new knowledge and experiences related to coronary heart disease and its specific form - stable angina pectoris.

These were the main reasons that a group of doctors from Bosnia and Herzegovina decided to write a monograph on coronary artery disease or a stable form of angina pectoris in order to fill the current lack of literature in this field. The goal of authors was that the doctors and medical students have an adequate contemporary monograph in this field in order to facilitate the learning and training about this difficult and serious problem. The whole material is presented on the basis of long term individual experience of the authors who participated in writing the book because each of them is an expert in cardiovascular pathology affirmed in the immediate area in which is working.

The book has 33 separate articles, or titles. These are:

- The definition of stable angina pectoris
- Anatomy of coronary blood vessels
- Physiology and pathophysiology of coronary blood flow
- Clinical picture and examination in patients with stable angina pectoris
- Laboratory tests for patients with stable angina pectoris
- Electrocardiogram and Holter ECG monitoring in patients with stable angina pectoris
- Ergometry and spirometry testing of patients with stable angina pectoris
- Nuclear medical examinations in patients with stable angina pectoris
- Radiological investigations in patients with stable angina pectoris
- Cardiac magnetic resonance imaging
- Coronary CT scan
- Role of echocardiography examination of patients with stable angina pectoris
- Stress test in cardiology. Advantages of stress echocardiography compared to nuclear stress test
- Preventive and treatment without medications of stable angina pectoris
- Beta adrenergic blockers in the treatment of stable angina pectoris
- ACE inhibitors in the treatment of stable angina pectoris
- Nitrate preparations in the treatment of patients with stable angina pectoris
- Treatment of patients with stable angina pectoris newer pharmacologic agents
- Inhibition of calcium channels in the treatment of patients with stable angina pectoris
- Statins in the treatment of patients with stable angina pectoris
- Anti aggregation therapy in patients with stable angina pectoris
- Hormonal treatment of diabetic patients with stable angina pectoris
- Treatment of malignant arrhythmias in patients with stable angina pectoris
- Percutaneous coronary insufficiency in patients with stable angina pectoris
- Syndrome X - or chest pain with normal coronography findings
- Precordial pain in children and adolescents
- Surgical treatment of stable angina pectoris
- Rehabilitation of patients with stable angina pectoris
- Monitoring of patients with stable angina pectoris with the team family medicine aspect
- Disability score of patients with stable angina pectoris

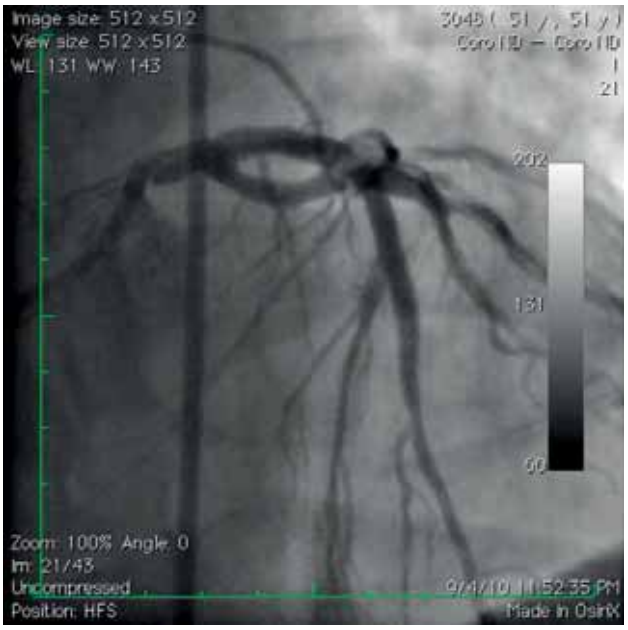

Figure 2. Final result in apical view

six months but he was on aspirin before admission.

In conclusion, very late ST may occur even after four years and in the absence of known risk factors. Using DES requires complete understanding benefits and risks .

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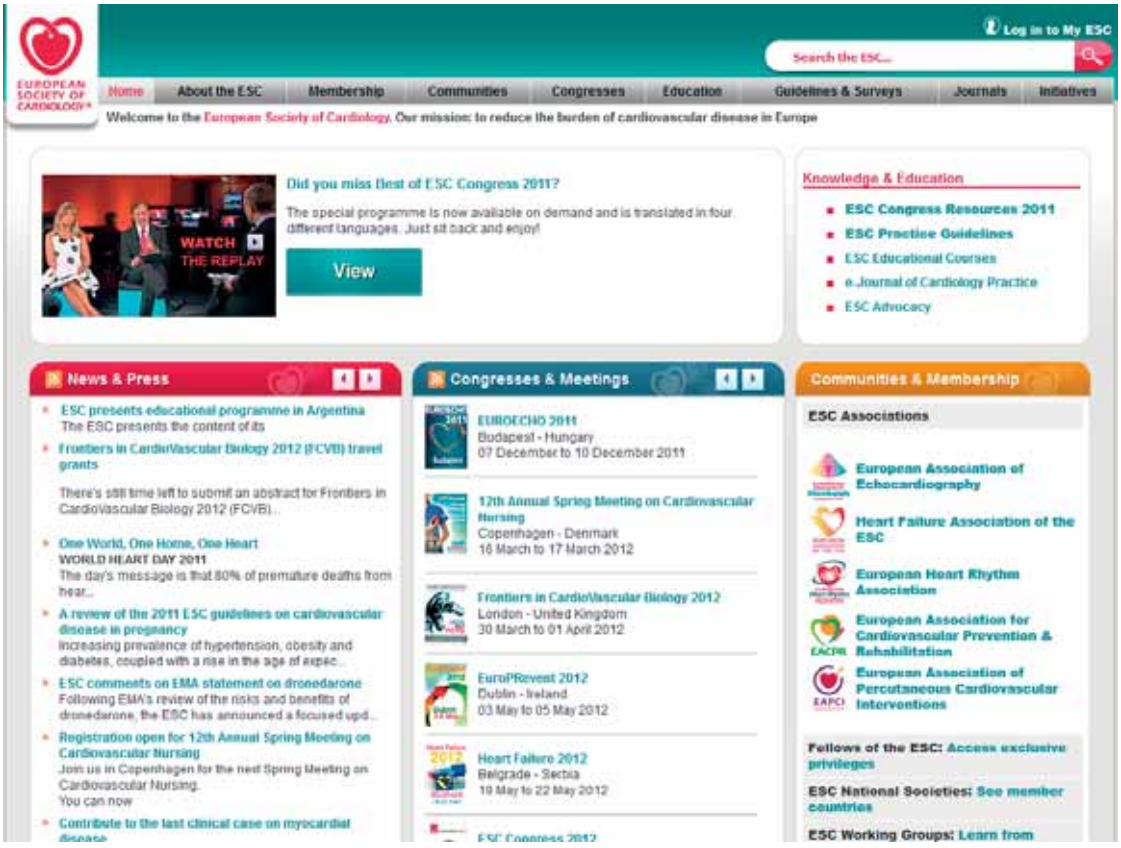

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A Stent Thrombosis 1465 Days After Implantation

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CASE REPORT

SUMMARY

Stent thrombosis is a fatal complication in patients after percutaneous coronary intervention. We report drug eluting stent thrombosis occurred over four years after implantation.

Key words: drug eluting stents, thrombosis, coronary angiography.

1. INTRODUCTION

Percutaneous coronary interventions (PCI) with drug eluting stents (DES) reduced restenosis rate (1). However, safety of DES due to stent thrombosis (ST) is a major concern.

We present very late sirolimus eluting stent (SES) thrombosis occurred 1465 days after implantation.

2. CASE REPORT

A 60-year-old man, a smoker presented with two hours after the beginning of chest pain. The patient had undergone PCI for the deployment of a SES (2.75mm diameter, 28 mm long) in the left anterior descending coronary artery (LAD) in 2006. He took clopidogrel for 6 months and continued taking aspirin. The physical examination was unremarkable. The ECG showed ST segment elevation in anterior leads. Coronary angiography elicited a total occlusion of the SES (Figure 1). A loading dose of 600 mg clopidogrel, heparin (10.000IU) and a glycoprotein IIb/IIIa antagonist (tirofiban) were administered. After manually aspiration of the thrombus, a BMS (3.0 mm diameter, 32 mm long) was implanted at 14 atm. The chest pain resolved quickly and good TIMI3 flow in LAD was achieved (Figure 2). The hospital course was uneventful and the patient was discharged four days later in good condition. He has been advised to continue on aspirin and clopidogrel indefinitely.

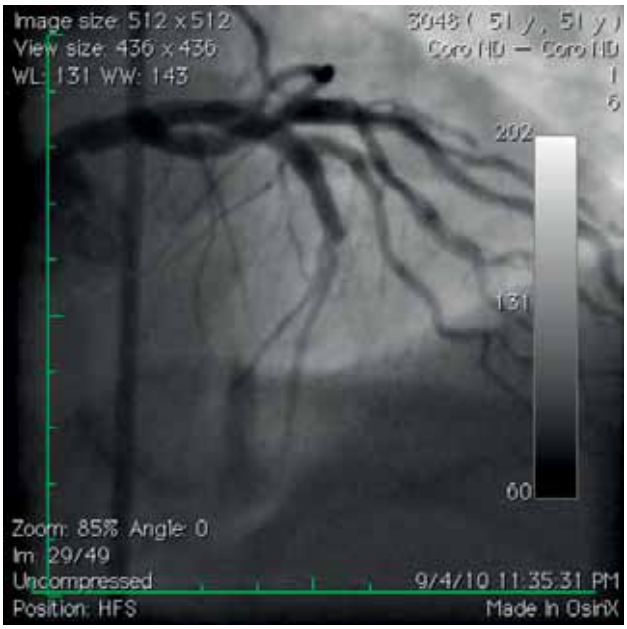

Figure 1. Total occlusion of the left anterior descending artery in apical view.

3. DISCUSSION

Clinical trials showed reduced target-lesion revascularization with DES. However, ST is a major limitation. Although most ST have been documented within the first 30 days, DES thrombosis may occur up to 4 years with annual incidence of 0.4-0.6% (2). Premature anti-platelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction were identified as predictors of ST (3).

The Academic Research Consortium (ARC) classified stent thrombosis according to the time; early (1day), subacute (1-39 day), late (30-360 day) and very late (>1 year) and level of certainty of stent thrombosis; definitive or probable (4).

It is unclear that very late ST is related to implantation of DES. ST occurs equally in DES and BMS when ARC criteria used (5). However, meta-analyses using per-protocol definition of ST showed higher very late ST with that DES (6).

Previously, only three DES thrombosis four years after implantation have been reported (7). All these patients had received SES for LAD stenosis. All patients were stop taking clopidogrel and two of these patients were on aspirin during the incident. Our patient took clopidogrel for only

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in primary line that easily identifies high-risk groups among their patients, to focus attention on high-risk patients and therapeutic possibilities for them, and point to high risk groups in an effort to encourage the reduction of risk factors to reduce and neutralize the occurrence of coronary disease.

Work should be done on strengthening preventive medicine, which today is increasingly losing its place importance which it deserves and it, or by its methods try to predict or stop the disease until it has not progressed or at least slow down and not deal with the consequences of the disease which is usually treated by aggressive methods. Namely, the results of these methods are very small and barely visible, and sometimes it's too late to apply therapy. All it costs society in terms of frequent absence from work, and increase the number of young disabled, which is a consequence disability by coronary disorders. We should not forget that health is a precious good about where care should be taken not to deal with it only when it is violated, it is important to work on developing the individual's consciousness from an early age, developing healthy eating habits and healthy living. Mentality of our people is such that they start to think about your health only when they lose health, which should be changed in people's mind.

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the entire spectrum of values–whether it is positive in the first predecessor in the family tree, or more distant, whether it occurred early or later.

It is understood that the use of tables, considering the fact that for example when it comes to age, they do not use the exact age (years) for decades, and as for smoking, not the number of cigarettes smoked and the smokers' overall experience, but only the fact of whether someone is a smoker or not, it is understandable that yield approximately a not absolutely accurate value of future risk. However, it is better than no value. In addition, the application of these tables has a very important role in education and health care professionals and patients, because it points to the total coronary atherosclerotic milieu, which exists in every individual, and as you pointed out, there is a relative balance of risks in the same person depending on how to modify risk factors or the relative risk relationships between people.

Practically, the table according to which an individual determines the risk, as well as changing of the risk of coronary heart disease, according to the correction of certain risk factors (smoking, hypertension, cholesterol) is a precious value that can direct the efforts of medical services in the further course of action.

The importance of prevention of risk factors confirmed the evaluation of the risk of coronary disease in primary care, comparing three different tables, and recently has shown that certain risk factors can be eliminated and others reduced, thus slowing the evolution of coronary heart disease and thus moving away occurrence of clinical events and improve prognosis (Isles CG, 2000).

For a correct assessment of the degree of coronary disease severity or risk for its occurrence, the estimated coronary risk, getting so far known and scientifically proven fact that, combined in absolute risk, an indication of the situation and suggest a strategy to modify and eliminate the risk (1). Assessment of coronary disease risk and that risk reduction is the responsibility of medical staff and doctors, particularly primary health care level.

The path of the coronary disease risk assessment and risk reduction is basically based on three steps: 1. assessment of risk factors and other clinical data collection related to patient risk, 2. interpretation of risk and risk indicators in absolute values (in relation to emergence of the dreadful event for a certain time period), or relative risk (presence, a strong middle, or high risk were compared with age-and sex), 3. based on results of recent risk-appropriate interventions to minimize and eliminate the risk of disease and prevention of risks in the future (65). Estimating total risk of cardiovascular disease we receive the clear data to determine the intensity of preventive measures.

Neither the European nor the American table to determine the future of the absolute risk is not excluded in the risk assessment a positive family history of coronary artery disease, improper nutrition, obesity, physical inactivity, psychosocial factors (personality type, life style, stress), ethnic characteristics, excessive alcohol consumption, hypertriglyceridemia, insulin resistance, the level of homocysteine, lipoprotein (a), fibrinogen, C reactive protein etc. In addition to the tables in some way provide a picturesque understanding and insight into the game and the mutual influence and synergistic risk factors increase or decrease the likelihood of diseases such as coronary heart disease, there are computerized programs that after completing the data input passing through all the tables and automatically reads the likelihood. Such programs are based on a Framingham study (U.S.) or PROCAM (Germany) study and other studies in the world. However, for any individual patient it is necessary to consider their absence or presence in estimating the absolute risk of diseases such as coronary heart disease. One of the weaknesses of these tables is that the absolute risk is underestimated if there is only one risk factor or long-term action may lead to cardiovascular disease (e.g., elevated blood pressure).

Regardless of all the tables and the opportunities that are now provided in the treatment of coronary disease in general should be accessible to every individual patient to assess his risk.

Identification of risk factors and estimates of absolute short term (ten years) and long-term risk of coronary heart disease is the first step in primary prevention. The second step is a kind of re-evaluation of the absolute risk, taking into account the conditional and predisposing risk factors which have not yet found their place in the table. Once determined the absolute risk, the second step is a modification of risk factors that can influence. Risk factors for cardiovascular disease can be divided into four categories according to the possibilities of interventions to modify them individually and so reduce the risk: (I) modify its proven to reduce the risk of CVD, (II) modify their likely reduces the risk of CVD, (III) their modification could reduce the risk of CVD, and (IV) the risk factors that can not be modified. Prediction of absolute risk for coronary disease is not determined by those patients who already have a coronary event, because it is considered that their risk of repeating is more than 20% over the next 10 years. However, no small number of younger patients who are seen in clinical practices that virtually had neither one of the risk factors and look healthy, it is necessary to evaluate cardiovascular risk, and therefore carry out preventive activities.

Regardless of the current research we does not yet know the exact etiopathogenesis of atherosclerosis and coronary heart disease caused by it, but our understanding of the concept of reduced exposure to various factors, and the theory of probability of action of these factors on the process of atherosclerosis. Since atherosclerosis is in some sense is a generalized disease, it is considered as equivalent to coronary disease, to begin with secondary prevention, it can take a peripheral vascular disease and/or cerebrovascular disease.

4. CONCLUSION

All the above mentioned impose conclusion that at all, especially at the primary health care level, where the determining role of family physicians need to conduct research which would include examination of risk factors for coronary heart disease. These data in this paper, based on the experiences of different studies in the world confirms the importance and significance of using a modified algorithm estimates the overall risk of coronary disease adaptable to our conditions in order to assist the physician practitioners

programs, reduced incidence of diseases of the circulatory system, close to 70%.

There are scientific evidences that lifestyle changes, while reducing risk factors may slow the development of coronary disease before and after the onset of clinical manifestations of disease (Raljević 2003). Until the mid-nineties, the intervention attempts to change people some of the risk factors were based on assessing the value of each factor and their changing (hypertension, smoking, dyslipidemia, etc.). However, since the mid nineties, the type and intensity of interventions to change risk factors are determined at a higher, more sophisticated level by determining the overall potential for atherosclerotic coronary artery disease (taking into account not all, but the main risk factors). Thus, in humans there is a multifactorial risk of coronary heart disease and the European Society of Cardiology determine the importance of multifactorial risk assessment in relation to the intensity of the intervention on individual habits, taking medication. The concept of probability of the emergence of coronary heart disease based on determining the risk factors, as well as set up tables for predicting the likelihood of the emergence of individual coronary heart disease by using their actual, measured data points that each of them shall give the probability of contracting, and people with coronary heart disease in the future. Although previously is published over 275 different tables for assessment of cardiovascular risk across the world for the occurrence of cardiovascular disease, there are specific characteristics of individual nations and of every population group, overall living standard, so we should take into account the significance that the tables are adequately adjusted. For all these reasons it is recommended the modification of "Tables for coronary risk" for each country (EuropenF. 2003).

Assessing the patient's ultimate or global risk of cardiovascular disease is the first level of prevention and enables physicians to identify and provide an acceptable method of treatment of risk factors (Assmann G.1999). A large study testing risk factors for asymptomatic patients showed the presence of risk factors, their ability to eliminate, so that only full knowledge of the status of the patient's risk factors is the basis in making decisions about how the treatment (JN Cohn 2003).

Since 1994 the European Society of Cardiology, the Association for arteriosclerosis and hypertension have been published "Recommendations for prevention of coronary heart disease in clinical practice" (Raljević 2003).

In 1996 was organized the meeting of 37 national cardiology organizations in France and reached was an agreement for the strategy and the adaptation, dissemination and implementation of these recommendations in daily clinical practice. Also in 1996 at 27 Bethesda Conference established that treatment of risk factors should be an integral part of optimal care for patients with established diagnosis of disease or risk that can occur after the development of coronary heart disease (Pyörälä K.1994). From that time until today, risk factors, such etiological factors draw attention. Risk factors directly or indirectly modify the degree of development of disease. The concept of risk factors presented in the Framingham study, more than 50 years ago remains the gold standard in assessment of risk factors for coronary heart disease (Pearson T. 2002). Tables that are used to assess coronary risk is most often recommended are basically all purpose use or are based on Framingham study that prospectively followed a total of 5127 Framingham residents (2282 males, 2845 females) aged 30-59 years at the entrance to the study in 1949. Otherwise Framingham is a town about 30 miles west of Boston in New England in the United States at that time had a total of 28000 inhabitants mostly of European origin. Framingham study indicates up to 10 times higher rate in multifactorial etiology of coronary heart disease (Lloyd-Jones DM 2004).

PROCAM (Prospective Cardiovascular Munster) study is based on nine risk factors, where the figures used for the quantitative assessment of risk, using the algorithm and applying it to persons aged 40-65 years. Four-year monitoring of 2754 men aged 40-65 years observed the impact of different risk factors for cardiovascular complications. For those who only had diabetes or hypertension as only risk was 2.5 times higher. But if they were present together, the risk was eight times higher. Or, the presence of abnormal lipid profiles increased the risk by 16 times. But if it was present with diabetes or hypertension, the risk increased by 20 times (Assmann G. 1999).

European Society of Cardiology is using the database from Framingham study in 1994 made the tables prepared on the basis of which the purpose of implementing primary prevention measures based on the values of total cholesterol, systolic blood pressure, as well as continual performance and membership of a particular age group, gender, smoking status and presence of diabetes as a categorical value (membership categories) could determine ten-year risk of coronary heart disease.

New European table for the risk based on HeartScore system (Systematic Coronary Risk Evaluation) and the recommended risk maps established on the basis of large prospective studies in Europe. Table for risk is the result of 3rd Joint Task Force and Joint CVD Prevention Committee, and it is not just about predicting coronary risk but the overall cardiovascular risk. Levels of risk in the next ten years are given in categories below 5%, 5-10%, 10-20%, 20-30%, 30-40% and over 40%. Famous INTERHEART study identified nine risk factors for acute myocardial infarction among others are: blood lipids, smoking, elevated blood sugar, elevated blood pressure, abdominal obesity. The study showed that the presence of the five most intense easily modified risk factors for coronary heart disease, making about 80% of the risk of acute myocardial infarction (Yusuf S.2005).

American Associations AHA/ACC in the risk assessment used a relationship of total cholesterol and HDL and to emphasize the advantage of the recent European tables. Since around Europe do not routinely measure HDL cholesterol, given the recommendation to use the total cholesterol that is accessible and tables can be used throughout Europe. When the AHA/ACC scoring system adds up all the points we get the so-called assessment of global risk for coronary disease. In the English tables also taken is HDL-cholesterol and factor in the presence or absence of signs of left cardiac ventricle hypertrophy.

In the French tables are also included family history and

can be protective. Mediterranean diet and the diet rich in fish oil may be helpful in preventing morbidity and mortality from coronary and cardiovascular diseases (54). An unhealthy diet–it is estimated that reducing the intake of fruits and vegetables leads to 31% of patients to coronary artery disease and 11% of cases of stroke worldwide. High intake of saturated fats increases the risk of coronary and cerebrovascular disease by activity of increased fat in the blood on the development of atherosclerotic changes in the vessel wall.

3.4. "NEW" RISK FACTORS

Homocysteine

By the research of the population health status it was found that 1-2% of the population has an increased value of homocysteine, which is determined by the frequency of cerebral and peripheral vascular disease by 20-40% and coronary heart disease by 10-25%.

Homocysteine is an amino acid which is one of the most important for the production of proteins and tissue regeneration. Increased values of homocysteine in the blood in combination with smoking and high blood pressure causes further thickening of the arteries. High levels of homocysteine are associated with early diagnosis of heart and blood vessels and are an independent risk factor for developing coronary disease. A recent prospective study exploration of risk factors to cardiovascular disease have shown that even moderately increased value of homocysteine in the blood, increasing the risk of coronary arteriosclerosis, cerebral and peripheral blood vessels and increase the risk for death from cardiovascular disease.

Meta analysis of 27 research studies of coronary disease showed that homocysteine levels increase for every 5 micromole/l, increases the risk for coronary heart disease by 60% in men and 80% in women. Elevated homocysteine levels showed a correlation with the risk of developing coronary heart disease, and are especially recommended for testing and inclusion of treatment for asymptomatic people who have coronary disease, but have a family history of the early coronary heart disease (55).

Thrombogenic factors

Abnormal coagulation of blood–elevated levels of fibrinogen and other markers of coagulation increases the risk of cardiovascular complications. Fibrinogen is a specific blood protein important for normal blood clotting, but an excess causes agglutination of platelets, causing the artery creates cloth. Fibrinogen can indicate inflammation that accompanies atherosclerosis and further aggravating the already existing damage to the artery walls. It has been noted that smoking, then sedentary lifestyle, alcoholism, use of estrogen significantly increases the concentration of fibrinogen in the blood.

In addition to fibrinogen and several other factors involved in blood coagulation, which are associated with increased risk of coronary heart disease. The level of factor VII was predictive factors of myocardial infarction in some studies. Plasminogen activator inhibitor 1 (PAI-1) was observed to increase the risk of re-occurrence of myocardial infarction. Increased platelet aggregation is related to increased risk of coronary heart disease. Activation of platelets may be risk factors for acute myocardial infarction and is related to the accelerated glukoprotein IIb / III

Inflammatory factors

It was confirmed that cardiovascular incidents have a higher incidence in patients who have had repetitive viral or bacterial infection. Epidemiological research studies of inflammatory factors and cardiovascular disease have confirmed the correlation of cardiovascular disease and acute incidents with chronic periodontal inflammation, Helicobacter pylori infection, Chlamydia pneumoniae infection, cytomegalovirus infection.

CRP–C-reactive protein has emerged as an interesting and powerful new clinically useful marker for increased cardiovascular risk (56). C-reactive protein is produced by the liver in the normal immune reaction to injury or infection. Studies have shown that women who have high CRP are seven times more likely to develop heart attacks than women with the low level is one of the explanations that the accumulated cholesterol and fat to burn the blood vessels and because the body reacts by creating an inflammatory elements occurs fat and plaque rupture, followed by vessel blockage (57). The results of the research levels of inflammation markers in patients with cardiovascular incidents–fibrinogen, CRP and others have shown elevated levels (58).

The combination of major coronary risk factors and CRP showed the highest relative risk for myocardial infarction. Large epidemiological studies have shown that increased concentrations of CRP in serum are associated with increased cardiovascular risk in both sexes of patients with coronary disease (24).

In elderly people–men and women, elevated levels of CRP were associated with increased 10-year risk of coronary heart disease, regardless of the presence or absence of other cardiac risk factors (59). Inflammation and several inflammatory factors associated with increased cardiovascular risk, such as elevated C-reactive protein–CRP (60). Results published meta analysis of inflammatory indicators and cardiovascular disease showed that fibrinogen, CRP, inverse protein and the total number of leukocytes in the blood indicate a strong relationship to cardiovascular risk (1)

Prevention of coronary heart disease risk factors

An important shift in the primary prevention of coronary heart disease is the attempt to look at the total atherosclerotic potential, which causes the disease, depending on the interaction of various risk factors.

The concept of risk assessment factors, their reduction, initially begun in the Framingham Heart Study and refined in other models, a basic form the basis for the management of patients by lowering the incidence of coronary heart disease (Pitt B 1999). Primary prevention measures to be taken are to changing lifestyles, reducing risk factors of paramount importance is to reduce morbidity and mortality from cardiovascular disease and improve the overall health of the population. Numerous studies and meta-analysis showed that lifestyle modification, risk reduction factors, particularly by changing diet, stopping smoking, increasing physical activity, blood pressure control can be effective in the prevention and reduction of coronary heart disease. Thus, in Finland, the implementation of prevention

vascular disease before the 50-year male gender, before 55-years for females) is indicative of the degree of coronary risk assessment.

Information about premature death due to cardiovascular diseases in a family history should be taken into account in assessing risk in healthy individuals. Needed are advice on positive habits and necessary are also appropriate treatment of risk factors in the case of families with a high prevalence of cardiovascular disease (8).

Special attention is directed to any family of hypercholesterolemia are related to high risk of cardiovascular disease and this requires urgent action because the complications of treatment starting from 30 years of age.

Age

By aging the human body is increasingly exposed to adverse environmental influences and consequences of complications are more common in all organic systems, including the heart and blood vessels.

Risk for coronary heart disease is higher in men above 40 years of age and women over the age of 50 with two or more risk factors.

Risk factors that are directly related to age, coronary heart disease are usually after the sixties, and reduction of risk factors is necessary and advisable in all years except when life is seriously threatened (48).

In an adult male incidence of coronary heart disease increases with age until 60 years of age, and a similar trend in women ranging from 50 years of age.

It is known that coronary heart disease effectively arises and begins in the younger years, and to accelerate in the presence of risk factors. That is why the necessity of correction of risk factors at an early age, and their detection and treatment of all living groups.

Old age is the most important independent risk factor for cardiovascular disease, the risk of stroke doubles in every decade after the age of 55.

Gender

It is known that male gender has a greater risk of developing cardiovascular diseases than women, as long as women are of childbearing age. This effect is attributed to the protective effect of hormones.

In men, cardiovascular risk increases with age. After menopause the incidence of coronary heart disease in men and women are gradually equalized.

At sixty years of age the ratio is 1:1. According to statistics, women get sick less often, but if they get sick more often die as it explains the greater the expected length of life.

3.3. OTHER RISK FACTORS WHICH CAN BE INFLUENCED

Low socio-economic status, such as continuous, inverse relationship with risk of coronary and cerebrovascular disease, then, the use of certain medications (some of oral contraceptives and hormone substitution therapy) may increase the risk of coronary heart disease. Expansion of the left ventricle of the heart is an important indicator of impending cardiovascular death.

Alcohol

Use alcohol at level, for example, one to two drinks a day may reduce coronary heart disease up to 30%, but higher intake can damage the heart muscle. Public recommendations for safe alcohol limit the amount of used and continue to be difficult to make because the harmful social and health effects of alcohol influence and reduce the possible positive effects of moderate alcohol consumption on coronary risk (49). The mechanism of the harmful effects of alcohol on the cardiovascular system refers to an increase in blood pressure and flow to the risk of stroke and coronary attack, the incidence of cardiomyopathy, an increase in the incidence of cardiac arrhythmias (50).

Protective effects of moderate alcohol consumption are related to the modification of several well-known pathological mechanisms that lead to atheroma and that the HDL cholesterol, a favorable effect on fibrinolysis, decrease in platelet aggregation. It is clear that it should be noted that moderate alcohol consumption up to 30 grams per day is not harmful to the cardiovascular system, but without pointing out its protective effects, since it would encourage alcohol consumption could be misinterpreted and lead to excessive intake of alcohol, which increases the risk for total mortality of the population (8).

Psychosocial factors

There is more information and many are professional records that stress, lack of social support, depression and lower social status represents associated (increased) risk factors for coronary heart disease (51). Psychosocial profile of the patient has the strongest argument in explaining the importance of socioeconomic gradient in coronary heart disease emerging.

Heavy physical exertion, inability to control the situation at work, lack of support at work and lack the psychological capacity to successfully cope with stressful situations in life makes it impossible to predict the occurrence of coronary heart disease (52).

There is a general opinion that stress is an important risk factor in the development of myocardial infarction. Among other things, the goal of a five-year INTERHEART study was to examine the relationship between psychosocial factors and stress globally, the incidence of myocardial infarction and results of studies have shown that depression is associated with increased risk for coronary heart disease (22). The results of INTERHEART study showed that the presence of psychosocial stressors is associated with an increased risk of developing acute myocardial infarction (22).

However, stress is a very broad term, consists of several interconnected elements, and therefore it is very difficult to objectify. Psychosocial stress concept includes external stressors such as workplace stress, severe life events, financial problems, and reactions to such factors as depression, fatigue, anxiety, sleep disorders, etc. Psychosocial stress (chronic life stress, social isolation and mental anxiety increase the risk of coronary and cerebrovascular disease. It is shown that the presence of psychosocial stressors is associated with an increased risk of developing acute myocardial infarction (53).

Nutrition

World Health Organization and other interest groups have shown that a diet with plenty of red meat and fat, excess salt and refined sugar are correlated with increased risk of heart disease (9). In contrast, the diet with more fruits, vegetables, whole grains, seeds, fish and chicken

nence). The presence of one or more comorbid conditions increase the health risks linked only for BMI.

Elevated blood sugar

The prevalence of diabetes is steadily increasing, especially in developed countries. It is estimated that 195 million people worldwide suffer from diabetes and this number will grow to at least 330 million in 2030. In patients with diabetes mellitus, coronary heart disease is among the leading causes of morbidity and mortality. The likelihood of developing coronary heart disease is 2-3 times higher in men and 3-5 times higher in women with diabetes compared to people without diabetes. In addition to microvascular changes, such as nephropathy, retinopathy and neuropathy, diabetes leads to atherosclerosis or macrovascular changes.

However, despite the obvious importance that diabetes has in the pathogenesis of coronary diseases, in approximately half of patients remain undetected. People with elevated blood sugar have a high risk of coronary heart disease, stroke, peripheral vascular disease and renal disease (42). Diabetes increases the risk of coronary heart disease by 2 to 3 times, stroke by 3-4 times, and peripheral arterial disease for 2 to 4 times.

According to the results of the Euro Heart Survey research, diabetes and abnormal glucose tolerance are present in most patients with coronary heart disease in a study GAMI (Glucose Abnormalities in Patients with Myocardial Infarction) found that 67% of patients with myocardial infarction without previously diagnosed diabetes have or newly discovered diabetes or abnormal glucose tolerance.

The young people who are healthy and have elevated blood glucose, often found and elevated levels of total cholesterol, low HDL cholesterol values and elevated or borderline high blood pressure. Elevated blood glucose values, even those who are still within the reference value are an independent prognostic predictor of early mortality in patients with acute myocardial infarction. The pathophysiological mechanisms responsible for cardiovascular changes in patients with diabetes include insulin resistance, hyperinsulinemia, hyperglycemia, elevated levels of free fatty acids, dyslipidemia and arterial hypertension are often present. Metabolic disorders leading to endothelial dysfunction, vasoconstriction, inflammatory response and prothrombotic state, and ultimately to atherosclerosis and its clinical manifestations.

Both types of diabetes mellitus type 1 and type 2 are correlated with significantly increased risk of coronary disease, cerebrovascular disease and peripheral vascular disease and these diseases are the leading cause of morbidity and mortality in patients with diabetes (43).

In people with altered glucose metabolism, progression to diabetes can be prevented or delayed with lifestyle changes and habits. Tendency to develop diabetes is present in those who are overweight (44). Lowering of blood glucose substantially achieve the reduction of incidence of cardiovascular and coronary heart disease according to a study STOP-NIDDM (Study To Prevent Non-Insulin-Dependent Diabetes Mellitus), where it is found that acarbose, which specifically reduces postprandial glucose levels jump, can reduce the incidence of cardiovascular complications, and meta-analysis of seven studies of acarbose in patients with type 2 diabetes showed that the risk of myocardial infarction was significantly lower in patients treated with acarbose compared to placebo.

In patients with diabetes is important the strict regulation of blood sugar, but also a comprehensive control of other cardiovascular risk factors, especially elevated blood lipids and elevated blood pressure.

Increased body weight

According to the World Health Organization estimates that approximately 1 billion people worldwide have increased weight or are obese. (9).

WHO estimates that about 18 million of children under 5 years old have increased body weight and these children are at increased risk for developing high blood pressure and dyslipidemia in early adulthood (9). Effect of obesity for the occurrence of cardiovascular disease can be divided into direct (effect on heart) and indirectly (through the development of dyslipidemia and hypertension). Indirect effect is a consequence of metabolic changes known as insulin resistance.

Already mentioned Framingham Heart Study showed that weight is the third most important risk factor for coronary disease in men. There are concerns that estimates of obesity index was the best predictor of cardiovascular risk and cardiovascular risk factors: body mass index (BMI), measurement of waist circumference (WC), or the ratio of waist and hip circumference (WHR).Recent studies have shown that the regional distribution of fat may be more important cardiovascular risk assessment of the total body weight. Abdominal obesity in particular has shown great association with metabolic and cardiovascular risk. (45).

Regardless, this measurement of cardiac risk are simple, inexpensive and widely accepted, and increased abdominal obesity (WC), and the relationship between waist–hips are at greatest risk for developing cardiovascular disease, as demonstrated cohort and case-control study (46). Follow-up study of obesity and abdominal fat distribution in older women in America (The Iowa Women's Health Study) showed that in general both measuring thickness distribution in addition to body mass index (BMI), may provide additional information to assess cardiovascular risk (47).

Report of the WHO and the American Institute of Cardiovascular and Lung Diseases (NHLBI) of obesity suggest that measures of abdominal obesity is used as an indicator of metabolic risk factors within each category of body mass index (BMI) (9). Worldwide trend of overweight has doubled in parts of the world where there has been increasing westernization of the traditional diet, as are vegetables, fruits and whole grains replaced with calorific foods, high concentrations of fat, sugar and refined carbohydrates.

3.2. RISK FACTORS FOR THAT CAN NOT BE INFLUENCED

Personal and family history

For most cardiovascular disorders, there are indications that the inherited tendency to get sick. It is not a classical hereditary transmission of the disease, but it is a clear correlation between the disease in parents and occurrence in children.

Genetic endowment or a family history (increased risk in first degree relatives who have had coronary or cerebro-

astatin group, indicating the efficiency of atorvastatin for primary prevention (37). The first study in the world ASCOT-LLA (The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm) has shown the benefits of lowering lipids in patients with high blood pressure and three assigned to cardiovascular risk factors in the reduction of cardiac stroke (1).

There is a statistically significant correlation between the reduction in vascular risk with the use of statins in patients with coronary heart disease. The evidence suggests that statins reduce the progression of plaque, a reduction in total serum cholesterol reduces the incidence of coronary attack (38).

Smoking

Tobacco smoking and cardiovascular risk are in a strong causal relation, continuous, stepped and independent, with a linear relationship between the risk of coronary disease and number of cigarettes smoked (8). It is estimated that 17 million people worldwide die from cardiovascular disease each year, a significant number of these deaths is attributable to smoking, which increases the risk of dying from coronary heart disease and cardiovascular disease by 2-3 times (9). It is estimated that in the U.S. total direct and indirect expenditures related to tobacco amount to 75 billion dollars. Nicotine increases the cardiovascular risk with age, up to 50 years the risk is two times higher in men, to be matched with women in post menopause period. The risk is even greater in women than in men. (39). Confirmed is the strong association of smoking status in heavy smokers, smokers experience and duration of early starting smoking, with the occurrence and death from coronary disease (40). Robson and colleagues have calculated how long after quitting the risk of former smokers is the same as the risk of smokers. The results suggest that only those persons, who have stopped smoking for at least 15 years ago, are similar to people who do not smoke (6). United INTERHEART case control study showed that smoking six to ten cigarettes a day by twice increased risk of heart attack, smoking 20 cigarettes a day increases the risk by four times and smoking 40 cigarettes increases the risk nine times (22). In contrast a heart attack decreases by 50% in people of both gender groups, who have stopped smoking, especially in the first two years after quitting. Quitting smoking has shown that the risk declines in patients with or without established coronary disease (8). People who have stopped smoking for a period of 5-15 years prior myocardial infarction, had levels of other risks, like the people who did not quit.

Reduced physical activity

Epidemiological and prospective studies that were conducted during 50-ies have shown that lifestyle which is passive, without physical work and sitting have a negative impact on health and present a risk of morbidity and death from all types of cardiovascular disease (8). WHO estimates that approximately 60% of the world's population has decreased physical activity (9). It is known that a certain level of physical activity is important in the prevention and correction of obesity, increased fat in the blood, elevated blood pressure, elevated blood sugar, or the risk of danger for the development of cardiovascular disorders, especially for developing coronary heart disease.

Regular physical activity, particularly in the middle and older age have a beneficial effect on reducing morbidity and mortality of cardiovascular diseases, as well as reducing the overall risk of heart disease and cardiovascular disease (41).

In physically inactive people there is two times higher risk of heart disease and cardiovascular disease in relation to persons who are physically active. Physical inactivity increases the risk of coronary heart disease by eight times, and stroke by two times compared to those who have a satisfactory physical condition. High levels of physical activity contribute, also, to reducing obesity, reducing plasma lipid levels and decrease in blood pressure. It has been shown that patients with Atherosclerotic changes in blood vessels are equally expressed in plaque regression when they are physically active and those who take medication for lowering blood fat.

Decrease in physical activity, and if you do add more and inheritance leads to obesity, which contributes to disease development cardiovascular diseases.

Obesity is a serious chronic disease that can lead to many medical complications that impair quality of life and reduce the life duration, and whose treatment has a high cost. Obese people have higher morbidity and mortality in the population of Bosnia and Herzegovina and even in the world.

The measurement of obesity is in some way, "Sisyphean task". However, various international groups have concentrated their work on finding appropriate measures of obesity. One of them is the BMI-- Body Mass Index. BMI is a single measure of obesity, independent of other parameters, adopted in 1990 as a method of choice for measuring obesity.

It is a relationship between weight and height used to estimate the impact of obesity as a risk factor to health. It is presented by the mathematical formula that correlates with body fat in adults, and is calculated as weight in kilograms divided by the bodily height in meters squared (2).

TT = Body weight ; TV = body height

BMI is used to assess health risks in adults. Does not depend on gender and age because there are a wide range of applications (19-70 years).

BMI	Body weight	Risk of illness based on BMI	Risk of illness based on BMI and co morbidity
< 18.5	Skinny	Minimal	Low
> 18.5–25	Normal weight	Low	Moderate
> 25–30	Over weight	Moderate	High
> 30–35	Moderately obese	High	Very high
> 35–40	Very obese	Very high	Extremely
> 40	Extremely obese	Extremely high	Extremely

Table 2: Body weight and health risk based on BMI; source: (2)

Comorbidity is a condition associated with obesity, which worsens with increasing BMI, and often improves if obesity is treated successfully. Co morbidities associated with obesity: hypertension, cardiovascular disease, dyslipidemia, type II diabetes, "sleep" apnea, osteoarthritis, and infertility, other pathological conditions (idiopathic intracranial hypertension, varicose veins of the lower extremities, gastroesophageal reflux, and urinary stress inconti-

	AGE (years)						
Illnesses, states and injuries according to ICD-10	Total	Under 1	1-6	7-14	15-18	19-64	65 and more
TOTAL NUMBER OF DISEASES (WITHOUTH INJURIES), CHAPTER I-XVII, No. 1-185	1927528	85299	271181	259523	100462	828011	383052
89. Acute rheumatic fever (I00-I02)	371	0	2	5	5	243	116
90. Chronic rheumatic heart disease (I05-I09)	2108	0	2	2	1	827	1276
91. Hypertension (I10-I05)	192392	0	1	69	256	110953	81113
92. Acute myocardial infarction (I21-I22)	3643	0	0	2	6	2185	1450
93. Other ischemic heart disease (I20, I23-I25)	22087	2	1	4	175	11051	10854
94. Heart rhythm disorders (I44-I49)	8311	1	5	19	28	4244	4014
95. Other heart diseases (I26-I43, I50-I52)	21288	2	3	20	33	9313	11917
96. Intracranial hemorrhage (I60-I62)	1132	0	0	0	4	503	625
97. Other cerebrovascular disease (I63-I69)	7279	0	0	4	17	3268	3990
98. Arteriosclerosis (I70)	2685	0	0	1	0	1216	1468
99. Phlebitis, thrombophlebitis, embolism and vein thrombosis (I80-I82)	3308	0	0	1	18	2059	1230
100. Other circulation diseases (I71- I99)	13154	3	32	89	178	8349	4503
Total (sum of items 89-100)	277758	8	46	216	721	154211	122556

Table 1. Review of the presence of cardiovascular disease in the B&H by the age groups in 2009. Source: Report on diseases, conditions and injuries identified in the Bosnia and Herzegovina for 2009.

The reason for this is the proper treatment of high blood pressure in the first, in relation to elevated blood pressure and its inadequate treatment in countries in transition (9). In addition to coronary artery disease, high blood pressure significantly affects the onset and course of cerebrovascular events, heart failure and chronic kidney disease, especially among the older population (31). Decrease in high blood pressure and its proper treatment shows a reduction in mortality from cardiovascular disease by 60% in the group of treated subjects, compared to the group who were not taking medication for high blood pressure by the results of the Framingham study (32).

In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) study confirmed the effect of lowering high blood pressure, reduce heart attacks and even in preventing cardiovascular events (33). Also worthy are the results of the HOPE study (Heart Outcomes Prevention Study) which showed that lowering systolic blood pressure–the effect of ACE inhibitors for only 3.3 mmHg and diastolic by 1.4 mmHg leads to a 20% reduction in heart attacks, compared with those who received placebo.

Elevated blood cholesterol

There is a strong independent relationship between elevated cholesterol levels and risk of coronary heart disease. Elevated total cholesterol in serum in addition to smoking are the strongest single risk factor for the occurrence of coronary heart disease (26). The elevated levels of total lipids in blood such as cholesterol and triglycerides, are associated with various proteins, lipoproteins, and according to their size determine the degree and severity of atherosclerosis. High density lipoprotein (HDL) enter the artery wall very easy and so go out and do not cause atherosclerosis, compared to low-density lipoproteins (LDL), which easily penetrate the wall of an artery, causing it to retain atherosclerosis.

Connection between cholesterol and the occurrence of coronary disease were confirmed in many epidemiological and clinical studies with a moderate increase in cholesterol values, if present additional risk factors such as smoking, high blood pressure, elevated blood sugar.

The Framingham study suggests that the risk of coronary heart disease increases with the increase in plasma cholesterol (32). Cholesterol reduction of 1% reduced by 2% risk of a heart attack. In people with a lower risk of developing cardiovascular disease (<5%) considered that the target values of total cholesterol should be lower than 5.0 mmol/l, LDL cholesterol <3.0 mmol/l and HDL cholesterol >1.0 mmol/l. The level of cholesterol increases in 40 years old men, when the values are 5.9 m mol/l, and in women continues to rise until the age of 60 and reaches a peak of 6.7 mmol/l.

Joint presence of hypertriglyceridemia, hypertension, lowering the concentration of HDL cholesterol and insulin resistance is called X syndrome by Reaven who in 1988 observed the correlation of the metabolic syndrome X and coronary heart disease (34).

Many American and European studies with a large number of patients have shown that lowering cholesterol significantly reduces the risk of coronary heart disease and heart attack, explaining that the reduction in cholesterol leads to atherosclerosis plaque stabilization and better functioning of the endothelium of blood vessels (35).

Results of the 4S study (Scandinavian Simvastatin Survival Study) clearly confirmed the beneficial effect of lowering cholesterol to reduce cardiovascular risk after myocardial infarction by 28%, and in patients with angina pectoris by 24% (36). Results of the LIPID study (Long-term Intervention with Pravastatin in Ischemic Disease) showed a favorable effect of pravastatin–drug for lowering cholesterol, by 20% reduction in risk of mortality from coronary heart disease in patients with acute myocardial infarction and unstable angina pectoris. Reduction of elevated cholesterol levels in patients with diabetes showed positive results and the CARDS (Collaborative Atorvastatin Diabetes Study) study examined the effect of medicines used to treat elevated cholesterol levels in the primary prevention of major cardiovascular events in patients with type 2 diabetes. Study results showed a 36% reduction in acute coronary heart disease and 48% reduction in infarction.

The mortality rate was reduced by 27% in the atorv-

independent risk factors, in explaining the occurrence of atherosclerosis in such cases, an attempt was made to the inclusion of other risk factors.

This is a group of predisposing risk factors: obesity, abdominal obesity, low physical activity, sedentary lifestyle, positive family history for ischemic heart disease in early life ages (<55 in men; <65 years for women, ethnic characteristics, psychosocial factors (21).

In estimating total cardiovascular risk are included also the conditional risk factors: elevated triglycerides, increased small LDL particles, elevated homocysteine, elevated lipoprotein Lp (a), elevated fibrinogen, elevated inflammatory markers (C reactive protein) prothrombogens (22).

Until the mid-nineties, the intervention attempts to change some of the risk factors were based on opinions regarding the value of each factor and their changing (hypertension, smoking, dyslipidemia, etc.). However, since the mid nineties, the type and intensity of intervention in risk factors are determined on a more sophisticated level by determining the overall potential for atherosclerotic coronary artery disease (taking into account not all, but the main risk factors).

One of the largest case-control study in the year 2002, the INTERHEART study investigated the assessment of materiality and risk factors of heart disease and the study results show that nine out of ten heart attacks can be predicted on the basis of nine risk factors that are the same and have been found in studies around the world (22). .

Increased fats and smoking are 2/3 of the total risk, other risk factors include high blood pressure, elevated blood sugar, increased body weight, lack of physical activity and stress (22).

Together these factors account for 90% of risk for heart attacks and are the same throughout the world. The study showed that the risk of coronary disease can be assessed, and it is known the most about the causes and we have enough information to implement strategies for the reduction and elimination of these (22).

Areas where the MONIKA project is done refer to a high prevalence of coronary risk factors, especially hypercholesterolemia, with a high incidence of disease in the referral area (13).

The results were consistent with expectations, for areas with high mortality from coronary heart disease, with more than 80% of persons aged 25-64 years, and were at increased risk for the disease (13).

The results of most recent and previous research on risk factors and health behavior in the Federation B&H show that among the present population of highly unhealthy lifestyles are linked to smoking, physical inactivity, unhealthy eating, and therefore represent a significant health risk. As cardiovascular disease is responsible for leading disease burden of illness and death in the FB&H and the prevalence of the leading cardiovascular risk factors, including hypertension (41%) smoking (35%), obesity (33%), elevated blood sugar (10%) elevated cholesterol levels in the blood (15%), sedentary lifestyle (85%), is quite high, as evidenced in conducted population research, by systematic approach to controlling risk factors among the adult population in the FB&H is a real need (18).

According to the results of the risk factors of cardiovascular disease, in the First Croatian Health Project of the Ministry of Health and the Croatian Health Insurance in Croatia, aged 18-65 years blood pressure was higher than 140/90 mmHg in 31.9% men and 23.6% women, increased body weight (BMI 25.0 to 29.9 kg/m2.) was for 48.1% men and 34.7% women, and obese (body mass above 30 kg/m2.) was 31.1 % men and 15.2% women.

Sebastian and colleagues have worked on patients in primary medical practice and identify them as carriers of multiple risks for coronary heart disease. This research puts the point in understanding the principles of assessment of multiple risk factors simultaneously to clinicians imposes primary prevention as a choice in the mass screening and early treatment of the risk of emerging diseases (23).

For health professionals, the challenge should be the inclusion of a large number of patients who are at an early stage of illness in assessing and reducing the overall cardiovascular risk, using the most appropriate interventions for primary prevention so that more individuals may realize the benefits of health care (24).

Stamler was reasonably recommended the seven criteria for assessing the importance of risk factors: the strength of the association of risk factors and diseases, partly step nature of association, temporal sequence of associations, consistency and independence of the association, and the ability to predict and coherence have been used in setting the proposed measures of prevention (25).

3.1. RISK FACTORS THAT CAN BE INFLUENCED

High blood pressure

High blood pressure is without any doubt a major independent risk factor for coronary morbidity and mortality in developed, but increasingly in developing countries (26). Prevalence of elevated blood pressure in the adult population is 20%, aged 65 years is 40-50%. For the development of coronary disease both systolic and diastolic blood pressure are equally responsible, with the proviso that in middle age are more common problems of coronary heart disease associated with elevated systolic blood pressure (27).

People with high blood pressure are twice the risk of heart attack compared to a person who does not have it (28). Epidemiological analysis and randomized clinical trials have shown the impact of high blood pressure as risk factors for microvascular and macrovascular disease in patients with diabetes (29).

Meta-analysis done on 14 large international studies of high blood pressure and cardiovascular disease, showed that treating high blood pressure, reduces the incidence of coronary heart disease by 14%, stroke by 42% during the period of 5 years (8).

Epidemiological study of high blood pressure in patients with diabetes showed that a high risk of cardiovascular events and death begins with blood pressure >115/75 mmHg in the general population and twice increases for each 20 mmHg systolic or 10 mmHg increase in diastolic BP (30).

It is estimated that in the period since 1970 to 2000 the mortality from cardiovascular disease has declined in European countries, Canada, USA, Australia, Japan, while in countries of Central and Eastern Europe along with Russia, the incidence of cardiovascular disease increases.

status in Central and Eastern Europe. There is a difference in morbidity and mortality within European countries and this is explained by the fact that there are significant socio-economic differences in conventional risk factors such as smoking, high blood pressure, elevated cholesterol and blood sugar (12).

However, since 1970 in Western Europe, because of taking a series of preventive measures, there has been a significant decline in mortality rates from cardiovascular diseases for the population of middle-aged and elderly. In the Central and Eastern Europe there is decline in mortality rates in recent years but still remains very high (12).

The decline in mortality rates of coronary heart disease is registered mainly in the countries where extensive preventive measures of population change in lifestyle were performed, especially diet and reduction of smoking in Western and Eastern Europe. Incidence of morbidity from coronary heart disease also dropped in Western Europe, but it increases in the Eastern Europe (13). Coronary heart disease in 1990 was the leading cause of mortality and the fifth leading cause of illness in the world. In the next few decades is expected to double the share of coronary diseases in it overall morbidity and mortality and will become the leading cause of morbidity and mortality worldwide (9). Coronary heart disease causes one third of the total permanent disability, and have a large share of total health care costs (14).

The basic epidemiological characteristics of coronary heart disease as the population disease of middle aged and elderly, but with a pronounced tendency to increase the number of patients at a younger age. So far, mostly men are affected. It is clear what are the individual, familial, economic and social consequences of this disease (15).

Coronary heart disease is the single largest killer of American women and men and a total of seven million Americans suffer from coronary heart disease and nearly half a million people die each year from heart attacks caused by coronary artery disease (16). In the USA during 1996 the mortality rate from coronary heart disease was 120/100000 men and 58/100000 women (16). In addition, Yugoslavia has been involved with four groups of population in one of the most cited epidemiological prospective observational study–The Seven Countries Study, with a population of Belgrade (university professors), Zrenjanin (workers in the food industry Combine "Servo Mihalj), Velika Krsna (farmers) and Croatia (Dalmatia and Slavonia) (17). Bosnia and Herzegovina belongs to the group of countries in transition and have a steady increase in morbidity and mortality from coronary heart disease. About 50% of all deaths in both genders in B&H occur due to cardiovascular diseases, where coronary heart disease represents half of this figure. According to statistics, since 1960 to 2000 the mortality from cardiovascular diseases increased thrice. Federation had the highest overall mortality from cardiovascular disease in the last three years with the rate in 2005 of 443/100000, in 2006 of 352/100000, in 2007–371/100000. Compared to neighboring countries (Slovenia–288/100000, Croatia 448/100000, EU countries–498/100000) B&H is at the middle score.

In the overall group of cardiovascular diseases, the leading cause of mortality is stroke: in 2005–10%, 2006–11%, 2007–10%, in second place is myocardial infarction: 2005–9%, 2006–8.5%, 2007–9.2%. Specific mortality from myocardial infarction by sex is: 2005–male–10%, women–7%, 2006–men–10%, women–7%, 2007–men–10%, women–7%, it means somewhat higher in women than in men (18).

Risk population for coronary heart disease accounts for 20% of the general population is exposed multifactorial etiology. Many developed countries, led by the United States have carried out an intensive campaign to eliminate smoking and physical inactivity, as a potential cause of coronary heart disease over the past twenty years.

3. RISK FACTORS FOR CORONARY DISEASE

Degenerative diseases of the heart and blood vessels are for decades at the first place of the morbidity and mortality in the developed world, as well as developing countries in the background are most atherosclerotic process and the development of this process affects cardiovascular risk factors.

Reports of the World Health Organization (The Comparative Risk Assessment Collaborating Group module of the Global Burden of Disease 2000 study World Health Organization initiative) (16) contain recommendations to significantly improve population health is possible if the successful modification of risk factors present. Expert Group has identified smoking, high blood pressure, high cholesterol levels, to become the most important factor in the lost years of healthy life (19).

An important shift in the primary prevention of coronary heart disease is the attempt to look at the total atherosclerotic potential (circles), which causes the disease, depending on the interaction of various risk factors.

The Framingham study as most extensive longitudinal epidemiological study of coronary disease in the world based on the concept of risk assessment factors, their reduction represents a basic form the basis for the management of patients by lowering the incidence of coronary heart disease (20).

The emergence of the process of atherosclerosis, we first explained the presence of the following risk factors: smoking, poor eating habits, high blood pressure, increased serum total (and LDL) cholesterol, low HDL cholesterol, diabetes mellitus, men aged >55 years and women after menopause and old age > 65, elderly.

One of the important indicators is the anthropometry, which makes a positive index of health in the fall and the value of psychometrics, sociometrics and biological standards. Anthropometric measurements can study the influence of external factors on human development: the impact of nutrition, housing, economic status, physical activity, and general living conditions. Physical indicators of the height, weight, sitting height, head circumference, the size of certain body parts, body volume and the power of man. Deviations from the normal body development under certain conditions it may be the cause of the disease, including coronary heart disease.

Since a significant number of patients with coronary heart disease does not had represented so called main

Coronary heart disease is characterized by pain, accompanied by fear of death. Symptoms of disease vary considerably among patients, so some feel pain, and no ischemia, while others have ischemia but do not feel pain, what is called a "silent" or "asymptomatic ischemia" (2).

Diseases of the cardiovascular system in spite of preventable risk factors are responsible for approximately 50% of all deaths in the developed world, and this ratio is higher in developing countries (3).

Heberden and Rougnon were first to describe in history the coronary disease, but this disease is known for hundred years before our era. Hippocrates known steno cardiac pain. Seneca described the pain of "illness that occurs suddenly like a storm, with anxiety and chest pains and pains that tear at your soul." In the eighteenth century Balkonius was among the first who related steno cardiac pain to the heart, and Heberden classic form of the disease called angina pectoris.

The complex etiology of coronary heart disease is associated with smoking, diet, genetic inheritance, high arterial blood pressure, lipid levels and blood sugar, increased body weight, stress, lack of physical activity, and sudden weather changes. Age, gender and family history, complicate the risks of disease (4).

Despite numerous limitations, prevalence and incidence of diseases of the heart and blood vessels are mainly based on the analysis of mortality statistics and results of the WHO MONICA Project (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) which is covered by the populations of 35 to 64 in 35 countries worldwide.

In industrialized countries, heart disease and blood vessels diseases make up one third to half of all deaths (from 33% in France and 39% in Japan to 48% in England and Wales and 52% in Finland) (5).

According to WHO estimates, in the world, during 1999 from cardiovascular disease died about 17 million of people, more than 4 million were the inhabitants of Europe. According to projections for 2020 nearly 25 million people will be victims of one of the diseases from this group. The increase in deaths from ischemic heart disease being greater in the developing (128% in women and 137% in men) than in developed countries (29% women and 48% in men), which is associated with changes in the structure of the population and the prevalence of factors risk. In the structure of dying from heart and blood vessels diseases, according to WHO estimates, ischemic heart disease, on average, is represented with 41%, infarction with 32% and other diseases of the heart with 27%.

Coronary heart diseases are the leading cause of death in Australia (30% of all deaths), during 1993-1994 they spent a total of 12%, or $ 3.9 billions of total annual cost for health care (Keirnan E 2003). In the USA in 2003 the total cost of heart disease and infarction was 351 billion dollars, 209 billion was spent on health care, 142 billion for lost productivity due to death and disability.

The new indices that are used for the analysis of global cardiovascular situation and development of new prevention strategies show that cardiovascular diseases are responsible for 10% of the "lost years of healthy life" (DALYs – disabilty adjusted life years) in the underdeveloped and developing countries, and 18% in developed countries, all of which naturally affects the entire economy of these countries. It is well known that this negative score can be prevented by the combination of simple, effective social and individual efforts to adverse action of major risk factors, such as high blood pressure, elevated blood cholesterol, obesity and tobacco smoking.

According to the guide of the World Health Organization to monitor cardiovascular disease and risk factors that lead to their creation, one of the goals is to combat the syndrome of atherosclerosis, thereby reducing the mortality from cardiovascular diseases in people under 65 years of age, for at least 15% by year 2010, as well as improving quality of life for people who suffer from cardiovascular diseases, which unfortunately has not been reached. Developed countries have set up preventive programs for control and monitoring of risk factors and reduce rates of morbidity and mortality from coronary heart disease (6). In Western Europe for the past 30 years there has been a continuous downward trend in morbidity and mortality from coronary heart disease, while in Eastern Europe and countries in transition, the trend is steadily increasing (7).

Thanks to the continuous implementation of prevention programs, research, and actively search for people at increased risk for coronary diseases reduction and elimination of risk factors, changing life styles, and the therapeutic application–pharmacological measures have significantly reduced the trend of morbidity and mortality from coronary heart disease in developed countries (8).

2. EPIDEMIOLOGIC CHARACTERISTICS OF CORONARY HEART DISEASE

Today we talk about the global epidemic of cardiovascular diseases. According to the World Health Organization (WHO), cardiovascular diseases are responsible for 16.6 millions of death out of which 4 milion in Europe. The leading diagnostic subgroups were coronary heart disease accounted for 43.3% at the world level and 48.1% in Europe, and cerebrovascular disease accounted for 32.9% at the world level and 29.4% in Europe. It is estimated that worldwide occurs 32 millions heart attacks and strokes, of which 12.5 million ending fatally (9).

Cardiovascular diseases are directly responsible for 4 million deaths across Europe in 2000 of which 1.9 million in the European Union, participating with 43% in overall mortality all ages for men and 55% of total mortality in women (10). Cardiovascular diseases are also the most common cause of hospital morbidity in Europe during 2002 with a rate 2557/100000. In addition, the rate of 695/100000 is caused by coronary heart disease and 375/100000 population of stroke, but more than half died from other chronic heart diseases. It is estimated that 32 millions of heart attack and strokes occurs worldwide out of which 12,5 million of cases ends fatally (11).

Mortality from cardiovascular disease is different depending on age, gender, socio-economic conditions, ethnicity and geographic area. Mortality increases with age, and is higher among people with low socio-economic

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Socio-medical Characteristics of Coronary Disease in Bosnia and Herzegovina and the World

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REVIEW

SUMMARY

The basic epidemiological characteristics of coronary heart disease is that it mainly affects middle aged and elderly, but there is also a pronaunced tendency affecting an increasing number of young people. So far, mostly men are affected. It is clear what are the individual, familial, economic and social consequences of this disease. Data described in this paper, based on the experiences of different studies in the world confirms the importance and significance of using a modified algorithm to estimate the overall risk of coronary disease adaptable to our settings in order to assist the physician practitioners in primary care that easily identifies high-risk groups among their patients, to focus attention on high-risk patients and therapeutic possibilities for them, and to point to high risk groups in an effort to encourage the reduction of risk factors to reduce and neutralize the occurrence of coronary disease. Work should be done on strengthening preventive medicine, which today is increasingly losing its importance which it deserves and it, or by its methods try to predict or stop the disease until it has not progressed or at least slowed down and not deal with the consequences of the disease which is usually treated by aggressive methods. Namely, the results of these methods are very small and barely visible, and sometimes it's too late to apply therapy. All it costs society in terms of frequent absence from work, and increase the number of young disabled, which is a consequence disability by coronary disorders. We should not forget that health is a precious good about where care should be taken not to deal with it only when it is violated, it is important to work on developing the individual's consciousness from an early age, developing healthy eating habits and healthy living. Mentality of our people is such that they start to think about your health only when they lose health, which should be changed in people's mind.

Key words: heart attack, coronary disease, risk factors, prevention of heart diseases.

1. CORONARY HEART DISEASE AS A HEALTH AND ECONOMIC PROBLEM

Knowledge of the social conditions of people's lives is important for proper understanding and explanation of the many changes related to health promotion, including the prevention and treatment of coronary heart disease.

The style and pace of life brought changes to the habits of the traditional family, the type and change of working conditions in factories, schools in the sphere of education, and in the spheres of political and social order, economic welfare, the extent of human rights and freedoms. All listed in different ways affects the quality of life and health.

Coronary heart disease and its etiology are complex socio-medical, epidemiological and clinical problem in this century, and perhaps in the near and distant future, unless something drastically changes in access to prevention and treatment of this disease. World Health Organization in 1957 defined coronary artery disease as acute and chronic heart ailments, which are due to disruption of flow and myocardial blood supply in relation to events in the diseased coronary arteries. Depending on the speed of development of narrowing of the arteries and the severity of consequences, coronary heart disease can be manifested as angina pectoris, myocardial infarction, heart rhythm disorder, heart decompensation and sudden cardiac death. Basically, atherosclerosis is a prerequisite for the occurrence of pathological changes in coronary blood vessels, and with the present state of medical science is inevitable. People who have no risk factors for atherosclerosis in the age of 85 in 60% of cases have atheromatous coronary arterial circulation covered with plaques, but if they were smokers they will experience it at age of 65 years and if there was an elevated blood pressure limit is 52 years, while with the diabetes the disease can start at the age of 42 years (1).

Coronary heart disease as the leading disease of the cardiovascular system, causing high morbidity, loss of work capacity and mortality in most productive age.

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protection against sudden arrhythmic death provided by the ICD.[104] A secondary analysis of DINAMIT has now confirmed a high risk of non-sudden death in patients who receive ICDs early after myocardial infarction, while the VALIANT investigators have reported that recurrent infarction or cardiac rupture are common causes of death during this period.[105 106] Taken together, these findings explain why ICDs fail to protect against death if implanted early after myocardial infarction. Decisions should, therefore, be deferred, and patients selected for ICD therapy according to measurement of LVEF at 40 days.

9. CONCLUSION

The management of acute coronary syndromes continues to evolve and improve. The challenge for cardiovascular researchers is to maintain this momentum and to ensure that the improvements in outcome seen in the developed world have a global impact.

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death, non-fatal myocardial infarction or unplanned revascularisation, was significantly higher in the group receiving immediate PCI (60% vs 39%).[84] The difference persisted at 6 months' follow-up. Delaying intervention beyond 96 h is unlikely to be helpful, yet registry data show that this is common, particularly in high-risk patients who have most to gain from revascularisation.[85] The evidence for timely revascularisation is largely based on PCI data but a small proportion of patients require coronary artery bypass grafting (CABG). An analysis of US registry data showed that the timing of CABG has no palpable effect on outcomes, the composite of death, myocardial infarction, congestive heart failure, or cardiogenic shock being similar (12.6% vs 12.4%) whether CABG is done within 48 h of admission or later.[86] In general, therefore, early surgery is recommended to limit hospital stay and reduce resource use.

8. SECONDARY PREVENTION

8.1. Cardiac rehabilitation

The benefit of cardiac rehabilitation among 30 161 Medicare beneficiaries, 20.5% of whom had recent myocardial infarction, was confirmed by a strong dose–response relationship between the number of rehabilitation sessions attended and long-term rates of death and myocardial infarction.[87] Yet a contemporary report of cardiac rehabilitation in the UK found that only 26% of eligible patients with myocardial infarction are recruited, with adherence rates of 65–85%.[88] Reasons for the poor uptake are complex but include the fact that many patients do not want to participate in centre-based group programmes. A systematic review has now reported that home-based programmes are equally effective in improving clinical and health-related quality-of-life outcomes and are more acceptable to many patients.[89] Healthcare costs are similar, supporting the further provision of home-based cardiac rehabilitation such as that described by investigators in Birmingham.[90] The recent demonstration of improved myocardial blood flow plus reductions in circulating angiogenic cytokines in patients undergoing cardiac rehabilitation provides some reassurance that clinical improvement is physiologically based.[91]

8.2. Lifestyle modification

An important component of cardiac rehabilitation is lifestyle adjustment to help protect against further coronary events. Top of the list is smoking cessation. A recent study of 1581 patients followed up for 13 years showed that the adjusted HR for all-cause mortality was lower by 43% in lifelong non-smokers and by 43% in patients who quit after myocardial infarction.[92] A new finding was that among persistent smokers, each reduction of five cigarettes smoked per day reduced the risk of death by 18%, providing some comfort for those patients for whom complete abstinence proves impossible. Even among patients who mange to quit, there remains the hazard of second-hand smoke exposure, as reflected by data from Scotland showing that adjusted all-cause and cardiovascular mortality among never-smoking survivors of myocardial infarction increases according to smoke exposure measured by serum cotinine concentration.[93] The message is clear that protection against recurrent events in survivors of myocardial infarction requires smoking cessation by the patient and also by those with whom the patient makes contact, particularly family members. Together with smoking cessation, advice about exercise and diet delivered in formal programmes can have a salutary effect on modifiable risk profiles, including serum cholesterol, blood pressure and body mass index.[94] Dietary recommendations usually include w-3 fatty acid supplements[95] but this has now been questioned by the findings of two studies. In the first, 4837 patients with previous myocardial infarction were randomised to margarines containing marine n-3 fatty acids and plant-derived a-linolenic acid in a 2×2 factorial design.[96] The rate of adverse cardiovascular events did not differ significantly among the study groups. In the second study, highly purified w-3 fatty acids were randomly allocated to 3851 patients with acute myocardial infarction followed up for 12 months.[97] There were no significant differences in rates of sudden cardiac death (1.5% vs 1.5%), total mortality (4.6% vs 3.7%), or major adverse cerebrovascular and cardiovascular events (10.4% vs 8.8%) between treatment and placebo groups. The results of these two trials make recommendations for secondary prevention with w-3 fatty acid supplements after myocardial infarction difficult to sustain.

8.3. Pharmacotherapy

The importance of optimal secondary prevention after myocardial infarction was emphasised in a modelling study, in which greater absolute gains in survival were achieved by optimising secondary prevention treatments compared with in-hospital reperfusion treatments (104 vs ≤30 lives/10 000).[98] Recommended are aspirin, b blockers, statins, renin–angiotensin system blockers and thienopyridines—a study of 5353 patients showing that treatment with all five drugs reduced 1-year mortality by 74% compared with treatment with one or none of them, with consistent effects in STEMI and NSTEMI.[75] Evidence that statins and clopidogrel provide the greatest independent pharmacological benefit (ORs for death 0.85 (0.73 to 0.99) and 0.84 (0.72 to 0.99)) was provided by the GRACE investigators in a nested case–control study of 5148 patients with acute coronary syndromes,[99] and two separate studies have now reported the adverse consequences of failing to adhere to treatment with these drugs during the first year after discharge.[100 101] The message is clear that prescribing secondary prevention treatment according to guideline recommendations and promoting adherence to treatment can together produce further mortality reductions in patients with myocardial infarction.

8.4. Implantable cardioverter-defibrillators (ICDs)

Left ventricular ejection fraction (LVEF) after acute myocardial infarction remains predictive of sudden death in the primary PCI era[102] and is the key determinant of which patients should be offered an ICD for primary prevention.[103] However, LVEF in the acute phase is an unreliable guide to LVEF at 3 months when significant recovery of contractile function has often occurred. But there is another reason for delaying decisions about ICDs beyond the guideline-recommended 40 days. Thus a recent randomised trial of ICD therapy in 898 patients with LVEF ≤40%, recruited within 31 days of acute myocardial infarction, showed no overall mortality reduction for the patients who received an ICD because a high rate of non-sudden death negated

7. OTHER ANTITHROMBOTIC DRUGS

7.1. Fondaparinux

Intravenous heparin during primary PCI further enhances thrombus resolution during primary PCI but ongoing treatment with low molecular weight heparin has now given way to fondaparinux, a synthetic factor Xa inhibitor. A recent individual patient-level combined analysis of 26 512 patients from the OASIS 5 and 6 trials who were randomised to fondaparinux 2.5 mg daily or a heparin-based strategy has resolved uncertainty about the clinical value of fondaparinux in patients undergoing primary PCI by showing a better net clinical composite of death, myocardial infarction, stroke, or major bleeding (10.8% vs 9.4%; HR=0.87; p=0.008) in the subset of 19 085 patients treated invasively.[65] A similar benefit was found in patients treated conservatively. Fondaparinux is now widely used in preference to heparin in acute coronary syndromes.

7.2. Bivalirudin

Bivalirudin is a direct thrombin inhibitor that showed superiority to a combined regimen of heparin plus a GPIIb/IIIa inhibitor in HORIZONS-AMI, largely owing to a lower rate of major bleeding (4.9% vs 8.3%).[66] All-cause mortality at 30 days was also lower in the bivalirudin group, with persistent benefit after 3 years (5.9% vs 7.7%), assuring a guideline recommendation for bivalirudin in primary PCI.[46] It should be noted, however, that femoral artery access was used in 94.1% of the HORIZONS-AMI population and whether the reduction in bleeding with bivalirudin applies equally to centres where radial access is the preferred approach is not known.

7.3. Fibrinolytic treatment

Evidence that fibrinolysis is less effective than primary PCI in the emergency management of STEMI, has now been reinforced by evidence of reduced cost-effectiveness,[67] yet a significant minority of patients in England and Wales continue to be treated with it.[32] This may be justified if fibrinolysis can be delivered within 30 min after presentation when primary PCI is not immediately available, because treatment delays by either modality are associated with substantial increases in mortality.[36] This has provided justification for programmes of pre-hospital thrombolysis, particularly in rural regions where transport times are prolonged, but enthusiasm for this approach may now be diminished by evidence from the MINAP registry showing higher rates of reinfarction compared with in-hospital thrombolytic treatment for patients with STEMI.[68] The difference in reinfarction rates was only significant for tenecteplase (9.6% vs 6.4%), not reteplase, and was particularly marked when transport times exceeded 30 min. It was attributed to differences in the use of adjunctive antithrombotic treatment in the two treatment environments. Interestingly, bleeding complications were more common in the hospital environment where adjunctive antithrombotic treatment was more aggressive, consistent with recent data from RIKS-HIA showing that major bleeding complications among patients receiving fibrinolytic treatment continued to increase from 2001 to 2006 as antithrombotic treatments became more effective.[69] The availability of potent ADP P2Y12 receptor blockers has raised further concerns about bleeding complications, and it was gratifying, therefore, that the PLATO trial substudy confirmed that event rates could be reduced with ticagrelor compared with clopidogrel without an increase in bleeding risk.[70 71] The role of invasive treatment after fibrinolytic treatment in STEMI has been clarified in two recent meta-analyses of small and medium-size trials comparing strategies of routine early angiography for all patients with deferred or ischaemia-guided angiography.[72 73] Both meta-analyses reported that routine early angiography was associated with reductions in the rates of recurrent myocardial infarction and death and this strategy is now recommended in international guidelines.

7.4. Non-ST-segment elevation myocardial infarction

NSTEMI has become the dominant mode of presentation for patients with acute myocardial infarction and in the recent analysis from Kaiser Permanente accounted for 66.9% of cases.[4] There has been a perception that NSTEMI is relatively benign despite evidence that prognosis after 2 months becomes substantially worse than with STEMI.[21 74] This may explain the tendency of doctors to under-treat NSTEMI based on a mismatch between perceived and actual risk that distorts management decisions, perpetuating the 'treatment–risk paradox'.[25] Thus, despite a worse prognosis, patients with NSTEMI are less likely than patients with STEMI to receive optimal secondary prevention treatment.[75] Moreover, in a study of 13 489 NSTEMI admissions recorded in the MINAP registry, invasive management was associated with better outcomes but was applied inequitably, with lower rates in high-risk groups, including older patients, women and those with cardiac comorbidities.[76]

7.5. Emergency management

Dual antiplatelet treatment with aspirin and clopidogrel is central to the management of NSTEMI.[77] The role of newer more potent ADP P2Y12 receptor blockers remains undetermined, although ticagrelor looks promising, based on its ability to reduce ischaemic events compared with clopidogrel in NSTEMI as well as STEMI, without increasing the risk of bleeding.[78] Simultaneous treatment with fondaparinux is now recommended in preference to enoxaparin, based on the findings in OASIS 5 which compared these agents in 20 078 patients with acute coronary syndromes.[79] Patients randomised to fondaparinux showed a 50% reduction in major bleeding compared with enoxaparin, with no difference in the incidence of ischaemic events. The reduction in bleeding risk was comparable whether clopidogrel or GPIIb/IIIa receptor blockers were co-prescribed[80] and cost-effectiveness has now been confirmed.[81] Indications for bivalirudin in NSTEMI have been harder to define and although it has a licence for use in combination with aspirin and clopidogrel, this is based principally on its safety profile (lower bleeding risk), its efficacy for reducing ischaemic events being no greater than either heparin plus GPIIb/IIIa receptor blocker or bivalirudin plus GPIIb/IIIa receptor blockers.[82]

The majority of patients with NSTEMI benefit from interventional management,[83] but recent data suggest this could be delayed for at least 24 h unless continuing clinical instability unresponsive to GPIIb/IIIa receptor blockers calls for earlier action. Thus, in a randomised comparison of immediate versus deferred PCI in 251 patients, the incidence at 30 days of the primary end point, a composite of

stents should be chosen.

4. CULPRIT LESION VERSUS MULTIVESSEL PCI

The main purpose of primary PCI is to achieve reperfusion of jeopardised myocardium by reopening the culprit coronary artery. Whether it is safe or desirable to treat disease within non-culprit vessels during the primary PCI procedure or as a staged procedure afterwards has been the subject of recent investigation. A small randomised trial of 214 patients with multivessel disease found that adverse event rates during a mean follow-up of 2.5 years were higher with culprit PCI than with multivessel PCI whether performed during the primary PCI procedure or, better, as a staged procedure afterwards.[47] This trial has now been included in a meta-analysis of four prospective and 14 retrospective studies involving 40 280 patients, which came to a similar conclusion in showing that staged PCI was associated with lower mortality compared with culprit PCI.[48] However, multivessel PCI during the primary procedure was associated with the highest mortality. A post hoc analysis of the HORIZONS-AMI trial also found that staged PCI was associated with lower 1-year mortality compared with culprit PCI (2.3% vs 9.2%).[49] These data, are consistent in showing that multivessel disease is best dealt with electively as a staged procedure after the primary PCI procedure has been completed.

5. THROMBECTOMY

Thrombotic coronary occlusion is the pathological event triggering STEMI and provides the logic for adjunctive thrombectomy during primary PCI. A variety of devices have been developed for this purpose but the simplest, manual thrombus aspiration, has emerged as the best, with evidence of better reperfusion during the acute phase of STEMI translating into a survival advantage at 1 year compared with conventional primary PCI.[50 51] MRI has confirmed that thrombus aspiration reduces microvascular obstruction during primary PCI and limits infarct size at 3 months.[52] A more recent analysis of pooled individual patient data from three randomised trials found that the trend for worsening myocardial reperfusion with time from admission to primary PCI was effectively abolished by thrombus aspiration, suggesting particular benefits in the event of procedural delay.[53] More complex thrombectomy devices are not recommended for use in STEMI. Thus assessments of infarct size reduction in two trials—JETSTENT comparing Angiojet rheolytic thrombectomy with primary direct stenting and PREPARE comparing simultaneous proximal embolic protection and manual thrombus aspiration with manual thrombus aspiration—showed no significant benefit of these device strategies.[54 55] Consistent with this is a meta-analysis of thrombectomy trials showing that the mortality benefit for patients randomised to thrombus extraction is confined to patients treated with manual thrombectomy.[56]

6. ANTIPLATELET STRATEGIES

Current recommendations are for loading doses of aspirin and clopidogrel immediately before primary PCI followed by maintenance treatment. Adjunctive treatment with GPIIb/IIIa receptor blockers provides more intensive platelet inhibition in the acute phase. The main purpose of treatment is to enhance thrombus resolution and to prevent recurrent thrombotic events, particularly stent thrombosis in the 9–12 months it takes for drug-eluting struts to endothelialise (1–3 months for bare metal struts). Newer, drugs that block the ADP P2Y12 receptor more potently than clopidogrel are now available[57] and have been evaluated in combination with aspirin in patients undergoing primary PCI. In the TRITON-TIMI 38 trial of dual antiplatelet treatment, prasugrel reduced the primary outcome of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke compared with clopidogrel (6.5% vs 9.5%), but this was associated with a significantly greater risk of major bleeding, including fatal bleeding, raising important safety concerns.[58] Ticagrelor has also been evaluated against clopidogrel in a substudy of the PLATO trial and like prasugrel it proved more effective in reducing the primary outcome of cardiovascular death, myocardial infarction or stroke, although the absolute difference was small (9.0% vs 10.7%).[59] Strikingly, however, there appeared to be enhanced bleeding, and ticagrelor now has a guideline recommendation for use in primary PCI, although its final place in the therapeutic arsenal must await cost-effectiveness and long-term safety studies.

Abciximab, given intravenously, has been the most widely used GPIIb/IIIa receptor blocker in patients with STEMI undergoing primary PCI. Benefits appear to be inversely related to inflammatory burden[60] and may be enhanced by intracoronary administration, a recent meta-analysis reporting improved clinical outcomes by this route.[61] However, abciximab is expensive and there are now studies confirming non-inferiority of 'small-molecule' GPIIb/IIIa receptor blockers. Thus, investigators using the Swedish Coronary Angiography and Angioplasty Registry compared 2355 primary PCI patients who received eptifibatide with 9124 who received abciximab and found similar rates of death or myocardial infarction during 1-year follow-up (15.0% vs 15.7%).[62] In a smaller study, 427 patients randomised either to eptifibatide or abciximab showed comparable rates of complete ST-segment resolution 60 min after primary PCI (62.6% vs 56.3%) with no significant differences between cardiovascular outcomes.[63] In the On-TIME 2 trial, another small molecule compound, tirofiban, in combination with aspirin and clopidogrel, provided more effective platelet inhibition than aspirin and clopidogrel alone in patients undergoing primary PCI. The degree of platelet inhibition showed significant relationship with major adverse cardiac events, including stent thrombosis.[64] These findings have yet to penetrate international guidelines but many centres are now switching from abciximab to small-molecule compounds to reduce pharmacological costs.

occlusion. The authors suggest that strain measurements in the acute phase of NSTEMI might be used for triaging patients for immediate reperfusion therapy.

2.6. Risk stratification

The risk of death and other ischaemic events in patients with acute coronary syndromes varies considerably across diagnostic phenotypes. Objective criteria to quantify risk are now increasingly used to guide treatment and determine prognosis.

3. CLINICAL FACTORS

Clinical factors are used intuitively by clinicians. They recognise that risk increases with age and shows important gender differences—young women with STEMI, for example, having a 15–20% higher mortality risk than men.[21] ECG criteria[22] and routine biochemistry are also used for risk stratification, outcomes worsening with admission hyperglycaemia and also it seems with admission hypoglycaemia.[23,24] Despite clinicians' reliance on clinical assessments of risk it is now clear that they often get it wrong and a recent study has shown little association with objective measures of risk using validated risk scores.[25]

3.1. Diagnostic biomarkers

Increasing troponin release in NSTEMI is associated with a proportionate increase in the risk of lethal arrhythmias, cardiogenic shock, new heart failure and death.[26] C-reactive protein, the most widely studied prognostic biomarker, is also moderately predictive of adverse outcomes in acute coronary syndromes, a recent meta-analysis reporting a pooled RR of 2.18 (1.77 to 2.68) for the top (>10 mg/l) compared with the bottom (≤3 mg/l) category of values,[27] Generally speaking, however, individual biomarkers have yet to find a useful clinical role—a recent 5-year follow-up of patients with NSTEMI included in FRISC II reporting that none of N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein, cardiac troponin I and estimated glomerular filtration rate provided incremental prognostic value to established risk indicators, except NT-proBNP for 6-week outcomes.[28] Combining multiple biomarkers may improve predictive power for adverse outcomes but confirmation of incremental value over established risk scores is still awaited.[29]

3.2. Risk scores

Validated risk scores based on a range of readily available factors provide the most effective means of risk stratifying patients with acute coronary syndromes. The GRACE score is widely used and in a comparative validation study involving 100 686 cases of acute coronary syndromes its discriminative performance in predicting mortality compared favourably with a range of other risk models including PURSUIT, GUSTO-1, GRACE, SRI and EMMACE.[30] The GRACE score appears to have lost none of its clinical value with the availability of high-sensitivity cardiac troponin assays. In an international cohort of 370 patients with acute coronary syndromes, the area under the curve of the GRACE score was 0.87 and 0.88 for in-hospital and 1-year mortality, and addition of high-sensitivity cardiac troponin produced no improvement in the mortality prediction.[31]

3.3. Primary percutaneous coronary intervention

The MINAP public report for England and Wales records that 70% of all patients with STEMI received reperfusion therapy in 2010/2011, of whom 81% received primary PCI.[32] The drive towards primary PCI, based on evidence of a sustained mortality benefit compared with fibrinolysis,[33] has been underpinned by the establishment of regional networks that have defined local standards of care and provided infrastructure for staffing heart attack centres.[34,35]

Timely treatment is essential to maximise prognostic benefit,[36,37] and important as it is to achieve door-to-balloon times within 90 min, other intrinsic delays within the healthcare process also need consideration. Thus, a Danish registry analysis of 6209 patients with STEMI found that 'system delay' (time from first contact with the healthcare system to the initiation of reperfusion therapy)—as well as door-to-balloon time—was a key modifiable risk factor, with an HR for mortality during the next 3.4 years of 1.22 (95% CI 1.15 to 1.29; p<0.001) per 1 h increase in system delay.[38] The findings emphasise the importance of minimising transfer times from non-PCI hospitals and introducing policies of prehospital diagnosis to permit direct delivery of patients with STEMI to interventional centres. Also important are strategies to reduce the time it takes people with chest pain to call the emergency services. Women take significantly longer than men but, despite a US campaign to increase women's awareness of their risk of heart disease, a recent study found it had no effect on the gender gap or the time it took women to call the emergency services.[39]

3.4. Vascular access

Primary PCI by radial rather than femoral access is the preferred approach for an increasing number of operators.[40] Its main advantage appears to be a lower rate of bleeding complications—the randomised RIVAL trial of radial versus femoral access in 7021 patients with acute coronary syndromes reporting a trend towards lower bleeding rates at 30 days (0.7% vs 0.9%), associated with significantly lower rates of access-site complications, including large haematomas and pseudoaneurysms.[41] Findings were similar in a recent observational study of 1051 primary PCI cases with vascular complication rates of 0% and 1.9% for radial versus femoral access.[42] However, RIVAL found no outcome advantage for radial access, and femoral access is still preferred by many operators[43] because access is more predictable and procedure times may be shorter than with the radial approach.[44,45]

3.5. Stenting

Concerns about stent thrombosis led to recommendations for bare metal stents in primary PCI but randomised trials have now confirmed important advantages for drug-eluting stents. The HORIZONS-AMI 3-year results showed lower rates of target lesion revascularisation for the 2257 patients randomised to paclitaxel-eluting stents than for the 749 patients randomised to bare metal stents (9.4% vs 15.1%).[46] There was no difference by stent type in rates of death, reinfarction, stroke or stent thrombosis. Drug-eluting stents are, therefore, preferred in primary PCI but they commit the patient to a full 12 months of dual antiplatelet treatment and if urgent surgery is planned or there is a high risk of bleeding for other reasons bare metal

to stenosis severity, are the sites at which recurrent plaque events usually occur.[7,8]

2. DIAGNOSIS

Diagnostic definitions of acute coronary syndromes are internationally agreed based on troponin release and symptomatic, electrocardiographic, or functional criteria.[9]

2.1. Troponins

Demonstration of a changing troponin concentration in the first 24 h with at least one value above the decision limit is central to the diagnosis of acute myocardial infarction. Now available are high-sensitivity troponin assays permitting significant reductions in the threshold for detection. An early study evaluated four high-sensitivity assays in 718 patients with suspected acute coronary syndrome, 17% of whom had acute myocardial infarction. Diagnostic performance was excellent, the area under the receiver operator curves ranging from 0.95 to 0.96 compared with 0.90 for the standard assay.[10] The implications for cardiac outcomes and clinical management were assessed in a more recent study in which high-sensitivity troponin I was measured in 1038 patients with suspected acute coronary syndrome.[11] Values below the previous limit of detection (0.20 ng/ml)—conventionally considered 'normal'—showed graded association with death or non-fatal myocardial infarction, with rates of 7% and 39% for troponin concentrations of <0.05 ng/ml and 0.05–0.19 ng/ml, respectively. When the investigators lowered the diagnostic threshold to 0.05 ng/ml in a further 1054 patients, communicating troponin values to clinicians, the risk of death and recurrent myocardial infarction in patients with troponin concentrations 0.05–0.19 ng/ml was reduced from 39% to 12%. The investigators concluded that lowering the diagnostic threshold by clinical application of high-sensitivity troponin assay has the potential to identify many high-risk individuals with suspected acute coronary syndrome and produce major improvements in their prognosis.

2.2. Other diagnostic biomarkers

Studies evaluating new biomarkers for the early diagnosis of myocardial infarction have been the subject of a recent systematic review.[12] The quality of these studies has often been poor with only 16% providing any information about incremental value compared with other diagnostic data. Myoglobin, for example, appears to be useful to rule out myocardial infarction in the first 6 h but evidence that it adds value to clinical symptoms, ECG and troponin testing is limited. Of the new diagnostic biomarkers, ischaemia-modified albumin and heart-type fatty acid-binding protein (H-FABP) showed initial promise, but already a meta-analysis has concluded that H-FABP does not fulfil the requirements needed for early diagnosis when used as a stand-alone test and called for evidence that it adds to clinical evaluation and other diagnostic tests.[13]

2.3. Point-of-care diagnosis with a panel of biomarkers

Whether biomarker panels have a specific role for early diagnosis of myocardial infarction in the emergency room has been evaluated in two recent studies, both using a point-of-care panel of troponin I, creatine kinase-MB (CK-MB) and myoglobin. RATPAC recruited 2243 patients with suspected myocardial infarction and randomised them to standard care or panel evaluation on admission to the emergency room and 90 min later.[14] Point-of-care panel evaluation was associated with a 32% rate of 'successful' (no re-attendance with major coronary events) discharge from the emergency room, compared with 13% for standard care; hospital bed use was unaffected. However, a substudy to examine the diagnostic efficiency of the individual cardiac markers and their accuracy for the final diagnosis of acute myocardial infarction showed that point-of-care myoglobin and CK-MB did not provide further diagnostic information over that provided by troponin I for early diagnosis or exclusion of myocardial infarction.[15] ASPECT was an observational study of 3582 patients in which an accelerated diagnostic panel (ADP) of TIMI score, coupled with the point-of-care panel of biomarkers and ECG findings, identified 352 as low risk.[16] Only three of these patients went on to experience a major adverse cardiac event, making the ADP a highly sensitive rule-out for myocardial infarction in low-risk patients, as reflected by a negative predictive value of 99.1%. However, there was no control group in ASPECT, nor an analysis of the incremental value offered by individual components of the biomarker panel. Based on the RATPAC subgroup analysis, therefore, it seems clear that troponin remains the most useful biomarker for diagnosis of myocardial infarction in the emergency room and current evidence is insufficient to advocate biomarker panels for this purpose.

2.4. Electrocardiogram

Guideline recommendations are for urgent reperfusion therapy according to STEMI pathways in patients with suspected myocardial infarction presenting with left bundle branch block (LBBB). However, a retrospective analysis of 892 patients in a Mayo Clinic STEMI registry, found that of the 36 who presented with new LBBB, only 12 (33%) had a final diagnosis of acute myocardial infarction.[17] These data show that LBBB is of limited diagnostic utility in suspected myocardial infarction and provide a case for new diagnostic strategies in this high-risk group. Also at high risk are patients with acute myocardial infarction caused by proximal left anterior descending coronary artery (LAD) occlusion. A report that this may be associated with a distinct ECG pattern has now been confirmed in a series of 35 patients who underwent primary PCI of the LAD, all of whom showed ST-segment depression at the J-point with up-sloping ST segments and tall, symmetrical T-waves in the precordial leads of the 12-lead ECG.[18,19] The authors recommend that this ECG pattern in patients presenting with suspected myocardial infarction should prompt triage for immediate reperfusion therapy.

2.5. Imaging

Echocardiography provides the most readily available imaging modality for acute phase diagnosis of myocardial infarction by identifying new left ventricular regional wall motion abnormality. A new diagnostic application for identifying those patients with NSTEMI who have complete coronary occlusions was recently described.[20] In such patients, circumferential strain measured within 1 h of admission was independently diagnostic, values ≥10% showing 90% sensitivity and 88% sensitivity for angiographic coronary

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Almanac 2011: Acute Coronary Syndromes. The National Society Journals Present Selected Research that has Driven Recent Advances in Clinical Cardiology

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REVIEW

SUMMARY

This overview highlights some recent advances in the epidemiology, diagnosis, risk stratification and treatment of acute coronary syndromes. The sheer volume of new studies reflects the robust state of global cardiovascular research but the focus here is on findings that are of most interest to the practising cardiologist. Incidence and mortality rates for myocardial infarction are in decline, probably owing to a combination of lifestyle changes, particularly smoking cessation, and improved pharmacological and interventional treatment. Troponins remain central for diagnosis and new high-sensitivity assays are further lowering detection thresholds and improving outcomes. The incremental diagnostic value of other circulating biomarkers remains unclear and for risk stratification simple clinical algorithms such as the GRACE score have proved more useful. Primary PCI with minimal treatment delay is the most effective reperfusion strategy in ST elevation myocardial infarction (STEMI). Radial access is associated with less bleeding than with the femoral approach, but outcomes appear similar. Manual thrombectomy limits distal embolisation and infarct size while drug-eluting stents reduce the need for further revascularisation procedures. Non-culprit disease is best dealt with electively as a staged procedure after primary PCI has been completed. The development of antithrombotic and antiplatelet regimens for primary PCI continues to evolve, with new indications for fondaparinux and bivalirudin as well as small-molecule glycoprotein (GP)IIb/IIIa inhibitors. If timely primary PCI is unavailable, fibrinolytic treatment remains an option but a strategy of early angiographic assessment is recommended for all patients. Non-ST segment elevation myocardial infarction (NSTEMI) is now the dominant phenotype and outcomes after the acute phase are significantly worse than for STEMI. Many patients with NSTEMI remain undertreated and there is a large body of recent work seeking to define the most effective antithrombotic and antiplatelet regimens for this group of patients. The benefits of early invasive treatment for most patients are not in dispute but optimal timing remains unresolved. Cardiac rehabilitation is recommended for all patients with acute myocardial infarction but take-up rates are disappointing. Home-based programmes are effective and may be more acceptable for many patients. Evidence for the benefits of lifestyle modification and pharmacotherapy for secondary prevention continues to accumulate but the argument for omega-3 fatty acid supplements is now hard to sustain following recent negative trials. Implantable cardioverter-defibrillators for patients with severe myocardial infarction protect against sudden death but for primary prevention should be based on left ventricular ejection fraction measurements late (around 40 days) after presentation, earlier deployment showing no mortality benefit.

Key words: acute coronary syndromes, advances in clinical cardiology.

1. INCIDENCE AND MODE OF PRESENTATION

Temporal trends for the global coronary epidemic vary by region but in most developed countries mortality is in decline.[1] Lifestyle adjustments have contributed to this decline—most recently, the implementation of comprehensive smoke-free legislation in many countries that has already caused significant reductions in acute coronary events.[2] Smoking, a potent thrombogenic stimulus, is a major determinant of STEMI[3] and a recent analysis from Kaiser Permanente in California—where smoke-free legislation is strictly enforced—showed a 62% decline in STEMI between 1999 and 2008 while NSTEMI increased by 30%.[4] Overall, there was a 24% reduction in hospitalisations for acute coronary syndromes despite lowering of diagnostic thresholds by sensitive troponin biomarkers.[5] This was accompanied by improvement in the age- and sex- adjusted 30-day mortality from 10.5% in 1999 to 7.8% in 2008. Increasing rates of interventional management no doubt contributed to the improved outcomes but parallel increases in plaque-stabilising treatment with high-dose statins must also have played a role[6] because vulnerable thin-cap fibroatheromas, often remote from the infarct-related artery and unrelated

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to the discovery of mutations in 15 individuals (23%), who were subsequently treated. This study provides evidence that targeted genetic testing may play a part in helping to diagnose genetically mediated arrhythmia syndromes, which may result in successful family screening.

An important study that investigated the presence of genetic factors or modifiers that could partly explain the phenomenon of incomplete penetrance seen in congenital long QT syndrome (LQTS) identified the nitric oxide synthase 1 adaptor protein (NOS1AP) as one such candidate.[115] This protein was chosen on the basis of previous studies that showed an association between genetic variants of NOS1AP and small quantitative increases in the QT interval and an increased risk of death in a general population.[77 116] In the study involving a South African LQTS population (500 subjects, 205 mutation carriers), NOS1AP variants were found to be significantly associated with the occurrence of symptoms, clinical severity (including cardiac arrest and SCD) and a greater likelihood of having a QT interval in the top 40% of values among all mutation carriers. In another study involving 901 patients enrolled in a prospective LQTS registry, three NOS1AP marker single nucleotide polymorphisms (SNPs rs4657139, rs16847548 and rs10494366) were genotyped to assess the effect of variant alleles on QTc and on the incidence of cardiac events.[117] The investigators found that variant alleles tagged by SNPs rs4657139 and rs16847548 were associated with an average QTc prolongation of 7 and 8 ms, respectively, whereas rs4657139 and rs10494366 were associated with an increased incidence of cardiac events. Furthermore, the rs10494366 minor allele was an independent prognostic marker among patients with QTc <500 ms, but not in the entire cohort. These two studies demonstrate that genetic testing for variants in the NOS1AP and tagged SNPs may be clinically useful for risk stratification of patients with congenital LQTS and potentially guide the choice of therapeutic strategies.

The FINGER (France, Italy, Netherlands, GERmany) registry, one of the largest series on patients with Brugada syndrome (BrS) so far, involved 1029 consecutive individuals (745 men; 72%) with BrS (with a spontaneous or drug-induced type I ECG) who were followed up for a median period of 31.9 months.[118] The cardiac event rate per year was 7.7% in patients with aborted SCD, 1.9% in patients with syncope and 0.5% in asymptomatic patients. This study provides important information that the event rate among asymptomatic patients with a Brugada ECG (which comprised 64% of subjects in the registry) is low. In addition, symptoms and a spontaneous type 1 ECG were predictors of arrhythmic events, whereas gender, familial history of SCD, inducibility of VTs during an EP study and the presence of an SCN5A mutation were *not* predictive of arrhythmic events.

In an interesting mechanistic study of BrS, in vivo high-density mapping using non-contact mapping array was performed in the right ventricle of 18 patients with BrS and 20 controls.[119] The investigators identified marked regional endocardial conduction delay and heterogeneities in repolarisation in patients with BrS and proposed that the slow-conduction zones may have a role in the initiation and maintenance of ventricular arrhythmias.

In line with these findings, an outstanding study was subsequently performed in which nine symptomatic patients with BrS who had recurrent VF episodes underwent endocardial and epicardial mapping of the right ventricle. Ablation at unique abnormal low voltage sites (clustering exclusively in the anterior aspect of the RVOT epicardium) rendered VT/VF non-inducible in seven of the nine patients, with no recurrence of ventricular arrhythmias in all patients over a follow-up period of 20±6 months. Interestingly, normalisation of the Brugada ECG pattern was seen in eight patients after ablation. This important proof-of-concept study lends further support to the notion that the underlying EP mechanism in patients with BrS is delayed depolarisation in the RV outflow tract (specifically over the anterior epicardial region) and demonstrates for the first time that substrate modification may be an effective strategy in patients with symptomatic BrS with recurrent VF episodes.

Flecainide has recently emerged as a promising new treatment for catecholaminergic polymorphic ventricular tachycardia (CPVT). In a mouse model of CPVT, flecainide was found to prevent arrhythmias by inhibiting cardiac ryanodine receptor-mediated calcium release.[120] In the same publication, flecainide also completely prevented CPVT in two patients who had remained highly symptomatic with conventional drug treatment. In a clinical study of 33 patients who had received flecainide because of exercised-induced ventricular arrhythmias despite conventional treatment, flecainide was found to either partially or completely reduce the arrhythmias in 76% of cases.[121]

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MADIT-CRT, RAFT demonstrated that CRT-D significantly reduced overall mortality and cardiovascular mortality compared with ICD alone, although more adverse device-related events were also seen in the CRT-D group. Possible reasons for mortality benefit seen in RAFT, but not MADIT-CRT, are that RAFT included patients with more advanced disease (and a higher proportion with ischaemic heart disease) and follow-up was longer and more complete.

A number of subanalyses of MADIT-CRT have since been conducted to provide further information on the findings. One subanalysis demonstrated that women experienced significantly greater reductions in all-cause mortality and heart failure than men, which was accompanied by greater echo evidence of reverse cardiac remodelling.[95] Another subanalysis looking specifically at the echo parameters and performance between the two groups found that CRT significantly improved cardiac size and performance compared with the ICD-only strategy, which probably accounted for the outcomes benefit in the CRT-D group.[96] Other studies have also provided additional echo evidence that CRT in mild heart failure (NYHA class I/II) results in major structural and functional reverse remodelling which may prevent disease progression.[97 98] The PACE (Pacing to Avoid Cardiac Enlargement) study explored whether biventricular pacing was better than right ventricular (RV) apical pacing in preventing adverse cardiac remodelling in patients with bradycardia and *normal* ventricular function at baseline.[99] In this small randomised study of 177 patients followed up over a 12-month period, the investigators found that the mean LVEF was significantly lower in the RV-pacing group than in the biventricular-pacing group (54.8±9.1% vs 62.2±7.0%, p<0.001), with an absolute difference of 7.4% points. However, the beneficial effects of biventricular pacing on echo parameters in this group of patients were not accompanied by any clinical benefit.

Other important and continuing areas of investigation in the field of CRT include how best to select candidates who are most likely to respond to CRT and how to optimise response. Parameters that have recently been studied to improve patient selection include QRS morphology in MADIT-CRT (left bundle branch block (LBBB), rather than non-LBBB, patterns appears to be the predominant morphology—that is, related to response),[100] baseline LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the region of the LV pacing lead,[101] and pre-pacing systolic dyssynchrony measured by tissue Doppler imaging velocity.[102] Consistent with existing knowledge, LV lead positioning has been reconfirmed to be important in MADIT-CRT patients[103] and patients with non-ischaemic dilated cardiomyopathy.[104] The prospective, randomised SMART-AV (SmartDelay determined AV optimisation: a comparison with other AV delay methods used in CRT) study compared three different methods of AV optimisation (fixed empirical AV delay of 120 ms, echo-optimised AV delay, or AV optimisation with an ECG-based algorithm) in 980 patients with a CRT device to determine if any method was superior.[105] The study found that neither echo- or ECG-based AV optimisation was better than a fixed AV delay of 120 ms and therefore concluded that the routine use of AV optimisation techniques was not indicated. However, the data did not exclude the possibility that AV optimisation might have a role in selected patients who do not respond to CRT with empirical settings.

The potentially deleterious effects of chronic RV pacing on cardiac function were re-examined in 103 patients with isolated congenital AV block. Long-term pacing was not found to be associated with the development of heart failure or deterioration of ventricular function in patients who were negative for antinuclear antibody, although patients who tested positive for the antibody were more likely to develop heart failure.[106] Pacing in hypertrophic cardiomyopathy was also recently re-examined in a single-centre study, which found some evidence of benefit from dual chamber pacing in patients with hypertrophic cardiomyopathy with NYHA III–IV symptoms, rest gradients of >50 mm Hg and who were refractory to other drugs, after follow-up periods of up to 10 years.[107] Another group of patients in whom the role of pacing has remained controversial are those with carotid sinus hypersensitivity (CSH) with syncope. In a double-blind, placebo-controlled, crossover study, 34 patients (aged >55 years) with CSH and more than three unexplained falls in the preceding 6 months were randomised to receive a dual-chamber pacemaker with rate-drop response programming which was switched on or off.[108] The investigators found that the pacing intervention had no effect on the number of falls and concluded that the role of pacing for this group of patients remains controversial. A similar conclusion was reached in a multicentre study of 141 patients (mean age 78 years) with cardioinhibitory CSH.[109]

6. INHERITED ARRHYTHMOGENIC DISEASES

Major advances have been made in our understanding of the basic mechanisms, genetics and clinical features of the inherited arrhythmogenic diseases (IADs) over the past 2 years. Since these cannot all be covered in this short overview, only some of the major studies with important implications for general cardiologists will be mentioned. The rapid expansion in our knowledge of the genetic basis of the IADs and rise in commercially available clinical genetic services has brought with it an additional dimension to how we manage these conditions. The reader is referred to a number of useful recently published reviews that examine these issues in more detail.[110–112]

SCD without morphological evidence of heart disease accounted for 23% of cases in a recent pathological study of UK athletes.[113] Potential causes of unexplained cardiac arrest were systematically evaluated in a prospective study involving 63 patients in nine centres across Canada.[114] The tests, which included cardiac MRI, signal-averaged ECG, exercise testing, drug challenge and selective electrophysiology (EP) testing, resulted in a specific diagnosis (IAD, early repolarisation, coronary spasm and myocarditis) in 35 patients (56%). The remaining 28 patients were considered to have idiopathic VF. Subsequent genetic testing performed in 19 patients found evidence of causative mutations in nine (47%) of these. Family screening of 64 family members of the nine patients with causative mutations led

poor LVEF (<30%), although the absolute number at risk was greatest in those with relatively preserved LVEF (>40%).

The Intermediate Risk Stratification Improves Survival (IRIS) trial published in 2009 further tested the hypothesis that early implantation of an ICD soon after an AMI could improve survival compared with optimal medical treatment.[83] This was a randomised, prospective, multicentre trial which enrolled 898 patients, 5–31 days after their AMI, who met the following clinical criteria: LVEF ≤40% and a heart rate ≥90 bpm on the first available ECG or non-sustained VT (≥150 bpm) during Holter monitoring. The main difference between this study and DINAMIT was a contemporary patient population (70% had undergone PCI and the majority were receiving optimal long-term medication) and additional non-invasive criteria to identify a population at potentially higher risk. However, the investigators did not find that ICD therapy reduced overall mortality after a mean follow-up of 37 months. Consistent with the findings from DINAMIT, the reduced incidence of SCD among ICD recipients in the IRIS study was offset by an increased incidence of non-SCD.

Catheter ablation of ventricular arrhythmias

The VTACH (Ventricular Tachycardia Ablation in Coronary Heart disease) study, involving 16 centres in four European countries, assessed the potential benefit of catheter ablation of VT *before* ICD implantation in patients with a history of VT, myocardial infarction and LVEF ≤50%.[84] Patients (n=110) were randomly allocated to receive catheter ablation and an ICD or an ICD alone and followed-up for a mean period of 22.5 months (SD 9.0). The investigators found that prophylactic VT ablation before ICD implantation prolonged the time to VT recurrence from 5.9 months (IQR 0.8–26.7) in the ICD only group to 18.6 months (lower quartile 2.4 months; upper quartile could not be determined) in the ablation and ICD group. Complications related to the ablation procedure occurred in two patients. This study is in accordance with an earlier prospective randomised study of 128 patients, which demonstrated that prophylactic catheter ablation of the ventricular arrhythmogenic substrate reduced the incidence of ICD therapy in patients with a history of myocardial infarction and previous ventricular arrhythmias.[85] It should be noted that VT ablation was performed in experienced centres in both these trials and that there was no significant effect of catheter ablation on overall mortality. Whether VT ablation should routinely be performed before ICD insertion for secondary prevention of SCD in stable patients with previous myocardial infarction remains to be determined.

There has been an increase in the number of publications on epicardial ablation for VT over the past few years in view of the realisation that not all VTs can be successfully eliminated by an endocardial-only approach.[86,87] In a retrospective study of 156 epicardial ablations for VT (out of a total of 913 VT ablations) in three tertiary centres evaluating the safety and mid-term complications of epicardial VT ablation, the risk of major acute (epicardial bleeding, coronary stenosis) and delayed (pericardial inflammatory reaction, delayed tamponade, coronary occlusion) complications related to epicardial access was found to be 5% and 2%, respectively.[88] Therefore, although this technique can be effective in some cases, especially where endocardial ablation has failed, it is associated with significant morbidity and should only be performed in centres experienced with this technique.

The prognostic significance of frequent premature ventricular contractions (PVCs) and the effect of catheter ablation of these ectopics has received further attention recently. In a study of 239 asymptomatic patients with structurally normal hearts and frequent PVCs (>1000/day) from the right or left ventricular outflow tract, a significant negative correlation between PVC prevalence and δLVEF and positive correlation with δLV diastolic diameter was observed over a 5.6 (SD 1.7)-year period.[89] In addition to PVC burden, other factors such as longer PVC duration, presence of non-sustained VT, multiform PVCs and right ventricular PVCs may be associated with a decline in LV function.[90,91] Although it is well known that catheter ablation of frequent PVCs can improve and restore LV function in some patients, the potential benefits of ablation in patients with normal LV function have been less well studied. A prospective study of 49 patients with frequent PVCs and normal baseline LVEF demonstrated that catheter ablation can improve the subtle LV dysfunction-detected pre-ablation using speckle tracking imaging analysis.[92] However, unanswered questions remain, including benefits of catheter ablation on hard end points (especially mortality) and when ablation should be performed (degree of PVC burden, LV function, after a trial of antiarrhythmic medication?).

5.3. Cardiac resynchronisation therapy and pacing

Two pivotal cardiac resynchronisation therapy (CRT) clinical trials have been published in the past 2 years that potentially expand the indications for CRT in patients with heart failure to those in NYHA class I and II symptoms. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-CRT) compared the use of ICD alone with CRT-D (CRT with a defibrillator component) in patients with asymptomatic or mildly symptomatic heart failure symptoms (NYHA class I or II), LVEF≤30% and QRS duration of ≥130 ms.[93] During an average follow-up of 2.4 years, fewer patients in the CRT-D group experienced the primary composite end point (all-cause mortality and heart failure) compared with the ICD group (17.2% compared with 25.3%, respectively, p=0.001). Although these results appear impressive at first glance, closer examination of the data reveals that the main superiority of CRT-D was in reducing the rate of hospitalisation for heart failure and that there was no significant difference in mortality between the two groups (which was 3% annually). Furthermore, the study failed to show that NYHA class I patients fulfilling the enrolment criteria benefited from CRT-D.

In RAFT (Resynchronisation-Defibrillation for Ambulatory Heart Failure Trial), CRT-D was compared with ICD alone in patients with NYHA class II or III heart failure, LVEF≤30%, intrinsic QRS duration ≥120 ms or a paced QRS duration of ≥200 ms.[94] The investigators found that over a mean period of 40 months, the primary outcome (all-cause mortality or heart failure hospitalisation) occurred in fewer patients in the CRT-D group (33.2% compared with 40.3% in the ICD group, p<0.001). Unlike

lation (VT/VF) occurred in 329 (5.7%). Clinical outcomes and 90-day mortality were found to be worse in those with VT/VF than in those without. Furthermore, outcomes were worse if the VT/VF occurred late (after the end of cardiac catheterisation) rather than early (before the end of cardiac catheterisation). The occurrence of ventricular arrhythmias remained associated with a significantly increased mortality after adjustment for potential confounders, although whether they were causally related to a poorer prognosis or simply a reflection of more severe heart disease is not yet clear.

In the Occluded Artery Trial-Electrophysiological Mechanisms (OAT-EP) study, PCI to open a persistently occluded infarct-related artery after an acute myocardial infarction (AMI) phase was compared with optimal medical treatment alone to determine which strategy reduced markers of vulnerability to ventricular arrhythmias.[67] There were no significant differences in heart rate variability, time-domain signal-averaged ECG, or T-wave variability parameters (all surrogate markers of ventricular instability) between either group at 30 days and 1 year after the AMI, which is consistent with the lack of clinical benefit from PCI in stable patients after AMI with persistently occluded infarct-related arteries in the main OAT study.

The Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction (CARISMA) trial was designed to investigate the incidence and prognostic significance of arrhythmias detected by an implantable cardiac monitor among patients after AMI with impaired left ventricular (LV) function.[68] A total of 297 patients (out of 5969 initially screened) who had had a recent AMI and had reduced LV ejection fraction (LVEF; ≤40%) received an implantable loop recorder within 11±5 days of the AMI and were followed up every 3 months for an average of 1.9±0.5 years. The investigators detected a clinically significant number of bradyarrhythmias and tachyarrhythmias in these patients (28% new-onset AF, 13% non-sustained VT, 10% high-degree AV block, 7% significant sinus bradycardia, 3% sinus arrest, 3% sustained VT and 3% VF). In particular, intermittent high-degree AV block was associated with a very high risk of cardiac death. The arrhythmogenic substrate for ventricular arrhythmias following reperfusion therapy for AMI was investigated in a study of 36 AMI survivors referred for catheter ablation of VT (13±9 years after the AMI).[69] Of these, 14 patients had early reperfusion during AMI, while 22 were non-reperfused. The investigators found, using detailed electroanatomical mapping, that scar size and pattern were different between VT patients with and without reperfusion during AMI, with early reperfusion and less confluent electroanatomical scar being associated with faster VTs.

5.2. Risk stratification for sudden cardiac death and implantable cardioverter defibrillators

A continuing area of active research in ventricular arrhythmias and sudden cardiac death (SCD) is in improved methods of risk stratification and selection of appropriate implantable cardioverter defibrillator (ICD) recipients.[70] A number of non-invasive cardiovascular tests have recently been evaluated among patients with an increased risk of SCD (eg, AMI survivors and patients with coronary artery disease and cardiomyopathies) with promising results. These include T-wave alternans,[71,72] single-photon emission CT myocardial perfusion imaging,[73] sympathetic nerve imaging with 123-iodine metaiodobenzylguanidine[74] and late-gadolinium enhancement on cardiac MRI.[75] In addition, plasma biomarkers, such as serum collagen levels, which reflect extracellular matrix alterations that may play a part in the generation of the arrhythmogenic substrate,[76] may have a future role in risk stratification. Genetic markers may also be relevant, as suggested by the observation from a combined population of 19 295 black and white adults from the Atherosclerosis Risk In Communities Study and the Cardiovascular Health Study that sequence variations in the nitric oxide synthase 1 adaptor protein (NOS1AP) were associated with baseline QT interval and the risk of SCD in white (but not black) US adults.[77,78]

Another important area requiring further clarification is the optimal timing of ICD insertion among AMI survivors who are deemed to be at greatest risk of SCD. The landmark DINAMIT study (Defibrillation IN Acute Myocardial Infarction Trial), which did not show any mortality benefit from prophylactic ICD insertion in patients after AMI if the device was inserted within 40 days of the index event,[79] has been used to guide current recommendations on ICD insertion among AMI survivors. A recent secondary analysis of this trial confirmed the original findings that the reduction in sudden death in ICD patients was offset by an increase in non-arrhythmic deaths, which was greatest in those who received ICD shocks.[80]

A postmortem study looking at 105 autopsy records of patients from the VALIANT (VALsartan In Acute myocardial infarctioN Trial) study who had died suddenly showed that recurrent myocardial infarction or cardiac rupture accounted for a high proportion of sudden death in the early period after an AMI, thereby partly explaining the lack of benefit of early ICD insertion on overall mortality.[81] Arrhythmic death was more likely to occur later on (after 3 months), which is consistent with the findings of improved survival among ICD recipients from other major ICD trials in which the devices were inserted at a later stage. It should be noted, however, that 20% of sudden deaths in the first month after AMI were presumed arrhythmic as there was no specific postmortem evidence of any additional abnormality that might have caused the sudden death. A significant proportion of patients who have an AMI therefore appear to continue to die suddenly in the early postinfarction period from cardiac arrhythmias. These patients are not included in current international guidelines for ICD insertion and remain a group for which more research is required. Another group of patients who are not covered by current primary prevention ICD guidelines are those with relatively preserved LVEF after an AMI. Although these patients are at lower risk of SCD than those with poor LVEF, they represent a larger proportion of AMI survivors.

Data from a multicentre Japanese study suggest that in the era of primary PCI there is a low incidence of SCD among AMI survivors (overall mortality was 13.1% and SCD 1.2% over an average follow-up period of 4.2 years among 4122 patients).[82] The risk was highest for those with

351 (7.9%) participants out of 4421 participants (11 971 examinations) during the period 1968–2007.[53] The association was not attenuated by adjustment for AF risk factors or reported AF-related genetic variants. Racial factors and ancestry also appear to be related to the risk of AF. Data from white and African-American subjects enrolled in the Cardiovascular Health Study (CHS) and Atherosclerosis Risk in Communities (ARIC) study suggest that European ancestry is a risk factor for incident AF.[54]

4. CATHETER ABLATION OF AF

In a large prospective, multicentre trial involving 19 centres, the use of catheter ablation was compared with antiarrhythmic drug treatment.[55] A total of 167 patients with paroxysmal AF for whom at least one antiarrhythmic drug had failed and who had experienced at least three AF episodes in the preceding 6 months were randomised (2:1) to undergo catheter ablation or medical treatment. After a 9 month follow-up period, the investigators found that catheter ablation resulted in a longer time to treatment failure and significantly improved quality-of-life scores. Major 30-day treatment-related adverse events occurred in five of 103 patients (4.9%) treated with catheter ablation and five of 57 patients (8.8%) treated with antiarrhythmic drugs. An improvement in the quality of life was also demonstrated in a prospective follow-up study of 502 symptomatic subjects who underwent AF ablation.[56] The improvement in quality of life was sustained at 2 years in patients with and without recurrence of AF, although the change was greatest in patients who remained free from AF and without antiarrhythmic drug treatment.

Several well-respected, high-volume centres have recently published their long-term outcomes following catheter ablation for AF. The Bordeaux group reported their 5 year follow-up data on 100 patients (86% male; age 55.7±9.6 years; 63% paroxysmal AF; 36% with structural heart disease).[57] Arrhythmia-free survival rates after a *single* catheter ablation procedure were 40%, 37% and 29% at 1, 2 and 5 years, respectively (most recurrences occurred over the first 6 months). A total of 175 procedures were performed with a median of two for each patient (51 patients underwent a second procedure and 17 a third). There were no periprocedural deaths, although major complications (cardiac tamponade requiring drainage) occurred in three patients (3%), and minor complications (arteriovenous (AV) fistula, femoral pseudoaneurysm and asymptomatic pulmonary vein stenosis) occurred in another three patients. The important point to note from this study is that even in experienced hands with a selected AF population (patients who are referred for AF ablation tend to be younger and have fewer comorbidities), there is a steady decline in arrhythmia-free survival with recurrences seen up to 5 years after ablation, although the majority occur within the first 6–12 months.

An experienced German centre also recently reported their long-term follow-up data of catheter ablation in 161 patients (75% male; age 59.8±9.7 years) with symptomatic paroxysmal AF and normal left ventricular function.[58] They found that 75 patients (46.6%) were in sinus rhythm after the initial procedure during a median follow-up period of 4.8 years (0.33 to 5.5 years). A second procedure was performed in 66 and a third procedure in 12 patients. One patient had an aspiration pneumonia that was successfully treated and two developed a sterile pericardial effusion that did not require drainage (no other procedural complications were noted). There was a low rate of progression to chronic AF during the follow-up period, which was seen in only four patients (2.5%).

A group from London, UK, similarly reported their long-term results following catheter ablation for AF in 285 patients (75% male; mean age 57 (SD 11) years; 53% paroxysmal AF; 20% with structural heart disease) undergoing a total of 530 procedures.[59] During a mean follow-up of 2.7 years (0.2 to 7.4 years), freedom from AF/atrial tachyarrhythmia was 86% for patients with paroxysmal AF and 68% for those with persistent AF. Complications included three strokes/TIAs. Late recurrence was three per 100 years of follow-up after >3 years. The investigators also found that targeting complex fractionated atrial electrograms (CFAEs) during the ablation procedure improved outcome in patients with persistent AF. However, this was not seen in a randomised study performed by another group in which 119 patients with persistent AF were randomised to additional CFAE ablation following pulmonary vein isolation or no additional ablation.[60]

In summary, the reports on long-term success rates following catheter ablation for AF demonstrate that the procedure is effective in a selected group of symptomatic patients with AF, although a significant proportion require more than one ablation procedure, there are risks of periprocedural complications and AF recurrence remains a possible problem, even after follow-up periods as long as 5 years. It should be noted that reported outcomes from the different centres cannot be directly compared, since there are differences in patient population (eg, percentage of patients with paroxysmal and permanent AF, patients with structural heart disease), techniques used (segmental pulmonary vein isolation vs wide area circumferential ablation), length of follow-up and methods used to detect AF recurrence.

A number of studies have been performed to search for new non-invasive parameters which may help to predict AF recurrence following catheter ablation. These factors include renal impairment,[61] novel echo parameters such as the atrial electromechanical interval,[62] atrial fibrosis assessed with echo[63] or MRI[64] and B-type natriuretic levels.[65]

5. VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

5.1. Ventricular arrhythmias after myocardial infarction

To further understand the significance of the occurrence and timing of ventricular arrhythmias in the context of primary percutaneous coronary intervention (PCI), a secondary analysis of the APEX AMI (Assessment of PEXelizumab in Acute Myocardial Infarction) trial was undertaken.[66] Of the 5745 patients with ST-elevation myocardial infarction presenting for primary PCI (across 296 hospitals in 17 countries), ventricular tachycardia/ventricular fibril-

was deemed to be unsuitable. The investigators found that apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of bleeding or intracranial haemorrhage and also reduced the risk of a first hospitalisation for a cardiovascular cause.

Recent studies in the field of new mechanical approaches to stroke prevention in AF include the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF) study.[33] In this non-inferiority study, the efficacy and safety of a new percutaneous left atrial appendage (LAA) closure device was compared with warfarin treatment in 707 patients with non-valvular AF. Study participants had to have at least one risk factor for stroke (in addition to AF) and were assigned in a 2:1 ratio to receive the LAA-closure device and subsequent discontinuation of warfarin or warfarin alone (with a target INR of between 2.0 and 3.0). The LAA-closure device was successfully implanted in 88% of subjects assigned to the intervention group. After a mean follow-up of 18±10 months, the primary efficacy event rate of stroke (ischaemic or haemorrhagic) was 3.0 per 100 patient-years (95% CI 1.9 to 4.5) in the intervention group and 4.9 per 100 patient-years (95% CI 2.8 to 7.1) in the control group. Primary safety events were more common in the intervention group than in the control group, and were mainly related to periprocedural complications (pericardial effusion in 4.8%, major bleeding in 3.5% and periprocedural ischaemic stroke in 1.1%). This important study demonstrates that the Watchman (Atritech, Plymouth, Minnesota, USA) LAA-closure device may provide an alternative strategy to oral anticoagulation for the prevention of stroke in patients at high risk with non-valvular AF and at high thromboembolic risk, although the trade-off is an increased risk of periprocedural complications related to device implantation. As with all new interventional procedures, safety of the Watchman LAA-closure device is likely to improve with increased operator experience and familiarity with the new technology.[34] Longer-term follow-up data with an earlier percutaneous LAA-closure device, PLAATO (percutaneous left atrial appendage transcatheter occlusion) system,[35] suggest that such devices can lower the annualised risk of stroke/TIA compared with the expected stroke/TIA risk assessed using the CHADS2 score (3.8% a year and 6.6% a year, respectively), although event rates still remain significant.[36]

3. EPIDEMIOLOGY AND GENETICS OF AF

Epidemiological studies have shed further light on the mechanisms underlying AF and identified new risk factors. Using data from the Framingham Heart Study, investigators identified a prolonged PR interval (>200 ms) as a predictor of incident AF, pacemaker implantation and all-cause mortality in 7575 individuals (mean age 47 years; 54% women).[37] This study contradicts the previously held belief that first-degree heart block is benign[38] and raises further questions about the mechanism by which a prolonged PR interval might increase the risk of developing AF. In another study using 4764 participants from the Framingham Heart Study, a new risk score was developed aimed at predicting an individual's absolute risk for developing AF.[39] Age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur and heart failure were all found to be associated with AF ($p<0.05$, except body mass index $p=0.08$). When incorporated in a risk score, the clinical model C statistic was 0.78 (95% CI 0.76 to 0.80).

In a subsequent study, the same investigators looked at the relation between a number of plasma biomarkers and incident AF using the Framingham cohort and found that B-type natriuretic peptide (BNP) was a predictor of incident AF and improved risk stratification, increasing the C statistic from 0.78 (95% CI 0.75 to 0.81) to 0.80 (95% CI 0.78 to 0.83).[40]

In another community-based population study of older adults (n=5445) who participated in the Cardiovascular Health Study, NT-proBNP was found to predict new-onset AF, independently of any other previously described risk factor.[41] Similar findings have now been reported in a Finnish cohort.[42] The potential role of biomarkers may extend beyond predicting incident AF—a recent study reporting that the kinetics of plasma NT-proBNP release in patients presenting acutely with AF provides a potential means of determining its time of onset and the safety of cardioversion.[43] There therefore appears to be a promising role for new biomarkers in predicting incident AF, which may help guide clinicians as to which individuals are most at risk of developing AF and who may benefit from prophylactic treatments. Other studies looking at population data in women have reported body-mass index[44] and birth weight[45] to be associated with incident AF. Furthermore, recent data from 34 722 participants of the Women's Health Study provided evidence that new-onset AF in initially healthy women was independently associated with all-cause and cardiovascular mortality.[46]

The past 2 years have seen important advances in our understanding of the genetics and heredity of AF. Following the landmark discovery using genome-wide association studies on subjects from European and Chinese descent that two sequence variations on chromosome 4q25 are associated with an increased risk of developing AF,[47] two new AF susceptibility signals have been identified on the same chromosome.[48] A meta-analysis of four independent cohorts of European descent (the Framingham Heart Study, Rotterdam Study, Vanderbilt AF Registry and German AF Network) confirmed a significant relationship between AF and intergenic regions on chromosome 4.[49] Interestingly, genetic variants in the chromosome 4q25 region also appear to modulate the risk of AF recurrence after catheter ablation[50] and are associated with the development of AF after cardiac surgery.[51 52] Whether genetic sequencing of chromosome 4q25 will prove useful in risk stratification for the development of AF after catheter ablation or cardiac surgery remains to be determined—at present, this remains a distinct and promising possibility. In line with the newly emerging genetic data on AF, studies on population-based cohorts have also provided evidence for a heredity component. Using data from the Framingham Heart Study, investigators found that familial AF occurred in 1185 (26.8%) and premature familial AF occurred among

periments and observational studies in humans,[18–20] the potentially beneficial effects of polyunsaturated fatty acids (PUFA) in atrial fibrillation have not been confirmed from the results of several prospective randomised trials reported recently. The largest and most comprehensive study to date designed to examine this subject was a prospective, multicentre, RCT of 663 patients with confirmed paroxysmal (n=542) or persistent (n=121) AF, with no substantial structural heart disease and in sinus rhythm at baseline.[21] Patients were randomly assigned to take prescription PUFA (8 g/day) or placebo for the first 7 days, followed by PUFA (4 g/day) or placebo thereafter for 24 weeks. Despite the assigned treatment being relatively well tolerated in both groups and plasma levels of eicosapentaenoic and docosahexaenoic acid being significantly higher in the prescription group than in the placebo group at weeks 4 and 24, the investigators found no reduction in AF recurrence over 6 months between the two groups. Two smaller prospective, placebo-controlled, randomised studies investigating the effects of PUFA in patients after electrical cardioversion of AF[22] and after cardiac surgery[23] have failed to demonstrate a beneficial action of PUFA in decreasing the recurrence or incidence of AF.

2. STRATEGIES TO DECREASE THROMBOEMBOLISM

Important advances have been made in stroke prevention in patients with AF over the past 2 years, which are likely to have a significant impact on future clinical management. In the RE-LY study (Randomised Evaluation of Long-term anticoagulation therapY), two fixed doses (110 mg or 150 mg twice daily) of a new oral direct thrombin inhibitor, dabigatran, were compared with warfarin in over 18 000 patients with AF and at least one additional risk factor for stroke.[24] The investigators found that patients taking the 110 mg dose of dabigatran had similar rates of stroke and systemic embolism to those receiving warfarin, but had lower rates of major haemorrhage, while subjects taking the 150 mg dose had *lower* rates of stroke and systemic embolism, with similar rates of major haemorrhage. Results from this study were so impressive that dabigatran has since been incorporated into the latest European and American guidelines on AF as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with paroxysmal and permanent AF.[9,25]

As 80% of the active drug is excreted by the kidneys, patients with a creatinine clearance of <30 ml/min were excluded from the RE-LY trial; dabigatran should be used with caution in patients with significant renal impairment. The dose of dabigatran approved by the US Food and Drug Administration in October 2010 was 150 mg twice daily in patients with non-valvular AF with a reduced dose of 75 mg twice daily for those with mild renal impairment (creatinine clearance of 15–30 ml/min). There are no dosing recommendations for patients with a creatinine clearance <15 ml/min or those undergoing dialysis. In addition to the superiority of dabigatran (150 mg twice daily) over warfarin for treatment of stroke and systemic embolism, another major advantage is that there is no need for international normalisation ratio (INR) monitoring. However, disadvantages include the lack of a specific antidote (its half-life is 12–17 h) and a slightly increased risk of non-haemorrhagic side effects, including dyspepsia. How this promising new oral anticoagulant drug will be incorporated into current local practices around the world will require future evaluation and consideration. For example, there may be little to be gained from switching patients already receiving warfarin and with excellent INR control to dabigatran, while patients with poor INR control or those who have newly started oral anticoagulation may derive greater benefit. Local standards of care for anticoagulation control and follow-up may also be an important consideration, as concluded in a subanalysis of the RE-LY study, in which the investigators found that sites with poor INR control and greater bleeding from warfarin may receive greater benefit from dabigatran 150 mg twice daily.[26] Other substudies following on from the original RE-LY trial have shown that the benefits of dabigatran are similar between patients who have never received a vitamin K antagonist (VKA-naive patients) and VKA-experienced patients,[27] and that dabigatran can be used as a safe alternative to warfarin in patients requiring cardioversion.[28]

In the ACTIVE A study, the ACTIVE (AF Clopidogrel Trial with Irbesartan for prevention of Vascular Events) investigators evaluated whether the addition of clopidogrel to aspirin would reduce the risk of vascular events compared with aspirin alone in patients for whom a VKA was considered unsuitable.[29] The ACTIVE W trial had previously demonstrated that the combination of aspirin and clopidogrel was inferior to oral anticoagulation for the prevention of vascular events in patients with AF at high risk of stroke.[30] In the ACTIVE A study, involving 7554 patients and a median follow-up of 3.6 years, the investigators found that the combination of both antiplatelet agents reduced the risk of major vascular events, especially stroke, compared with aspirin alone but at the price of increased risk of major haemorrhage. The clinical implications of the ACTIVE A and ACTIVE W trials are that oral anticoagulation is better than the combination of aspirin and clopidogrel in stroke prevention in patients with AF, but for patients for whom oral anticoagulation is unsuitable, the combination of antiplatelet agents is better than aspirin alone, although the risk of major haemorrhage is also greater. This reinforces the need for appropriate counselling and risk stratification of patients when deciding upon the most suitable strategy to lower the risk of vascular events in patients with AF.

Another important randomised controlled clinical trial including patients for whom a VKA was not suitable involved the use of new oral direct and competitive inhibitor of factor Xa, apixaban.[31] The AVERROES (Apixaban vs acetylsalicylic acid to prevent stroke in patients with AF who have are unsuitable for vitamin K antagonist treatment or for whom this treatment has failed) study involved the random assignment of 5599 patients with AF (involving 522 centres in 36 countries) to apixaban (5 mg twice daily) or aspirin (81–324 mg/day).[32] In that study, patients with AF were aged ≥50 years and had to have at least one risk factor for stroke in addition to being unable to take a VKA, either because it had already been shown to be unsuitable or

flutter) trial was a ground-breaking study published in early 2009 evaluating the effect of dronedarone on cardiovascular events in patients with AF.[6] In this trial, 4628 patients with AF (paroxysmal or persistent) or atrial flutter who had an additional risk factor for death (age ≥70 years, diabetes, history of stroke/transient ischaemic attack (TIA), systemic embolism, left atrial diameter ≥50 mm and ejection fraction ≤40%) were randomly assigned to receive dronedarone (400 mg twice daily) or placebo. Over a mean follow-up of 21±5 months, the investigators found that patients in the dronedarone group had significantly lower primary outcome of first hospitalisation due to cardiovascular events or death than the placebo group (734 (32%) vs 917 (39%), respectively, p<0.001). Mortality from cardiac arrhythmias was significantly lower in the dronedarone group, although there was no overall difference in all-cause mortality. Interestingly, there was also a small but statistically significant reduction in acute coronary syndromes in the dronedarone group—the exact reason for this remains unclear. Patients taking dronedarone had higher rates of bradycardia, QT-prolongation, nausea, diarrhoea, rash and increased serum creatinine than those receiving placebo. There were no significant differences in rates of thyroid- and pulmonary-related adverse events between the two groups, although, as acknowledged by the investigators in their discussion, the follow-up period of 21 months might have been too short to detect such adverse effects, which may take more than 2 years to develop, as is often observed with amiodarone.

In the original ATHENA trial and also a subsequent post hoc analysis,[7] there was no evidence of harm in patients with heart failure or those with a low ejection fraction and New York Heart Association (NYHA) class II or III symptoms. This contrasts with results from the earlier ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse) study, which was terminated early owing to excess mortality in the dronedarone group.[8] The reason for this difference may be attributed to the exclusion of patients with NYHA class IV symptoms in the ATHENA study and the fact that the ANDROMEDA study also included patients with a recent exacerbation of heart failure. Nonetheless, in view of the results from the ANDROMEDA study, the authors warned against use of dronedarone in patients with severe heart failure and left ventricular dysfunction. This is reflected in the latest European and American guidelines, which propose that dronedarone can be used as a first-line pharmacological option in patients with symptomatic AF, including those with structural heart disease, coronary artery disease, hypertensive heart disease and stable heart failure with NYHA class I or II symptoms, but should not be used in patients with NYHA class III or IV symptoms or recently unstable heart failure.[9,10] A number of post hoc analyses of the ATHENA trial have been published providing further evidence for several beneficial effects of dronedarone. These include a reduction in stroke risk from 1.8% a year to 1.2% a year,[11] and favourable effects on rhythm and rate control.[12]

Another newly emerging drug that may have a role in the pharmacological cardioversion of AF is the atrial-selective antiarrhythmic drug vernakalant (RSD1235).[13] Vernakalant is one of several new agents that have been designed to target atrial-specific ion channels and in doing so, theoretically reduce or limit the risk of ventricular proarrhythmia. In an open-label trial assessing the efficacy of vernakalant in the cardioversion of AF, the intravenous agent was found to convert 50.9% of patients with AF (out of a total of 236) to sinus rhythm with a median time to conversion of 14 min among responders.[14] There were no episodes of ventricular arrhythmias and the drug was relatively well tolerated, apart from 10 patients (4.2%) who had to discontinue treatment owing to side effects (most commonly hypotension). In a more recent small randomised trial of 254 patients with recent onset AF (3–48 h duration), vernakalant (10 min infusion of 3 mg/kg followed by a second 10 min infusion of 2 mg/kg if patient was still in AF after a 15 min observation period) was compared with intravenous amiodarone (5 mg/kg over 60 min followed by 50 mg maintenance infusion over 60 min).[15] A greater number of patients achieved the primary end point of conversion to sinus rhythm within 90 min in the vernakalant group compared with the amiodarone group (60/116 (51.7%) compared with 6/116 (5.2%), p<0.0001, respectively). The median time of cardioversion in the patients receiving vernakalant who responded was 11 min and this was associated with a higher rate of symptom relief than with amiodarone. Both drugs were well tolerated in this study and there were no cases of ventricular arrhythmias.

A small randomised study of 61 patients with heart failure and persistent AF contributed additional useful data towards the continuing topic of rate versus rhythm control in patients with heart failure and AF.[16] Patients in this study were randomly assigned to a rhythm control strategy (oral amiodarone and electrical cardioversion) or rate control with β blockers and/or digoxin (target heart rate <80 bpm at rest and <110 bpm after walking). The investigators found that restoration of sinus rhythm in patients with AF and heart failure improved quality of life and left ventricular function compared with a strategy of rate control (66% in the rhythm control group were in sinus rhythm at 1 year and 90% in the rate control group achieved the target heart rate). For patients with AF for whom a rate control strategy has been decided upon, the optimal target heart rate has remained controversial. Guidelines have previously recommended strict rate control, although this was not based on clinical evidence. In an attempt to examine this issue, a prospective, multicentre, randomised trial was conducted to test the hypothesis that lenient rate control was not inferior to strict rate control in preventing cardiovascular events in patients with permanent AF.[17] The investigators found that of the 614 patients recruited into the study, the frequencies of symptoms and adverse events were similar between patients assigned to a lenient rate control strategy (resting heart rate <110 bpm) and those assigned to a strict rate control strategy (resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm). A lenient-control strategy was easier to achieve as more patients in this group attained their heart rate target compared with the strict-control group (97.7% vs 67.0%, p<0.001).

Despite some promising results from preclinical ex-

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Almanac 2011: Cardiac Arrhythmias and Pacing. The National Society Journals Present Selected Research that has Driven Recent Advances in Clinical Cardiology

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EDITORIAL

1. ATRIAL FIBRILLATION

1.1. Clinical trials

In the past 2 years, a number of landmark clinical trials have been published which further our understanding and clinical management of patients with atrial fibrillation (AF). Two of the major goals in the treatment of this condition include reducing progression or recurrence of the arrhythmia and decreasing the risk of cardiovascular events, thereby improving quality of life and decreasing morbidity. Following on from a large body of evidence from preclinical studies, small clinical trials and meta-analyses suggesting that blockade of the renin–angiotensin system has beneficial effects on the pathophysiology of AF,[1] two large multicentre, placebo-controlled, randomised trials were conducted to determine the effects of angiotensin II receptor blockers (ARBs) on AF.

The first of these trials, published in 2009, tested the hypothesis that the ARB valsartan could reduce the recurrence of AF in patients with underlying cardiovascular disease, diabetes or left atrial enlargement *and* a history of documented AF, in addition to established treatments.[2] A total of 1442 patients were enrolled into the study—722 assigned to the valsartan group (target dose 320 mg) and 720 to the placebo group. The investigators found that treatment with valsartan had no significant effect on AF recurrence (AF recurrence 51.4% in the valsartan group and 52.1% in the placebo group, p=0.73) over a relatively short follow-up period of 1 year.

The second large ARB randomised controlled trial (RCT) published this year evaluated whether irbesartan would reduce the risk of cardiovascular events in patients with AF.[3] Patients with a history of risk factors for stroke and a systolic blood pressure of at least 110 mm Hg were randomly assigned to receive either irbesartan (target dose of 300 mg once daily) or placebo. Patients for this study were already enrolled in one of two other AF trials looking at clopidogrel plus aspirin versus aspirin alone or versus oral anticoagulants. The investigators found that irbesartan did not reduce cardiovascular events or hospitalisation rates for AF (total of 9016 enrolled with a mean follow-up of 4.1 years) and that, not surprisingly, more patients in the irbesartan group had symptomatic hypotension and renal dysfunction than those in the placebo group.

Although the main findings from both of these large RCTs were negative, it should be noted that they were *secondary* prevention studies—that is, patients already had established AF, and also had more advanced stages of disease (over 80% of patients in both studies had a history of persistent or permanent AF), implying that the substrate for AF was already well established in both study groups. It might be argued that blockade of the renin–angiotensin system may be a more effective strategy if performed earlier during the natural history of the disease or even *before* AF develops (ie, primary prevention), since ACE inhibitors and ARBs may prevent, but not necessarily reverse, the electrical and structural remodelling that leads to the development and progression of the arrhythmia. In support of this, a smaller randomised single-centre study of 62 patients with lone AF, with no history of hypertension or heart disease, presenting to the emergency department reported that patients given ramipril (5 mg/day) had significantly fewer AF relapses during a 3-year follow-up period than patients given placebo.[4]

A significant new addition to the pharmacological options available for treating AF has been the emergence of dronedarone, a multichannel blocker with similar structural and electrophysiological properties to amiodarone with the main exception being removal of iodine and the addition of a methane-sulphonyl group.[5] These structural changes result in decreased lipophilicity, shortened half-life (to approximately 24 h), reduced tissue accumulation and theoretically fewer side effects than associated with amiodarone.

The ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg twice daily for the prevention of Hospitalisation or death from any cause in patiENts with Atrial fibrillation/

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relatively small trials with inappropriate end points led to the nesiritide debâcle, whereas investigation of rolofylline followed an appropriate sequence with early small-scale studies informing the design of a properly powered end-point study.

The correct diuretic dosing regimen for patients admitted with fluid retention has often been a controversial question and the DOSE trial[76] was designed to help guide this aspect of acute heart failure management. Three hundred and eight patients with fluid retention due to heart failure were randomised to receive furosemide either as a bolus every 12 h or by continuous infusion: both were given as either low or high dose. There were two co-primary end points: patients' global symptom assessment over 72 h and change in creatinine level from baseline to 72 h.

No significant difference was found between bolus and infusion regimens, but a small (and statistically non-significant) greater improvement in symptoms in the high-dose versus low-dose groups was seen. The high-dose groups had a substantially greater diuresis.

It can be difficult directly to compare practice in the USA with Europe. Typically, patients with acute heart failure are in hospital for around 5 days in the USA, but 11 days in Europe and any acute weight loss during admission (presumably reflecting fluid loss) is very much smaller, implying that patients are admitted in the USA with very much less fluid overload than in Europe. Whether there are differences between furosemide given by bolus or continuous infusion over a longer time scale cannot be addressed by DOSE, but the message that high doses of furosemide (defined here as 2.5 times the patient's usual oral dose) cause a greater diuresis is clear.

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Better still, restoration of sinus rhythm in such patients may improve both quality of life and LV function[60] while ensuring a more favourable response to CRT.

A more far-reaching question is whether patients with a standard bradycardia pacing indication would benefit from biventricular pacing. A small study using echocardiographic end points suggested that biventricular pacing was associated with less deterioration in left ventricular function,[61] but whether widespread use of biventricular pacing is indicated will have to await the outcome of larger outcome studies.

4.6. Exercise training

The case for exercise training as a standard part of the management of patients with chronic heart failure has been building over several years.[62] Training undoubtedly improves patients' symptoms and several of the predictors of an adverse prognosis.[63] Mounting a properly powered survival study has proved difficult, not least because of the problems of blinding and the difficulty of cross-overs.

The HF-ACTION study managed to recruit 2331 patients randomised to usual care or an intensive training regimen (36 supervised 30 min sessions three times a week, followed by home exercise five times a week at moderate intensity for 40 min).[64] Although the primary end point of all-cause mortality and hospitalisation was no different between the two groups at a median follow-up of 30 months, there was a signal that training might be beneficial as after adjustment for baseline differences in predictors of outcome, training was associated with an 11% reduction in the primary end point. More importantly, perhaps, training was associated with a marked improvement in quality of life, which appeared early during the intervention and continued throughout the course of the study.[65]

It is still unclear whether the *type* of training stimulus is important: most evidence relates to aerobic training. A recent systematic review of trials of resistance training found that the quality of the studies has been poor and effects were inconclusive for quality-of-life outcomes.[66]

Incorporating exercise training into standard heart failure management is difficult.[62] Compliance will always be a challenge—even in HF-ACTION, and after a year, patients' compliance with exercise was only about 80%. Although home exercise is safe,[64] initial supervision may be helpful for both patients and their carers and the resource implications are substantial. Whether a training programme is possible for many patients, who may be elderly, frail and have multiple comorbidities, is debatable. Nevertheless, patients can be reassured that exercise is safe and will improve their symptoms.

4.7. Revascularisation

The commonest cause of heart failure is underlying ischaemic heart disease. However, there is no good evidence that treatments directed at ischaemia with, for example, statins,[67] are beneficial, despite the intuitive feeling that treating ischaemia should be effective. One of the more challenging questions has been whether revascularisation for patients with heart failure and no angina might be beneficial. Observational studies suggest that revascularisation might indeed improve prognosis, particularly in those with demonstrable viability on functional testing,[68] but we now have two randomised trials that examine the problem directly.

In HEART,[69] patients with heart failure and viable but dysfunctional myocardium were randomised to two strategies of care: conservative management or angiography with a view to revascularisation. There was no difference in survival between the two groups at 59 months. Although the trial recruited slowly and only 138 of the planned 800 patients were enrolled, there was no signal suggesting benefit.

STICH[70] included 1212 patients with an ejection fraction ≤35% who were considered suitable for coronary artery bypass grafting (CABG). The patients were randomised to CABG or continued medical treatment. Over a median follow-up of 56 months, there was no difference in all-cause mortality, the primary end point, between the treatment groups. The combined end point of all-cause mortality and cardiovascular hospitalisation was reduced in the CABG group, but the analysis excludes hospitalisation for the original operation, which is scarcely a negligible event: the 60 hospitalisations prevented by CABG required 555 hospitalisations for the CABG procedure itself.[71] There were more deaths in the CABG group for more than 2 years after randomisation, emphasising that this is not a benign intervention.

Together, HEART and STICH show that there is, at most, a marginal benefit for revascularisation in patients with heart failure and underlying ischaemic heart disease. How the results relate to clinical practice is not clear: in STICH, the average age of patients was around 60, resting heart rate was >70 (suggesting, perhaps, inadequate β blockade) and fewer than 10% had 'chronic renal insufficiency' (creatinine is not reported in the paper). Despite the enormous effort expended to answer the question, it is still not clear whether revascularisation is helpful for patients with heart failure.

Acute heart failure

After many years of clinical trials in patients with chronic heart failure, there has been renewed interest in the problem of acute heart failure—in part, driven by the availability of new drugs as potential treatments.

One of the most widely used new treatments for acute heart failure has been nesiritide, licensed for use in the USA, largely as a results of trials showing some improvement in haemodynamics.[72] It has always seemed a little strange from a European perspective that nesiritide has been so widely used and the European Medicines Agency did not allow its use in the EU. A 7000 patient trial comparing nesiritide with placebo in addition to standard treatment has now been completed.[73] No statistically significant difference in symptoms scores was found between the two groups, or in rehospitalisation or death at 30 days.

Another agent for possible use in patents with acute heart failure is rolofylline, an adenosine antagonist. Rolofylline might help to prevent decline in renal function with diuretic treatment by interrupting glomerulotubular feedback. However, in a 2000 patient study, rolofylline had no effect on the primary end point (a composite 'treatment success' score), renal function or mortality.[74 75]

Taken together, the trials of rolofylline and nesiritide highlight the importance of using clinical trials appropriately to drive the evolution of treatment. Reliance on

ment in patient self-reported global assessment (50% 'much or moderately improved', compared with 28% of patients in the placebo group) as well as in secondary end points, including distance covered in a 6 min walk test (about 40 m increase compared with no change in the placebo group). There were similar improvements regardless of starting haemoglobin.

The results have to be treated with some caution: FAIR-HF was not a large trial, blinding was difficult and the end points were to a varying degree subjective. Nevertheless, iron treatment appeared safe and is now an option for patients who remain symptomatic despite medical treatment. An absolutely essential question to answer, though, is the extent to which patients with heart failure should be further investigated for an underlying cause for any iron deficiency, a question not dealt with by FAIR-HF.

Another possible approach for correcting anaemia in heart failure is the use of erythropoiesis-stimulating proteins. A meta-analysis of six randomised controlled trials found that treatment was associated with a significantly lower risk of hospitalisation compared with placebo.[44] Mortality was unaffected. These outcomes are in contrast with studies in cancer and kidney disease and prompted the authors to a call for a large phase III morbidity and mortality trial of anaemia correction with erythropoiesis-stimulating proteins in patients with chronic heart failure.

4.4. Metabolic manipulation

The energy-generating processes of the failing cardiac myocyte are abnormal. Some investigators have focused on substrate use: fatty acid metabolism produces a lower yield of ATP for each molecule of oxygen consumed than glucose metabolism (although fatty acid oxidation yields more ATP per mole) and so it makes sense to try to switch metabolism from fatty acids to glucose.[45]

Various approaches have been tried: perhexiline, for example, blocks mitochondrial free fatty acid uptake by inhibiting carnitine palmitoyltransferase. In a small study, perhexiline led to improvements in exercise capacity and left ventricular function and more rapid recovery of phosphocreatine after exercise.[46] Trimetazidine inhibits lipid β-oxidation and its use has been associated with both an increase in left ventricular ejection fraction and reduction in resting energy expenditure (known to be high in heart failure).[47] A meta-analysis of the available data for trimetazidine[48] even suggests that its use might improve mortality and it is surely time for a large-scale trial of metabolic modulators.

4.5. Cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT: or biventricular pacing) is one of the most exciting new developments for patients with chronic heart failure and left bundle branch block (LBBB) introduced in recent years. Particularly important is its effect on reducing mortality,[49] but around two-thirds of patients get marked symptomatic benefit from their devices.[50] That one-third do not has led to the concept of the 'non-responder' to CRT. How to define 'non-response' varies from paper to paper, with some using symptomatic criteria and others using measures of left ventricular function. What has proved difficult to answer is whether 'non-response' is related to lack of mortality benefit.

A great deal of time and effort has been expended on trying to identify which patients might benefit from CRT. The severity of symptoms does not seem to matter greatly: those with modest symptoms appear to gain as much mortality benefit as those with worse NYHA class of symptoms.[51] In MADIT-CRT,[52] 1820 patients with NYHA class I or II symptoms and LBBB were randomised 2:1 to receive CRT (or not) in addition to a defibrillator. There was a 34% reduction in the risk of death or a heart failure event (defined as congestion treated either with intravenous treatment (diuretics, nesiritide or inotrope) for more than 2 h, regardless of the setting, or: with an increased heart failure regimen during formal hospital admission). The reduction in risk was driven by a reduction in heart failure events. In RAFT,[53] which included 1438 patients with mild (NYHA class II) symptoms, CRT added to a defibrillator led to a reduction in the rate of death and hospitalisation for heart failure.

Another possible selection criterion is the presence of dyssynchrony on some form of cardiac imaging. Underlying this approach is the assumption that CRT works by improving ventricular coordination, which in turn must in some way be measurable. However, of the large, randomised trials showing a mortality benefit for CRT, none used measures of dyssynchrony as an entry criterion other than a minority of patients in CARE-HF. Vigorous efforts to prove the robustness of any of the very many potential measures of dyssynchrony have failed thus far, with the PROSPECT study of nearly 500 patients being the largest available set of data.[54] There was poor reproducibility of the measures, none of which related strongly to the assessment of response.

The only selection criteria consistently shown to be related to outcome are electrocardiographic. It is a commonplace observation that the mean QRS duration in the mortality trials of CRT was around 150 ms and where it has been analysed, the broader the QRS, the greater the benefit. Subgroup analysis of PROSPECT showed some symptomatic benefit for CRT in patients with mechanical dyssynchrony and a narrow QRS complex[55] and similar findings have been reported in small single-centre trials.[56] There is no doubt, however, that the benefits of CRT are largely confined to patients with left bundle branch block,[53] and it may even be that benefit is restricted to those with a QRS >150 ms.[57]

Similarly, while small non-randomised studies have reported variable benefit of CRT for patients in atrial fibrillation (AF), there is almost no evidence to support the practice from randomised trials.[58] The few trials that included patients in AF showed no benefit with CRT.[53] Although the European Society of cardiology guideline updates suggest that CRT might be considered in patients in AF,[59] the class of recommendation was only IIa, level B or C.

What should all this mean in practice? CRT should certainly be considered for all patients with left ventricular systolic dysfunction and symptomatic heart failure who are in sinus rhythm and have left bundle branch block. CRT might be tried for those patients with intractable symptoms and AF (and left bundle branch block), but only if the ventricular rate is well controlled to maximise pacing.

While it remains a very active area of research, the cardinal problem with HeFNEF and the main reason it has no (proven) treatment is the absence of a satisfactory case definition. The incorporation of natriuretic peptides into the diagnostic pathway for HeFNEF should help as a raised level makes it more certain that the heart is the cause of any symptoms. However, natriuretic peptides may show that there has been considerable overdiagnosis of HeFNEF in the past. Potentially relevant in this respect is the recent analysis of mode of death data from I-Preserve: in patients with HeFNEF, death from heart failure was surprisingly rare, the majority succumbing to other cardiovascular events.[28]

4. TREATMENT

4.1. Neurohormonal manipulation

ACE inhibitors, ARBs and β blockers, are of course, the mainstays of medical treatment for patients with chronic heart failure. ACE inhibitors or ARBs should be given to all patients with left ventricular systolic dysfunction, regardless of symptom class, and there is general appreciation that the highest tolerated dose should be used, side effects permitting. Evidence for this approach comes from trials such as ATLAS,[29] in which patients randomised to higher-dose lisinopril fared better than those receiving a lower dose.

There has been little evidence that a high dose of ARBs is better until the HEAAL study,[30] in which 3846 patients with heart failure and left ventricular ejection fraction <40% and who were intolerant of ACE inhibitors were randomised to receive high-dose (150 mg) or low-dose (50 mg) daily losartan. After a median 4.7 years' follow-up there was a lower rate of deaths or hospitalisation for heart failure in the high-dose group (HR=0.90, 95% CI 0.82 to 0.99; p=0.027). Thus it does thus seem that up-titrating ARB doses confers clinical benefit.

With RALES[31] (spironolactone) and EPHESUS[32] (eplerenone), aldosterone blockade has also become important, with the proviso that aldosterone blockade has not been shown to be beneficial in patients with mild heart failure, at least until recently. In EMPHASIS-HF,[33] 2737 patients with heart failure due to systolic dysfunction and New York Heart Association (NYHA) class II symptoms were randomised to eplerenone (up to 50 mg daily) or placebo, in addition to standard treatment. There was a 37% reduction in the risk of the primary end point (cardiovascular death or hospitalisation for heart failure) in the eplerenone group, at the cost of a small increase in the risk of hyperkalaemia. It seems likely that guideline groups will now recommend the use of eplerenone in all those with heart failure due to left ventricular systolic dysfunction.

A problem with the more widespread use of aldosterone antagonists is that the risk of life-threatening hyperkalaemia may increase. Certainly after the RALES report, there was a rapid uptake of spironolactone usage resulting in a marked increase in morbidity and mortality from hyperkalaemia.[34] A possible approach to preventing hyperkalaemia is to use potassium-binding resins. In PEARL-HF,[35] 105 patients with heart failure and a history of hyperkalaemia which had interfered with medical treatment, or who had chronic kidney disease, were recruited. The potassium binder, RLY5016, was given in addition to spironolactone and led to a marked reduction in the risk of hyperkalaemia compared with placebo (7.3% vs 24.5%, p=0.015); and a higher proportion of patients reaching spironolactone 50 mg/day (91% vs 74%, p=0.019). These are encouraging data, but lead to the obvious unanswered question: to what extent is the benefit of aldosterone antagonism mediated by hyperkalaemia? If the answer is 'most', or 'all', then potassium binding may not have much to offer.

4.2. Ivabradine

The mechanism by which β blockers mediate their beneficial effects is not clear, but has long been thought to be related to their ability to reduce heart rate.[36 37] Ivabradine reduces heart rate by reducing sinus node discharge rate while having no other haemodynamic effect and might thus both test the heart rate hypothesis and provide an alternative for patients intolerant of β blockers.

In SHIFT,[38] 6558 patients with heart failure and a low ejection fraction and who were in sinus rhythm with a heart rate of at least 70 beats/min were randomised to receive ivabradine or placebo in addition to usual treatment (including β blocker, where tolerated). Ivabradine was associated with an 18% reduction in the primary end point (cardiovascular death or hospital admission for worsening heart failure), driven mainly by a reduction in hospital admission.

The findings of SHIFT have been much discussed. It is important to point out that the benefits of ivabradine were much more striking in those with a higher resting heart rate,[38 39] and that although around 90% of patients were taking a β blocker at baseline, only 23% were taking a target dose, only 49% were receiving ≥50% of a target dose and 16% were receiving a β blocker not shown to be beneficial.

The SHIFT findings do suggest that there is a role for ivabradine in patients with chronic heart failure, but it is not a substitute for β blocker use. There is an enormous body of evidence supporting the use of β blockers, which improve mortality as well as hospitalisation. Ivabradine should be considered only in those patients who still have a resting heart rate above 70 despite maximally tolerated doses of β blockers (or perhaps used in patients truly intolerant of β blockers). Data from 'real-world' populations of patients with heart failure suggest that the proportion of patients who might be eligible is low, perhaps around 5%.[40]

4.3.Iron

Is iron deficiency a target for treatment? Anaemia is very common in patients with heart failure,[41] but iron deficiency without anaemia is also common. The best way to manage iron deficiency is not clear: oral iron treatment is widely believed to be ineffective, yet intravenous iron treatment is also thought to be difficult or dangerous. However, a new generation of intravenous iron preparations is now available which allows both rapid and safe administration of iron to patients.

Some preliminary studies suggested that intravenous iron repletion might lead to an improvement in exercise capacity,[42] and the FAIR-HF study was designed to see if iron might be beneficial in a larger group of patients.[43] Four hundred and fifty-nine patients were randomised 2:1 to receive iron or placebo infusions (with only the patient blind to treatment). After 6 months, there was an improve-

angioplasty for patients with acute myocardial infarction (MI) (including for patients with non-ST elevation MI on rather flimsy evidence[10]). We should do so for patients with heart failure, for whom reconfigured services will have a more far-reaching benefit.

2. TELEMONITORING

An exciting possible advance in patient care is the use of remote monitoring to guide changes in treatment. Typically, automated devices in the home can measure weight, pulse rate and heart rhythm and blood pressure and transmit the data to a centre. Abnormal results then trigger patient contact with possible change in treatment. Initial trials have suggested that there may be a benefit from such systems, particularly when coupled with telephone contact.[11]

A particular problem with telemonitoring is what to do with the data. With a large number of patients potentially transmitting quantities of data daily, the resource required to deal with the data might become impossibly large. Attempts to use automated systems have proved disappointing: in a study of 1653 patients who had recently been hospitalised for heart failure, which used telemonitoring with an interactive voice-response system collecting daily information about symptoms and weight, Chaudhry *et al* found no impact on re-admissions and mortality at 6 months.[12] In another recent study,[13] remote monitoring did not improve outcomes among 710 patients randomised to remote monitoring using a system that transmitted ECG, blood pressure and weight and included a home emergency call system.

It is important to remember that telemonitoring itself does not save lives or admissions, but that actions taken in response to monitoring might do so. The reason recent trials have been neutral may be that 'usual care' in these studies has progressed to the point at which home monitoring can have little additional beneficial effect and it may be that remote monitoring is only likely to be helpful in people at particularly high risk. It may be, too, that the variables measured are simply too crude to be helpful guides to changing treatment.

Another approach to remote monitoring is to use implantable devices to measure haemodynamic changes invasively. The Chronicle device allows pulmonary artery pressure to be measured continuously and an early trial (COMPASS) suggested that it might be helpful.[14] A more promising technique, perhaps, is the use of smaller devices implanted directly into the pulmonary artery and communicating using acoustic wireless communication.[15] In the CHAMPION trial,[16] 550 patients were randomised to have a CardioMEMS device or usual care. The device was used to measure pulmonary artery pressure once a day: it has no internal power source, but uses externally applied radiofrequency energy. Its use was associated with a 30% reduction in the primary efficacy end point of hospitalisation for heart failure at 6 months. It is not, of course, the devices that improve outcome, but the changes in treatment that follow from device readings. In COMPASS[14] and CHAMPION,[16] for example, patients with the device were receiving higher doses of medication to treat heart failure.

The final stage in the evolution of remote monitoring is likely to be to further empowerment of the patient. The devices can be used to transmit data to the person most concerned with the disease—the patient—who can then use the information to make daily changes to his or her treatment. In HOMEOSTASIS, 40 patients with severe heart failure were implanted with a device measuring left atrial pressure and made changes to treatment based on the readings using a preprogrammed hand-held patient advisor module.[17] It is impossible to draw firm conclusions from such a small observational study, but while diuretic treatment fell as a result of the intervention, β blocker and ACE inhibitor/ARB treatment increased. At the same time, mean left atrial pressure fell and there did seem to be a reduction in clinical events.

Invasive monitoring leads to an increase in prescription of medical treatment for heart failure, which highlights another nagging question: although we have clinical trial results to guide us towards 'target' doses of, for example, β blockers and ACE inhibitors, how are we to know how much is enough? One possible guide is the use of natriuretic peptides: perhaps treatment should continue to be increased until the natriuretic peptide level is normal. Some small studies point in that direction, others do not: but there is evidence of publication bias in a meta-analysis.[18] A recent single-centre trial in 364 patients with heart failure showed that treatment guided by N-terminal pro-brain natriuretic peptide was associated with a 1-year mortality identical to treatment guided by a clinical score.[19] The finding lends some weight to the argument against biomarker-guided treatment but the question will only be resolved by a definitive large trial.

3. EPIDEMIOLOGY

3.1. Heart failure with a normal ejection fraction

Heart failure with a normal ejection fraction (HeFNEF) remains enigmatic. Epidemiology suggests that it is common,[20,21] perhaps accounting for half of the cases of heart failure. However, researchers recruiting patients to trials have often found it extremely difficult to identify suitable patients. No clinical trial has as yet identified any successful treatment for HeFNEF and some are sceptical of its existence as a single, well-defined entity.[22,23] Problems arise because, at least in part, breathlessness is very common in older people and because some of the diastolic echocardiographic changes thought to indicate that the heart is failing are simply consistent with ageing.

One possibility that has been under-researched is that HeFNEF is more obviously a condition appreciated during exercise, and echocardiographic measurements during exercise may highlight diastolic abnormalities.[24] An important observation from a study of echocardiography and exercise of over 400 patients with possible HeFNEF[25] was that very few—possibly as few as 3%—actually had heart failure. Holland and colleagues[25] emphasised the importance of measuring the ratio between E and E☒ as an index of left ventricular filling pressure, but others have concentrated on much more subtle abnormalities of both systole and diastole in patients with HeFNEF that worsen with exertion.[26] Impaired left atrial function during exercise may also contribute.[27]

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Almanac 2011: Heart Failure. The National Society Journals Present Selected Research that has Driven Recent Advances in Clinical Cardiology

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EDITORIAL

1. NICE, AUDIT AND HEART FAILURE CARE

The national heart failure audit[1] in England and Wales continues to grow and provides vital data for planning heart failure services. The first formal report relates to over 6000 patients who were the first 10 patients admitted with a primary diagnosis of heart failure each month to one of 86 hospitals contributing data in 2008–09. Most had left ventricular systolic dysfunction, but an echocardiogram result was available in only 75%. In-patient mortality was 12% and in survivors, 80% were receiving an ACE inhibitor (or angiotensin receptor blocker (ARB)), 50% a β blocker and 30% an aldosterone antagonist at discharge.

The audit for 21 000 patients hospitalised with heart failure in 2009–10 is also available.[2] In-hospital mortality had fallen slightly to 10.5%, but there was no dramatic change in drug prescription rates. Some subsets of patients were particularly likely to be actively treated (men aged 55–64, β blocker prescription rate >70%), and others much less likely (women aged >85, β blocker prescription rate 40%). Aldosterone antagonists were still prescribed for less than half the population.

Two striking features stand out from the data from both audits. First, prescription rates vary greatly, with age—older patients and women being less likely to be treated—and with admission ward—patients admitted to cardiology wards being much more likely to receive active treatment. Second, pharmacological treatment was better for patients admitted under cardiologists, and so was survival. Although a minority of patients admitted with heart failure are managed by cardiologists, the survival benefit persists after correction for age and sex (and other confounders).

The undertreatment of elderly patients with heart failure is a particular cause for concern at a time when patients aged >80 represent an increasing proportion of admissions for heart failure.[3] Treatment of older patients is hampered by their associated comorbidities and polypharmacy and also by their systematic exclusion from clinical trials, depriving doctors of the evidence base they need to guide management decisions.[4] Exclusion of the elderly by trial organisers shows no signs of going away: among 251 trials recruiting patients in December 2008, more than 25% had an upper age limit for enrolment and more than 80% excluded patients with comorbid conditions.[4]

The National Institute for Health and Clinical Excellence (NICE) has produced updated guidelines for heart failure care.[5,6] While there has been a lot of comment on the importance of measuring natriuretic peptides as an entry point to heart failure care, NICE has also firmly recommended that care led by a specialist in heart failure should be the norm. This is true at assessment and diagnosis (a patient suspected of having heart failure associated with a previous myocardial infarct or with a very high natriuretic peptide level should receive "…specialist assessment within 2 weeks") and during admission to hospital ("when a patient is admitted to hospital because of heart failure, seek advice on their management plan from a specialist in heart failure").

Such recommendations will impose new burdens. What is a 'specialist'? NICE thinks it is "…a doctor with subspecialty interest in heart failure (often a consultant cardiologist) who leads a specialist multidisciplinary heart failure team of professionals …", but there are few such individuals available to take up the responsibility. However a specialist is defined, there is no doubt that patients with heart failure fare better when cared for by professionals with a particular interest in their condition. This is reflected in recent US data that have shown lower mortality and readmissions for patients with heart failure managed in high-volume compared with low-volume centres.[7]

One of the problems for a specialist heart failure service is access to advanced treatments such as heart transplantation. Transplantation in the UK is falling, partly owing to a fall in the availability of donor organs,[8] but just as important is access to expert heart failure care.[9] We have managed to reconfigure health services to provide primary

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in the off-pump group (24% vs 15%; HR 1.66, 95% CI 1.02 to 2.73; p=0.04).[104] These trials have not provided evidence of clinical superiority for off-pump CABG, although it is premature to consider abandoning the procedure. Conventional cardiopulmonary bypass has important deleterious effects that include platelet and neutrophil activation, consumption of coagulation factors, complement generation and the release of proinflammatory mediators with generation of a systemic inflammatory response. If off-pump surgery cannot deliver better clinical outcomes it may be prudent to take heed of the editorialist and consider 'better-bypass' in the form of a miniaturised bypass system.[105] This was the subject of a recent meta-analysis which found that miniaturised cardiopulmonary bypass in comparison with conventional cardiopulmonary bypass was associated with a somewhat lower rate of death (1.1% vs 2.2%, OR 0.58, 95% CI 0.23 to 1.47, p=0.25) and stroke (0.2% vs 2.0%, OR 0.25, 95% CI 0.06 to 1.00, p=0.05) in the immediate postoperative period.[106] Now needed are larger trials to further evaluate miniaturised cardiopulmonary bypass.

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6.2.High residual platelet reactivity

An alternative approach for protecting against stent thrombosis is to target more aggressive treatment at patients with high residual platelet reactivity after clopidogrel loading. Such patients appear to be at significantly increased risk of adverse events, and in a recent study of 215 patients undergoing unprotected left main stem PCI the risk of cardiac death at 1 year was more than doubled in those with high residual platelet activity.[87] The GRAVITAS investigators have now reported their randomised comparison of standard dose (75 mg) versus high-dose (150 mg) clopidogrel after drug-eluting stenting in 2214 patients with high on-treatment platelet reactivity.[88] Although high-dose clopidogrel was effective in reducing platelet reactivity, cardiovascular event rates (death, myocardial infarction, stent thrombosis) after 6 months were identical at 2.3% in both groups. The failure of aggressive antiplatelet treatment to reduce event rates in patients with high residual platelet reactivity was, perhaps, surprising but will not be the last word on this subject, as other such studies are in progress. Meanwhile, calls for platelet reactivity monitoring in patients receiving clopidogrel seem premature.[89]

A potential mechanism of high residual platelet reactivity in some patients treated with clopidogrel relates to conversion of the prodrug to an active metabolite by the hepatic cytochrome P-450 system. Conversion is genetically determined and is reduced in carriers of common loss-of-function CYP alleles, who show decreased platelet inhibition and a 1.53 to 3.69 increased risk of cardiovascular events compared with non-carriers.[90–92] This led to calls for higher clopidogrel dosing in carriers of the loss-of-function alleles but this policy has now been questioned by a study that stratified patients enrolled in two large randomised trials of clopidogrel therapy by genotype status.[93] In neither trial did loss-of-function carrier status affect the primary composite efficacy outcomes, or safety outcomes with respect to bleeding. The authors concluded that carriers of loss-of-function CYP alleles should receive clopidogrel at currently recommended doses in acute coronary syndromes, although for atrial fibrillation the conclusion was qualified by a need for larger studies. Meanwhile, genotyping of patients with acute coronary syndromes enrolled in a head-to-head comparison of clopidogrel with ticagrelor (PLATO) reported that the hazard of the primary endpoint was lower for patients randomised to ticagrelor compared with clopidogrel but RR reduction was unaffected by CYP or ABCB1 (coding for a protein influencing clopidogrel absorption) genotype.[94] On present evidence, therefore, genetic testing does not appear to be helpful in determining clopidogrel's effectiveness in comparison with placebo or ticagrelor and is unlikely to provide a useful basis for determining dosing strategies.

Drug interaction

Another potential mechanism of high residual platelet reactivity in some patients receiving platelet inhibitors is an interaction with some proton pump inhibitors (PPIs), which may reduce clopidogrel's conversion to its active metabolite by interfering with the hepatic cytochrome P-450 system and may also reduce the platelet response to aspirin.[95] However, in a large cohort study event rates among patients discharged on PPIs were increased independently of whether or not they were also discharged on clopidogrel, indicating that drug interaction was not the responsible mechanism.[96] Moreover, the COGENT trial of 3873 patients receiving DAPT and randomised to omeprazole or placebo was reassuring in showing no difference in the primary cardiovascular end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, revascularisation, or stroke.[97] COGENT found that patients randomised to omeprazole had a significantly lower rate of gastrointestinal bleeding and, given the gastro-protective effects of PPIs in patients on low-dose aspirin, recently confirmed in the OBERON trial,[98] the benefits seem to outweigh any potential risk related to clopidogrel interaction. Other drugs that have come under recent scrutiny include calcium channel blockers which, like PPIs, are metabolised by the hepatic cytochrome P-450 system and have the potential therefore to interact with clopidogrel. Observational data in patients taking clopidogrel have shown that high residual platelet reactivity is more common in those co-prescribed calcium channel blockers than in those who are not,[99] and an earlier observational study reported that this may be associated with a higher cardiovascular event rate 2 years after PCI.[100] Interpretation of these studies needs to be cautious, however, and more prospective data are needed, ideally in the form of randomised trials.

7. CORONARY ARTERY BYPASS SURGERY IN STABLE CORONARY DISEASE

Among key technical innovations of the last 15 years has been off-pump CABG but its potential benefits for myocardial and cerebral protection have had to be weighed against problems of incomplete revascularisation and reports of an increased risk of myocardial infarction and early graft attrition compared with on-pump procedures. Two randomised trials have now clarified some of these issues. The ROOBY investigators randomised 2203 patients to on-pump or off-pump CABG and found no significant difference in rates of the 30-day composite outcome (7.0% vs 5.6%, respectively for death, reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure).[101] After 1 year the same composite was higher for off-pump than for on-pump CABG (9.9% vs 7.4%, p=0.04) and graft patency was lower (82.6% vs 87.8%, p<0.01) in the 1371 patients who had follow-up angiography. Meanwhile, a careful assessment of 12-month cognitive outcomes found no difference between the groups, although the rate of impairment by either procedure was reassuringly low.[102]

Shortly after the ROOBY report, the 'Best Bypass Surgery' trialists published their results in a higher risk group (EuroSCORE ≥5, three-vessel disease) of 341 patients randomised to on-pump or off-pump CABG.[103] Again, the composite primary outcome (all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention) was similar for the on-pump and off-pump groups (15% and 17%; p=0.48) and after 3 years all-cause mortality was significantly increased

receive second-generation everolimus-eluting stents (EES) or first-generation paclitaxel-eluting stents (PES).[70] The study confirmed superiority of EES over PES for the composite clinical end point (4.2% vs 6.8%), and also for stent thrombosis (0.2% vs 0.8%). The single-centre COMPARE trial compared second-generation EES with second-generation PES in 1800 patients and again showed superiority of the EES, which at 12 months was associated with a 6% incidence of the primary end point compared with 9% in the PES group.[71] The second-generation zotarolimus-eluting stent (ZES) has been evaluated against sirolimus-eluting (SORT OUT III, n=2332) and EES (Resolute All Comers Trial, n=2292). In SORT OUT III, ZES proved inferior to SES, with primary end point rates of 6% versus 3%, a difference sustained at 18 months.[72] In Resolute All Comers the composite clinical end point at 1 year occurred in almost identical (8.2% and 8.3%) proportions of ZES and EES groups, but the ZES group showed a tendency for more frequent stent thrombosis (2.3% vs 1.5%) and greater in-stent late lumen loss (0.27 mm vs 0.19 mm). These observations raise further concerns about ZES that will not be resolved until the 5-year follow-up data become available.[73] Long-term results of ZES have been favourable in registries,[74] but the results of these four randomised trials have ensured that second-generation EES are now the first choice for most interventionists.

Moving beyond the second generation of DES, polymer-free and biodegradable polymer DES are now entering the clinical arena. A randomised comparison of rapamycin delivery using these novel platforms versus conventional (permanent) polymer coated sirolimus-eluting stents, showed comparable safety and comparable efficacy for prevention of clinical restenosis during the 2-year follow-up. However, angiographic surveillance confirmed more sustained neointimal suppression with the polymer-free rapamycin-eluting stent than with the other platforms.[75] Everolimus delivery by a bioabsorbable stent in 30 patients also produced impressive 2-year outcomes with no cardiac deaths, ischaemia-driven target lesion revascularisations, or stent thromboses recorded.[76] Interestingly, vasomotion was restored in the stented segment after bioabsorption. These results will doubtless ensure continuing interest in the development of polymer-free DES.

5.5. Bare metal stents

The advantages offered by DES in management of coronary artery disease have seen continuing indications for BMS diminish almost to the point of extinction. The superiority of DES compared with BMS for primary PCI is driven by significantly lower rates of target lesion revascularisation, and recent data show that the benefit is sustained after 3 years (9.4% vs 15.1%) with no significant differences in the rates of death, reinfarction, or stent thrombosis.[77] Current recommendations are for the preferential use of DES in ST elevation myocardial infarction, particularly in patients with high-risk features for restenosis such as long lesions, small vessels, or diabetes.[78] The BASKET-PROVE study now also challenges the notion that BMS have residual indications in large coronary arteries.[79] These investigators randomised 2314 patients requiring 3–4 mm diameter coronary stents to receive first-generation SES, second-generation EES, or cobalt-chromium BMS. After 2 years cardiovascular event rates and rates of stent thrombosis were comparable between the three groups, but the rates of clinically driven target lesion revascularisation [Marion, the author had TVR here but I think it should have been TLR as expanded] were only 4.3% with SES and 3.7% with EES compared with 10.3% with BMS. Although cost-effectiveness was not reported, these findings confirm that the benefits of DES for safety and protection against restenosis in small coronary arteries extend to procedures undertaken in larger vessels.

5.6. Paclitaxel-coated balloon

PCI in very small vessels (<3 mm) remains a challenge. Use of DES has improved safety and longer-term outcomes relative to BMS,[80] and in a randomised trial proved better than the newly available paclitaxel-coated balloon for restenosis after 6 months.[81] Nevertheless, a potentially important coronary application of the paclitaxel-coated balloon for treatment of in-stent restenosis has now been identified. A recent randomised trial in 131 patients with bare metal in-stent restenosis reported 6-month binary restenosis rates of only 7% for the drug-coated balloon compared with 20% for a paclitaxel-eluting stent.[82] However, longer-term data will be needed. A recent registry study reported that SES used for treatment of bare metal in-stent restenosis exhibited sustained efficacy at 4 years with a target lesion revascularisation rate of only 11.1%.[83]

6. ANTIPLATELET THERAPY

6.1. Stent thrombosis

Dual antiplatelet therapy with aspirin and clopidogrel (DAPT) is considered an essential adjunct to PCI to protect against stent thrombosis. Guidelines recommend that DAPT is continued for 12 months in patients who have received a DES to allow for complete endothelialisation of the struts, whereupon treatment can continue with aspirin alone. However, very late stent thrombosis remains a real concern and has received attention in a number of recent studies either by evaluating the potential benefits of prolonging DAPT beyond 12 months or by up-titrating antiplatelet therapy against the results of platelet function tests. The impact of prolonged DAPT beyond 12 months has been evaluated in a registry study, which found no additional protection against death or MI compared with DAPT for ≤12 months.[84] This was confirmed in a randomised trial of continuing aspirin and clopidogrel versus monotherapy with aspirin in 2701 patients who had already received DAPT for 12 months after PCI.[85] At 2-years' follow-up, rates of MI and death were similar in the two groups (1.8% vs 1.2%), providing support for the guideline recommendation to continue DAPT for 12 months after PCI with DES. However, the importance of strict adherence to DAPT in the first 12 months is emphasised by the finding in another recent study that patients who delayed filling their prescription for clopidogrel after hospital discharge had almost twice the risk of MI or death compared with those who filled their prescription on the day of discharge, even though the median delay was only 3 days.[86]

in a study of 1 522 935 patients entered in the National Cardiovascular Data Registry CathPCI Registry.[53] The study showed that vascular closure devices and bivalirudin therapy together were associated with a reduction of bleeding events from 2.8% to 0.9%, yet these strategies were used least often in patients with a high pre-procedural risk of bleeding assessed with the National Cardiovascular Data Registry bleeding risk model.[54] Based on these findings it seems clear that there remains considerable scope for improving the safety of PCI by pre-procedural identification of patients with most to gain from individualised bleeding avoidance strategies.

Myocardial injury

Myocardial injury during PCI is common and a recent meta-analysis of 15 studies embracing 7578 patients found troponin elevation in 28.7% of procedures.[55] Any level of raised troponin was associated with an increased risk of cardiovascular events and for those with myocardial infarction according to the universal definition[56] the OR for major adverse cardiac events at 18 months was 2.25 (1.26 to 4.00). Direct evidence of peri-procedural myocardial injury has now been made available from cardiovascular magnetic resonance imaging, which documented new myocardial hyperenhancement (median mass 5.0 g) in 32% of 152 patients undergoing PCI. After adjustment for age and sex, these patients had a 3.1-fold (95% CI 1.4 to 6.8; p=0.004) higher risk of adverse outcome than patients without new hyperenhancement.[57] These data have enhanced interest in pharmacological and mechanical interventions directed at protecting the myocardium during elective PCI. High-dose statins show promise in this regard, and in one study of 668 statin-naïve patients, peri-procedural myocardial infarction (defined as a CK-MB elevation >3´ upper limit of normal) occurred in 9.5% of those randomised to a single loading dose of atorvastatin 80 mg, compared with 15.8% in the control group.[58] Most patients should already be taking statins before elective PCI but for those who are not, these data indicate that pre-procedural loading together with aspirin and clopidogrel is a potential means of enhancing patient safety. Also promising is remote ischaemic preconditioning, which in a recent randomised trial of 242 patients undergoing elective PCI was associated with reduced troponin I release at 24 h compared with controls (0.06 vs 0.16 ng/ml; p=0.040).[59] The major adverse cardiac and cerebral event rate at 6 months was also lower in the remote ischaemic preconditioning group (4 vs 13 events; p=0.018). However, this was a small unblinded trial and further research is needed before this inexpensive means of myocardial protection can be recommended in routine clinical practice.

5. PCI IN SPECIAL GROUPS

5.1. Prior radiotherapy

Thoracic radiotherapy in women with breast cancer increases the long-term risk of cardiovascular death,[60] possibly by induction of a sustained inflammatory response in irradiated arteries.[61] It is also associated with adverse outcomes for coronary stenting, with a HR for all-cause death after 6 years of 4.2 (95% CI 1.8 to 9.5) compared with people who have not undergone radiotherapy.[62]

5.2. Diabetes

CABG has long been the preferred revascularisation strategy in patients with diabetes and multivessel disease, and the publication of BARI-2D and CARDia has done little to challenge this orthodoxy. In BARI-2D, 2368 patients with type 2 diabetes (31% with three-vessel disease) were stratified as being appropriate for either PCI or CABG and then randomised to contemporary medical treatment or revascularisation.[63] After follow-up for an average of 5.3 years, rates of all-cause mortality (the primary end point) were similar for the medical and revascularisation groups, but in the CABG stratum, patients assigned to revascularisation had lower cardiovascular event rates (death, myocardial infarction (MI) or stroke) than patients assigned to medical treatment. However, the patients in BARI-2D randomised to revascularisation obtained greater symptomatic benefit than the medically treated group.[64]

In CARDia, 510 patients with diabetes, 93% of whom had multivessel disease, were randomised to PCI or CABG.[65] The composite rate of all-cause mortality, non-fatal MI, and non-fatal stroke at 1 year was 13.0% for PCI and 10.5% for CABG; this difference was not statistically significant but the study was powered and non-inferiority for PCI compared with CABG was not confirmed. It is the BARI-2D findings, therefore, that generated greater interest by showing that contemporary medical treatment of diabetic patients with complex coronary artery disease compares favourably with revascularisation.

5.3. Outcomes for PCI

Outcomes for PCI (and for CABG) continue to improve.[66] Pre-procedural risk factors for adverse outcomes are well defined and include impaired LV function, complex lesion morphology, emergency procedures and diabetes. To this list may now be added the EuroSCORE, which showed excellent discrimination for predicting hospital mortality (area under the receiver operating characteristic curve 0.91 (95% CI 0.86 to 0.97)) in 1173 PCI patients, with the odds of death increasing as the score rose.[67] The EuroSCORE is already validated and widely used to predict surgical risk and the authors suggest that it is therefore well placed to help cardiologists and cardiac surgeons individualise the risk profile of patients in order to better select the appropriate revascularisation strategy. External validation of the EuroSCORE in other PCI cohorts is now needed before its clinical application can be confidently recommended. Meanwhile the SYNTAX score, based on specific anatomical characteristics of the coronary angiogram, remains the best validated means of anticipating the risks of PCI and CABG, although its value for predicting 12-month outcomes is confined to PCI.[68]

5.4. Second-generation DES

DES have produced important reductions in rates of restenosis compared with bare metal stents (BMS), albeit at increased risk of late stent thrombosis.[69] This has provided impetus for the design of more effective 'second-generation' DES that have been the subject of investigation in four recent trials, all of which were powered for clinical events with a primary composite end point of cardiac death, myocardial infarction, or target-vessel revascularisation. The largest of these, SPIRIT IV, randomised 3687 patients in a 2:1 ratio to

multivessel disease, particularly if the SYNTAX score is low (≤22) when cardiovascular end points at 3 years are comparable to those for CABG, and this is reinforced by comparable quality-of-life outcomes.[34–36] More recently, a prespecified subgroup analysis of the ARTS-II registry has reported comparable outcomes for patients with multivessel disease involving the proximal left anterior descending coronary artery treated with either sirolimus-eluting stents (SES) or CABG.[37] These comparisons of PCI versus CABG in high-risk disease, and medical treatment versus CABG in ischaemic cardiomyopathy begin to erode confidence in the long-held view that surgery is the most appropriate treatment option in such patients.

3. PROCEDURAL FACTORS

3.1. Radial versus femoral access

Debate about the merits of radial versus femoral access for interventional procedures has not been resolved by RIVAL, the first comparative study powered for cardiovascular outcomes.[38] Among 7021 patients with acute coronary syndrome undergoing cardiac catheterisation with a view to intervention, the primary outcome (a composite of death, myocardial infarction, stroke or non-CABG-related bleeding at 30 days) occurred in similar proportions of radial (3.7%) and femoral (4.0%) access groups. The marginal difference in favour of radial access was driven by a trend towards lower bleeding rates at 30 days (0.7% vs 0.9%), associated with significantly lower rates of access site complications, including large haematomas and pseudoaneurysms. Smaller studies[39] have reported less bleeding with radial access which, coupled with earlier mobilisation, has encouraged its adoption in many European centres. Femoral access, however, is still preferred by many operators because access is more predictable, procedure times may be shorter and radiation exposure lower than with the radial approach.[40 41] Ultimately, it seems, institutional experience is a major determinant of procedural success, high-volume radial centres in RIVAL recording the lowest hazard of the primary outcome.

3.2. Pressure wire

Pressure wire measurement of fractional flow reserve (FFR) is now widely used by interventionists for per-procedural assessment of the functional significance of coronary stenoses. In the FAME study 1005 patients with multivessel coronary artery disease undergoing drug-eluting stent (DES) implantation were randomised to procedures guided by angiography alone or by angiography plus FFR measurement, values <0.80 providing indication for stenting.[42] In the FFR group, the number of stents per patient (1.9±1.3 vs 2.7±1.2) and the primary end point of death, non-fatal myocardial infarction or target vessel revascularisation at 1 year (13.2% vs 18.3%) were both significantly lower than for the angiography group. Benefits were largely sustained at 2 years[43] and evidence of cost-effectiveness[44] completes the case in favour of FFR-guided PCI in multivessel procedures.

3.3. Bifurcation PCI

Debate surrounding bifurcation PCI has been largely resolved by studies showing that simple stenting of the main branch—with 'provisional' stenting of the side branch only if flow becomes compromised—is better than strategies that involve complex stenting of both limbs of the bifurcation. A recent meta-analysis of randomised trials has confirmed superiority of the simple stenting strategy which yields better results for in-hospital and late myocardial infarction and similar rates of restenosis and target vessel revascularisation compared with the complex strategy.[45] Further refinement of the simple stenting strategy has now been tested by randomising 477 patients either to final kissing balloon inflation or to no-final kissing balloon inflation.[46] Final kissing balloon inflation was associated with a significantly lower rate of angiographic side branch restenosis (8% vs 15%) at 6 months compared with no-final kissing balloon inflation, although rates of the primary end point—cardiac death, myocardial infarction, stent thrombosis, or target-lesion revascularisation—were similar (2.1% vs 2.5%). The data, therefore, do not provide a compelling argument for final kissing balloon inflation after simple birfurcation stenting, although the strategy does seem to provide some protection against side branch restenosis.

3.4. LV support devices

Intra-aortic balloon pump support in high-risk PCI is widely recommended, but a recent randomised trial in 301 patients with severe LV dysfunction (ejection fraction ≤30%) and advanced coronary artery disease found no evidence of benefit.[47] Rates of in-hospital major adverse cardiac events were similar with (15.2%) or without (16.0%) the intra-aortic balloon pump, arguing against its elective use in this group of patients. Alternative methods of circulatory support during PCI are now being investigated and registry data for the Impella 2.5 percutaneous LV assist device confirm that it can be safely positioned across the aortic valve from the femoral approach and supply flow rates of up to 2.5 l/min during interventional procedures.[48] These promising data distinguish the Impella from most other LV assist devices, which require surgical deployment and have no role in the catheter laboratory.[49]

4. COMPLICATIONS

4.1. Acute kidney injury

Contrast-induced acute kidney injury (AKI) is a well-recognised complication of angiographic procedures, and a recent Canadian study shows that it has important association with adverse long-term outcomes.[50] Among 14 782 adults undergoing cardiac catheterisation, the adjusted risk of death during a median 19.7 months' follow-up increased progressively with the post-procedural severity of AKI—patients with stage 2 or 3 AKI during the first 7 days after catheterisation having nearly four times the hazard of death compared with patients with no AKI. Risks of subsequent hospitalisations for heart failure also increased. Interestingly, AKI has been reported less commonly with catheterisation using the radial approach compared with the femoral approach.[51] Pre-hydration may be protective in high-risk individuals, particularly people with diabetes, but no other specific treatments have shown unequivocal benefit.

4.2. Bleeding

Peri-procedural bleeding, associated with adverse outcomes after PCI, has declined notably in recent years.[52] Radial access has probably contributed (see above) but other bleeding avoidance strategies have been emphasised

ments such as ivabradine and ranolazine, and also because of the recognition that it can compete favourably with revascularisation in many patients, both for controlling symptoms and for improving prognosis. Thus, COURAGE showed that in patients receiving optimal medical treatment (aspirin, b blocker and statin, plus ACE inhibitor as indicated), percutaneous intervention (PCI) does not improve cardiovascular outcomes and incremental benefits in quality of life disappear by 36 months.[10 11] More recent meta-analyses of trials that have randomised patients with stable angina to PCI or medical treatment have come to similar conclusions.[12 13] This has led guideline groups to recommend optimal medical treatment for the initial management of stable angina, with revascularisation reserved principally for patients whose symptoms are not satisfactorily controlled.[14]

1.4. Prognosis of angina

From the early Framingham finding that angina has 'a mortality surprisingly close to that which follows the post-hospital phase of myocardial infarction'[15] to the trialists' assertions that 'cardiovascular risk (is) reduced to normal levels with contemporary therapy',[16] we now appear to have gone full circle with two recent outcome studies for patients with angina. The first included 1609 adults with ischaemic heart disease who were identified in primary care and were not, therefore, prone to the selection bias that affects secondary care cohorts.[17] The investigators found the hazards of all-cause and coronary death in patients with angina alone compared with patients who had had previous myocardial infarction were 0.73 (95% CI 0.55 to 0.98) and 0.65 (0.44 to 0.98), respectively. Although statistically significant at the $p<0.05$ level these differences were not significant at the $p<0.01$ level suggested as appropriate for observational research. The investigators also found that physical functioning was consistently lower among those with angina alone. In the second study, the same group examined the prognosis of 1785 patients with angina as a first manifestation of ischaemic heart disease.[18] Within 5 years, 116 (6.5%) had an acute myocardial infarction, and 175 (9.8%) died. Male sex and each year of increasing age were both associated with increased HRs for acute myocardial infarction (2.01 (1.35 to 2.97) and 1.04 (1.02 to 1.06), respectively) and all-cause mortality (1.82 (1.33 to 2.49) and 1.09 (1.07 to 1.11), respectively). An important finding was that an acute myocardial infarction after the index episode of angina greatly increased the risk of subsequent death. The authors concluded that appropriate control of risk factors and optimal use of preventive medical treatments should be aggressively pursued in patients with angina who represent a high-risk group in primary care.

2. INTERVENTIONAL MANAGEMENT OF STABLE CORONARY ARTERY DISEASE

2.1. Clinical trials

Expectations that COURAGE would lead to changes in the management of stable angina, with renewed emphasis on optimal medical treatment (OMT) as the primary strategy,[19] have yet to be fulfilled, raising questions about how well informed patients are about the risks and benefits of PCI.[20] These questions have been amplified by recent studies showing that PCI is recommended rather than coronary artery bypass grafting (CABG) substantially more often than indicated by international guidelines, and fulfils the US societies' criteria for appropriateness in only 50.4% of cases.[21 22] Rates of PCI in the USA have shown no tendency to decline since the publication of COURAGE[23] and a majority of patients are not being treated with OMT. In a large study of elective PCI procedures, rates of OMT were only 43.5% in the 19 months before publication of COURAGE and 44.7%, in the 24 months afterwards, confirming that COURAGE has not yet had a palpable effect on interventional practice.[24]

Notable among recent reports from other PCI trials are the 10-year follow-up data from MASS II and the results of the STICH trial. MASS II randomised 611 patients with angina, multivessel coronary artery disease and preserved left ventricular (LV) function to initial strategies of medical treatment or PCI or CABG.[25] The study was underpowered for the primary end point of total mortality, Q-wave myocardial infarction, or refractory angina needing revascularisation, which occurred less frequently in the CABG group than in the PCI and medical treatment groups (33%, 42% and 59%, respectively). MASS II excluded patients with significant left main stem disease, and total mortality was similar in all three groups. Nevertheless, the findings bear comparison with those reported in the early randomised trials of CABG versus medical treatment[26] where patients with multivessel disease who were randomised to CABG survived longer than those randomised to medical treatment.

STICH also has raised some doubt about the contemporary validity of those early randomised trials. In STICH 1212 patients with multivessel disease and severe impairment of left ventricular function (ejection fraction <35%) were randomised to coronary artery bypass surgery or medical treatment, to test whether surgical revascularisation would improve survival in this high-risk group with ischaemic left ventricular dysfunction.[27] After nearly 5-years' follow-up all-cause mortality (the primary end point) was similar between the groups, both in the main trial cohort and in a subgroup with demonstrable myocardial viability.[28] STICH confirms earlier reports[29] that the benefits of revascularisation in patients with ischaemic cardiomyopathy may have been exaggerated, even in patients with demonstrable viability. As the editorialist commented, contemporary medical treatment should not be underestimated in the management of severe coronary artery disease.[30]

Meanwhile, further trials of PCI versus CABG in selected groups with left main stem disease have been consistent in favouring CABG, based almost exclusively on lower rates of repeat revascularisation compared with PCI.[31–33] None of these trials showed significant mortality differences between the two revascularisation strategies, making PCI an option for those patients unwilling to undergo surgery and prepared to accept further interventional procedures as necessary. The SYNTAX trial has already identified PCI as a reasonable strategy for symptomatic

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Almanac 2011: Stable Coronary Artery Disease. The National Society Journals Present Selected Research That Has Driven Recent Advances in Clinical Cardiology

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EDITORIAL

1. STABLE ANGINA PECTORIS

1.1. Diagnostic strategies

The widespread application of specialist clinics for early evaluation of patients with chest pain has focused attention on the effectiveness of diagnostic testing. In a study of nearly 400 000 patients with suspected coronary artery disease, the diagnostic yield of cardiac catheterisation was only 37.6%, leading to calls for better strategies for risk stratification.[1] As pointed out in correspondence, the low yield was probably due to verification bias, itself a consequence of basing referral decisions in low-risk populations on non-invasive tests such as exercise ECG.[2] Similar considerations prompted the NICE guideline group to recommend a more selective approach to non-invasive testing based on a careful clinical assessment of disease probability in patients presenting with stable chest pain.[3] For those, with unequivocal histories at the extremes of diagnostic probability (<10% or >90%) no diagnostic tests were considered necessary, while for patients with a high probability of disease (60–90%) invasive angiography without prior ischaemia testing was recommended. The NICE call for CT calcium scoring in patients with a low (10–30%) probability of disease generated greatest concern, particularly after a report that 19% of patients without coronary calcification—who would have been ruled out for angina in the NICE algorithm—had obstructive (>50% stenosis) disease.[4] However, the population referred for angiography in this study had a high pre-test probability of disease and in lower-risk populations CT calcium scoring retains a high diagnostic sensitivity.[5] NICE recommendations were driven largely by cost-effectiveness analysis but whether they will improve the diagnostic yield of cardiac catheterisation remains to be seen.

1.2. Circulating biomarkers in stable angina

The clinical role of circulating biomarkers for diagnosis of obstructive coronary artery disease in patients with suspected angina has yet to be defined. In one study, blood samples for the N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) and various inflammatory markers were obtained in 243 patients before myocardial perfusion imaging. Only NT-proBNP proved significantly diagnostic, a cut-off concentration <25 ng/l predicting a normal perfusion scan with a negative predictive value >95%.[6] Similarly, in an angiographic study of 848 men and women with clinically suspected coronary artery disease, NT-proBNP performed better than high-sensitivity C-reactive protein (hsCRP) and γ-glutamyltransferase, showing significant association with three-vessel coronary artery disease, but it did not add to the predictive value of traditional cardiovascular risk factors. The authors were forced to conclude that it was of limited incremental value as a diagnostic tool.[7] The prognostic application of circulating biomarkers in stable coronary artery disease has also been disappointing. In a meta-analysis of 83 prospective studies reporting the association of CRP with death and non-fatal cardiovascular events, the authors found that the quality of the studies was so poor (only two reported a measure of discrimination), with evidence of reporting bias and publication bias, that they were unable to make clinical practice recommendations.[8] Nevertheless, the data suggested that CRP measurements are unlikely to add anything to the prognostic discrimination achieved by considering blood pressure and other clinical factors in this patient group. In another study it was concluded that conventional clinical information provided an effective means of risk-stratifying patients with stable coronary disease awaiting coronary bypass surgery and that additional prognostic information from CRP, measured singly or in combination with other biomarkers, was unlikely to be cost-effective.[9]

1.3. Medical treatment of angina

The medical treatment of angina has been the subject of renewed interest, because of the availability of new treat-

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On behalf of the Editors' Network - the Task Force of European Society of Cardiology (ESC)

EDITORIAL

The Editors' Network is a task force of the European Society of Cardiology (ESC), representing the 44 National Society Cardiovascular Journals that are published across 37 countries (1). Among the operational goals enshrined in its mission statement is a commitment to improve the diffusion of scientific knowledge through distribution of common academic material and joint education initiatives (2). Heart already has a strong education section and its content, approved by the European Board for Accreditation in Cardiology (EBAC), is available for free access via the Heart and ESC websites. However, a recent joint publication of the Editors' Network called for educational initiatives to be extended throughout the national cardiology journals of Europe (3), and it is in response to that call that a series of Almanac 2011 papers are appearing more or less simultaneously in many of the Network Journals. Almanac–a late Middle English word derived via medieval Latin from Greek *almenikhiaka*–is defined as an annual calendar containing important dates and statistical information. It provides an approximate description of the new series of papers presenting selected recent research that has driven clinical advances in six major topic areas. The content is educative and clinically relevant and its presentation across the national society cardiovascular journals of Europe represents a milestone in collaborative publishing. Plans for Almanac 2012 are yet more ambitious and pave the way for a new era of joint educational initiatives driven by the Editors' Network of the ESC.

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