Ischemic Heart Disease: from a sudden death in Chicago to fibrinolysis and angioplasty

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Angina pectoris was named and accurately described by Heberden in 1772, but coronary thrombosis was only formally recognized as the cause of acute myocardial infarction by Herrick at the beginning of the 20th century. Diagnosis of acute myocardial infarction was facilitated by the ECG findings noted by Pardee, Parkinson, and Bedford. No effective treatment (other than bed rest) was available until the development of defibrillation and closed chest cardiac resuscitation by Zoll and Kouwenhoven in the 1950s. Since then, mortality has been greatly reduced by the use of antiplatelet and antithrombotic drug therapies as well as fibrinolysis and angioplasty. Prevention through reduction in risk factors and secondary prevention with drugs has proven to be extremely effective and will doubtless further contribute to reducing mortality in coming decades.

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Myocardial infarction is one of the most familiar ailments known to today's increasingly medically mature "lay" population the world over. Knowledge of this syndrome has undergone one of the most dramatic and complex developments in modern medicine. In applying the "tree metaphor" used as a leitmotiv throughout this issue of *Dialogues,* the history of ischemic heart disease at once conjures up the image of multiple trunks emerging from a common base, as occurs, for example, with birches or willows. I would see the seeds of the ischemic heart disease tree as planted by Heberden's description of the clinical syndrome, the base of the tree symbolizing James Herrick's recognition of the underlying disease in the coronary arteries, from which grow three trunks of pathophysiology, diagnosis, and the thickest of them all—and quite fortunately might one add—management.

Figure 1. *William Heberden. Mezzotint by James Ward after Sir William Beechey. Copyright © Wellcome Library, London.*

THE SEEDS: WILLIAM HEBERDEN

The seeds of the tree were sown by a master clinician, William Heberden *(Figure 1),* in 1772. In a presentation to the Royal College of Physicians in London, Heberden (1710-1801) described "a disorder of the breast," which he named angina (from the Greek, meaning strangling or suffocation), with an accuracy never bettered:

> Those who are afflicted with it are seized while they are walking, more especially if it be up hill, and soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this uneasiness vanishes... The termination of the angina pectoris is remarkable. For, if no accidents intervene, but the disease go on to its height, the patients all suddenly fall down, and perish almost immediately.[1]

John Hunter (1728-1793), the greatest surgeon of his day, performing, at Heberden's request, autopsies

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of patients having so perished, "could discover no fault in the heart, in the valves, in the systemic arteries…" Heberden, having offered an unmatchable delineation of a symptom, and without a clue as to the pathological substrate of the disorder, classified it as "a spasmodic, not inflammatory complaint," presumably similar to a condition such as epilepsy. He offered even less guidance as to its treatment, freely confessing "I have little or nothing to advance."

However, postmortems soon revealed telltale abnormalities. The eminent Quaker physician John Fothergill (1712-1780, *Figure 2*) called upon surgeons to conduct a postmortem in one of his patients, a 58-year-old man with "a spasm in the breast… chiefly when he walked up hill," who had died suddenly. They found "near the apex a small white spot, as big as a sixpence, resembling a cicatrix."[2] A second patient, with a similar history, was autopsied, this time again by John Hunter, who reported:

> Many parts of the left ventricle… were become almost white and hard, having just the appearance of a beginning ossification… The two coronary arteries, from their origins to many of their ramifications upon the heart, were become one piece of bone.

Fothergill commented, anticipating what today is described in terms of mismatch of oxygen delivery and demand:

> Under such circumstances, it is impossible [for the heart] to bear with impunity the effects of sudden and violent agitation, whether they arise from gusts of passion, or suddenly accelerated muscular motion.[3]

Within his own lifetime, Heberden's new entity had acquired an accurate pathological explanation, ascribing angina to a disease of the coronary arteries. Yet, although prescient, Fothergill's findings failed to convince all, and progress stalled. Some 75 years after his death, William Stokes (1804-1878), the Dublin physician, whose name is commemorated in Stokes Adams attacks and Cheynes-Stokes respiration, commented:

Figure 2. *John Fothergill. Mezzotint by Valentine Green, 1781, after G. Stuart. Copyright © Wellcome Library, London.*

> Obstruction of the coronary arteries may or may not be present, and is probably not infrequent, but as a cause of angina its actions are remote, and its existence unnecessary.[4]

THE ROOTS

New impetus to the knowledge of myocardial infarction required transplantation of our tree to Germanic soil. In Vienna, Karl Rokitansky (1804-1878), a physician turned pathologist, described "fatty degeneration" of cardiac muscle as "very frequently associated with ossification of the coronary arteries."[5] In Leipzig, Carl Weigert (1845-1904) published a landmark study of coronary thrombosis and embolism generally regarded as the first manual of myocardial infarction histology,[6] and Julius Cohnheim (1839-1884, *Figure 3*), in 1882, incorporated its conclusions into his own pathology textbook, assigning the majority of "so-called cardiac infarcts" or fatty degeneration to advanced coronary artery sclerosis and superimposed thrombosis.[7] However, Cohnheim remained skeptical as to whether the connection between coronary thrombosis and angina was causal or coincidental. What was missing was incontrovertible evidence, from the cadaver and/or living patient, of a kind inconceivable in his day, and that was only ultimately obtained a century later by coronary angiography. Once again, the growth of the ischemic heart disease tree of knowledge slowed down, until it found fertile ground in the USA.

THE BASE OF THE TREE: JAMES HERRICK, THE PIONEER

James Herrick of Chicago (1861-1954) is widely acknowledged as the first to describe the causes of myocardial infarction as we know it today *(Figure 4, next page)*. It was he, more than anyone else, who made clinicians aware that patients suffering a "coronary thrombosis" had a characteristic clinical presentation and, sometimes, survived. Curiously, when he presented his initial 1912 paper on the subject, entitled *Clin-*

Figure 3. *Julius Cohnheim. Wood engraving, after a photograph by N. Rashkow Jr, Leipzig, 1879. Copyright © Wellcome Library, London.*

ical Features of Sudden Obstruction of the Coronary Arteries, it aroused little interest, as Herrick subsequently wrote,

> It fell like a dud. Recognizing the radical nature of the view I held... I doggedly kept at the subject, doing what I called "missionary work"... I hammered away at the topic. When in 1918 I showed lantern slides and electrocardiograms (of coronary obstruction), physicians in America and later in Europe woke up [to the diagnosis which was] later to become a household word translated by the layman into "heart attack."[8]

Figure 4. *James Bryan Herrick.* *Copyright © Archives of the Chicago Literary Club. All rights reserved.*

Electrocardiography was for Herrick's coronary thrombosis what Heberden's angina had never had: coronary thrombosis could now be diagnosed during life.

While it is Herrick who deserves the credit for drawing the attention of the Western world to this common condition, there were many others, as he acknowledged, who had previously reported survival from coronary occlusion. Perhaps foremost among these were Obrastzow and Straschesko of Kiev who described the diagnosis of patients with coronary artery thrombosis at the first Russian Congress of Internal Medicine in 1909. Even after the publication of Herrick's seminal paper, it took a considerable time before clinicians accepted the diagnosis. Herrick describes how an unnamed American physician said that to make a clinical diagnosis of coronary thrombosis "was ridiculous because it was impossible."

In the United Kingdom, it was a paper by McNee of Glasgow in 1925, describing his experience in the United States, that really put coronary thrombosis on the British agenda. Even then, few cases were recognized until Parkinson and Bedford[9] of London described the clinical picture of the condition together with the sequential changes in the electrocardiogram in 1928. The diagnosis of "coronary thrombosis" was made with increasing frequency in the 1930s. At that time, there was speculation as to whether the rise in incidence was real, due to increasing recognition, or to the aging of the population. By the 1970s, when the "epidemic" of this syndrome seems to have peaked, it became clear that there had been a real increase in the frequency of the disorder, but the reason for this remains a matter of conjecture. An important observation was that of Morris.[10] Based on the meticulous postmortem data from the London Hospital, he found that the numbers of cases of coronary heart disease increased sevenfold between 1907-1914 and 1944-1949, yet there was an apparent reduction in the extent of coronary atheroma. It was thought that this discrepancy might be accounted for by an increase in thrombosis as an etiological factor.

THE THREE TRUNKS

After this brief overview, it is now time to look at how, from the sturdy base of the ischemic heart disease tree, multiple trunks grew, each of which developed a profusion of branches and dense foliage. These are the trunks of pathophysiology, diagnosis, and—undoubtedly the most vigorous trunk of the three—management.

The trunk of pathophysiology

It was not long after Heberden had described and named angina pectoris in 1772 that the pathology of coronary artery disease was first elucidated by Parry, Jenner, and others. As mentioned above, a century was to pass before the clinical syndrome of myocardial infarction was recognized. In the intervening period, there were many reports of abnormalities in the coronary arteries and in the myocardium, but they were not linked to infarction. Furthermore, it was believed that the coronary arteries were end arteries and, therefore, that their obstruction would be fatal. The evolving concepts of atherosclerosis are described by Anton Becker elsewhere in this issue of *Dialogues.* The role of thrombosis in patients dying acutely of coronary disease was widely recognized, both Obrastzow and Herrick using this term in their description of the clinical syndrome. Physicians in the middle of the twentieth century, such as Levine, used to refer to their patients as suffering a coronary thrombosis rather than a myocardial infarction. Yet Levine questioned the role of thrombosis in causing infarction as, in the succeeding decades, did a number of eminent pathologists including Willam Roberts,[11] who wrote in 1972:

> The infrequency of thrombosis in patients dying suddenly of cardiac disease and in those with transmural necrosis who never had shock or congestive heart failure suggests that the thrombi may be consequences rather than causes of acute myocardial infarction.

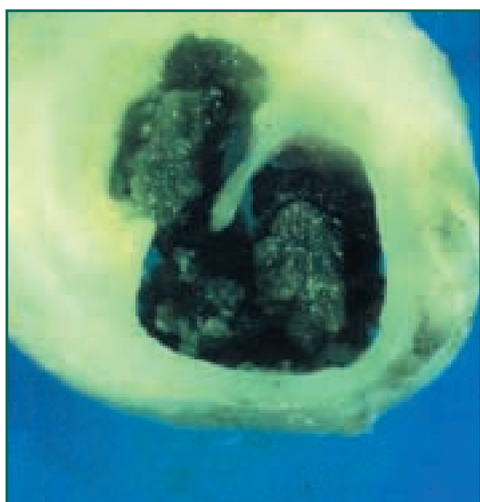

Figure 5. *Occluding coronary thrombosis due to plaque disruption. There is a bilobed mass of thrombus, one part in the plaque, another occluding the lumen. The two lobes join through the disrupted plaque cap.*

Reproduced from reference 15: *Davies MJ. The birth, growth, and consequences of the atherosclerotic plaque.* Dialogues Cardiovasc Med. *1999;4:115-130. Copyright © 1999, LLS.*

This observation, which we now recognize as having resulted from postmortem lysis of intracoronary clots, cast doubt on the potential role of thrombolysis. Some elegant studies eventually put an end to this heresy. Fulton of Glasgow[12] gave radiolabeled fibrinogen to patients coming into hospital with chest pain. In those who died, he used autoradiography to provide evidence as to whether thrombosis had occurred prior to or after the fibrinogen injection. Thrombosis was found in all cases, and most cases demonstrated thrombosis that was radionegative, ie. it had preceded the injection. Further evidence of its essential role was provided by the in vivo angiographic studies of DeWood of Spokane,[13] which demonstrated thrombus when the patient was first examined, but occluded arteries often opened spontaneously in the next few hours.

Constantinides of Vancouver[14] is credited with being the first to report, in 1966, that it is usual to find fissuring of an atheromatous plaque underlying the thrombus, although "rupture of an atheromatous 'abscess'" had been described in the 19th century. A number of pathologists, notably Davies[15] of London, Falk of Copenhagen, and Libby of Boston, have demonstrated that, prior to rupture, the offending plaque is the victim of a "self-destruct" inflammatory process, involving high concentrations of macrophages and metalloproteinases *(Figure 5).*

In the 1970s, Reimer, Jennings and coworkers[16] reported the spread of a "wave" of necrosis from the subendocardial to the subepicardial tissue over a period of some 4 to 6 hours, which occurs after a coronary vessel is occluded in animal models *(Figure 6).* Patchy areas might survive, depending upon collateral supply. There was evidence that reperfusion might save some tissue if instituted early enough. Initially, this was thought to imply that fibrinolysis was unlikely to be successful unless initiated very early, but human observations have shown that, although the earlier reperfusion is started the better, some benefit is achieved even as late as 6 to 12 hours.

The trunk of diagnosis

Two main types of test have evolved to validate the diagnosis of myocardial infarction—the electrocardiogram and measurements of cardiac proteins released in the blood.

Herrick, in his publication of 1918, commented on alterations in the contour of the T wave, his colleague Smith having observed similar changes in dogs that had undergone coronary ligation. A more detailed description of the changes was provided by Pardee of New York in 1920. He referred to the fact that the "T wave does not start from the zero level... and... quickly turns away

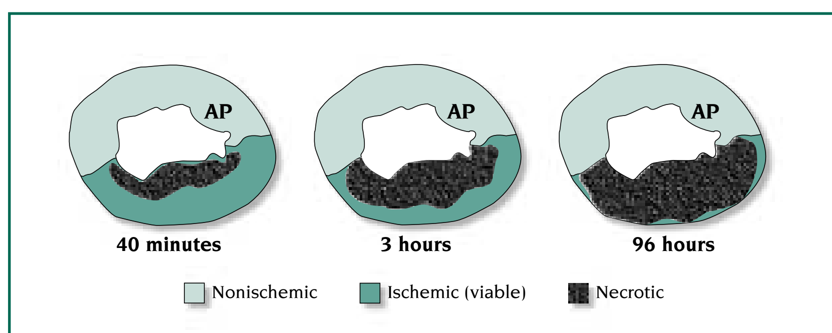

Figure 6. *Progression of cell death versus time after left circumflex coronary artery occlusion. Necrosis occurs first in the subendothelial myocardium. With longer occlusions, a wavefront of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. Thus, there is typically a large zone of subepicardial myocardium in the ischemic bed that is salvageable by early reperfusion, but that dies in the absence of such an intervention. In contrast, the lateral margins of the infarct are established as early as 40 minutes after occlusion and are sharply defined by the anatomical boundaries of the ischemic bed.*

Reproduced from reference 16: *Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow.* Lab Invest. *1979;40:633-644. Copyright © 1979, Nature Publishing Group.*

in a sharp curve." In 1928, Parkinson and Bedford of London integrated clinical observations and laboratory findings and described the characteristic evolution of the ECG changes.[9] Although Wolferth and Wood had introduced precordial leads in 1932, these were not widely used by physicians until after World War II. Unipolar chest leads, pioneered by Wilson, became standard only in the 1950s.

The accurate diagnosis of myocardial infarction was greatly aided by the development of blood tests for cardiac markers. In 1954, LaDue, Wroblewski, and Karmen, in New York, introduced cardiac enzyme estimations.[17] Cardiac muscle is rich in glutamic oxaloacetic transaminase, and they found that the serum level of this enzyme appeared in the blood of dogs after experimental coronary artery ligation and in humans after infarction. Other enzymes, such as creatine kinase and specific isomers, have subsequently been used in the diagnosis of myocardial infarction. The development of troponin as a marker of cardiac necrosis by Hamm of Bad Nauheim and Katus of Heidelberg has substantially enhanced the sensitivity and specificity of cardiac markers.

The trunk of management

General

From the time that myocardial infarction became accepted as a clinical condition, the keystone of management was rest. Because pathological studies had shown that it can take up to 6 to 8 weeks for firm scarring of the lesion to occur, it was considered that to minimize the risk of ventricular rupture, this was the appropriate duration for strict bed rest. Some authorities recommended absolute rest for most of this period, forbidding these patients even to brush their own teeth. Lewis, in the third edition of his book, *Diseases of the Heart,*[18] published in 1946, wrote

> Rest in bed should continue for from 6 to 8 weeks to ensure firm cicatrization of the ventricular wall: during the whole of this period the patient is to be guided by day and night nursing and helped in every way to avoid voluntary movement or effort. Patients have lost their lives and especially those who have early recovered from their symptoms by neglect of these precautions.

Even as late as 1959, Wood recommended total bed rest for 3 to 6 weeks. Levine and Lown had, in fact, put forward the concept of the armchair treatment in 1952,[19] but this more liberal approach took a long time to gain acceptance. Over the succeeding decades, however, patients were confined to bed for shorter and shorter periods, so that by the 1990s, patients were allowed up within 24 to 48 hours if their progress was uncomplicated.

Until the end of the 1950s, aside from the use of β-adrenergic agonists to treat cardiogenic shock, there was little effective treatment for patients with a myocardial infarction. Trials in both the United States and the United Kingdom suggested that anticoagulant treatment reduced mortality substantially and patients were admitted to hospital for this to be initiated. With the benefit of hindsight, it can be appreciated that the trials were defective and that the benefit, if any, was mainly achieved by preventing the pulmonary embolism that was a common complication in patients treated by complete immobilization.

Management of cardiac arrest and Coronary Care Units (CCUs)

It was known that heart attacks often caused sudden death due to ventricular fibrillation, but this was regarded as irreversible. However, in 1955, when Claude Beck, a surgeon in Cleveland, corrected this arrhythmia in a 65-year-old physician, using an open thoracotomy,[20] the possibility of successful resuscitation became a reality. With remarkable foresight, he wrote,

> This one experience indicated that resuscitation from a fatal heart attack is not impossible and might be applied to those who die in the hospital and perhaps those who die outside the hospital.

He coined the phrase "hearts too good to die," thus challenging the prevailing pessimism about the potential of resuscitation. In 1956, Zoll in Boston introduced external electrical defibrillation and, shortly afterwards, Kouwenhoven, Jude, and Knickerbocker, of Baltimore, showed the effectiveness of combining mouth-to-mouth breathing, sternal compression, and closed-chest electrical defibrillation in restoring normal cardiac function in the victims of ventricular fibrillation.[21] (It is, perhaps, worth mentioning that sternal compression, artificial ventilation, and the passing of electrical shocks through the chest were all described in 1775 in the Proceedings of the Royal Humane Society of London, but this information may not have reached America at this time because other issues might have seemed more pressing!)

Experiences in the Royal Infirmary, Edinburgh, in 1960, showed that while the potential for cardiac resuscitation in myocardial infarction was great, this could not be achieved with the current organization of hospitals. Patients with myocardial infarction were scattered throughout the medical wards and were being cared for by staff without the necessary expertise or equipment. This led Julian[22] to write, in 1961:

> Many cases of cardiac arrest associated with acute myocardial ischaemia could be treated successfully if all medical, nursing and auxiliary staff were trained in closed-chest cardiac massage and if the cardiac rhythm were monitored by an electrocardiogram linked to an alarm system... The provision of the appropriate apparatus would not be prohibitively expensive if these patients were admitted to special intensive-care units. Such units should be staffed by suitably experienced people throughout the 24 hours.

The first coronary care units (CCUs), as they came to be known, were created in Sydney, Kansas City, Philadelphia, and Toronto in 1962, and new units sprung up rapidly in the succeeding years, particularly in the United States. Although it was soon shown that cardiac resuscitation was saving many lives, it was obvious that this arrhythmia should be prevented, if possible. A strong correlation was reported between what were termed "warning arrhythmias" and the subsequent development of ventricular fibrillation. This led Lown to claim that if warning ventricular arrhythmias were treated promptly with lidocaine, primary ventricular fibrillation did not occur. As a consequence, nurses were taught that they must be able to identify and treat the relevant arrhythmias. Immense resources were devoted to this end, but it eventually became apparent that the "warning arrhythmias" were not as predictive as had been believed and that routine use of lidocaine might cause more deaths from asystole than they saved from ventricular fibrillation.

The introduction of CCUs was not without controversy, the eminent epidemiologists Archie Cochrane (commemorated by the Cochrane Reviews) and Geoffrey Rose being particularly skeptical. They were impressed by two randomized clinical trials, based in Bristol and Nottingham, which claimed to show that CCUs achieved no reduction in mortality. However, in retrospect, it is apparent that these trials were too small and deeply flawed. Indeed, the large trials that have established the effectiveness of many treatments in the management of myocardial infarction would not have been practicable without the environment provided by the CCUs.

Although the CCUs were effective in reducing the mortality of those patients who reached hospital, epidemiological studies showed that a high proportion of patients died of myocardial infarction in the community. Pantridge of Belfast, recognizing this problem, instituted a doctor-manned Mobile CCU and reported encouraging findings in 1966.[23] This was taken up only slowly as few centers considered that this was an economic use of highly qualified medical personnel. When it was found that paramedics could be as effective as doctors in this context, prehospital coronary care became widespread.

Cardiogenic shock, acute heart failure, and infarct size limitation

By the end of the 1960s, it became clear that, with the successful prevention and treatment of ventricular fibrillation, malfunction of the heart as a pump, leading to cardiogenic shock and cardiac failure, was now the main mechanism of death in myocardial infarction. Hypotension is a common feature of myocardial infarction; it was traditionally treated with vasoconstrictors or inotropic drugs in the belief that restoration of blood pressure was the priority, in spite of the fact that this might result in a reduction in cardiac output. In 1959, Paul Wood, in his classic textbook, described the reports of the benefits of norepinephrine, in one case reducing the fatality of shock from 80% to 48%. More carefully conducted experiments showed that this and similar drugs were actually harmful. Indeed, although it is still common practice to use drugs such as dopamine, their benefit remains unproven. While most cases of severe and persistent hypotension are a result of extensive myocardial damage, a substantial proportion in the early hours are associated with bradycardia (sometimes with heart block) and are a consequence of the induction of the Bezold-Jarisch reflex in some patients with inferior or posterior infarction. At one time, it was fashionable to treat such cases with artificial pacing; in one New York hospital in the 1960s, some 30% of patients had pacing electrodes inserted. However, as Pantridge showed in his experience with a mobile CCU, most cases will respond well to the intravenous injection of atropine if given early enough.

The introduction of invasive hemodynamic monitoring with the Swan-Ganz catheter greatly enhanced the understanding and facilitated the treatment of pump failure. In spite of this, the results of treating shock and heart failure remained poor. It was observed that these conditions were closely related to the extent of muscle necrosis and it was concluded that their prevention could be achieved only if myocardial damage could be limited. The National Institute of Health–led Myocardial Infarction Research Units in the United States provided evidence from animal experiments that a variety of drug therapies could reduce the extent of damage. Among these, there was particular interest in β-blockers, calcium channel blockers, and hyaluronidase. Experiments in humans failed to replicate the promising laboratory experience. β-Blockers were, indeed, found to reduce mortality in the first Inter-

national Study of Infarct Survival (ISIS-1), but the beneficial effect was probably due mainly to the prevention of cardiac rupture rather than to infarct-size limitation.

The idea of infarct size limitation was critically important, but it had to await successful reperfusion of the occluded artery before the concept was realized in clinical practice.

Fibrinolysis

Sherry and his colleagues in St Louis had pioneered the use of intravenous streptokinase in 1958,[24] but this excited little interest. In 1960, Boucek and Murphy in Miami reported favorable experiences when they undertook what they described as "segmental perfusion of the coronary arteries with fibrinolysin following a myocardial infarction," in which they triggered release of fibrinolysin into the coronary sinus relevant to the infarct-related artery. There was little interest in fibrinolytic therapy in the English-speaking world, but it became widely used in the Soviet Union and Germany. Indeed, there was considerable opposition to this treatment for a variety of reasons, particularly in the United States. For one thing, the role of thrombosis was seriously questioned by the highly regarded pathologists Roberts[11] and Spain. For another, there were doubts about the safety of thrombolysis both because of the risks of bleeding and also because reperfusion had been shown to cause myocardial damage and arrhythmias in animal experiments. At least 22 clinical trials of fibrinolytic therapy were undertaken in the 1970s and 1980s, but the results were not convincing. The scenario changed with the publication of the Gruppo Italiano per lo Studio della Soppravvivenza nell'Infarto miocardico (GISSI) and ISIS-2 trials in 1988-1989. Furthermore, the latter trial showed that aspirin also reduced mortality whether it was combined with streptokinase or not *(Figure 7)*.[25] However, it was evident that this form of therapy was not beneficial for all infarction patients. The trials found no evidence of benefit in patients who did not exhibit Q waves (what had previously been termed transmural infarction). Subsequently, myocardial infarction patients were categorized as having ST-segment elevation or non–ST-segment elevation infarction, the former being recommended for fibrinolytic treatment and the latter not.

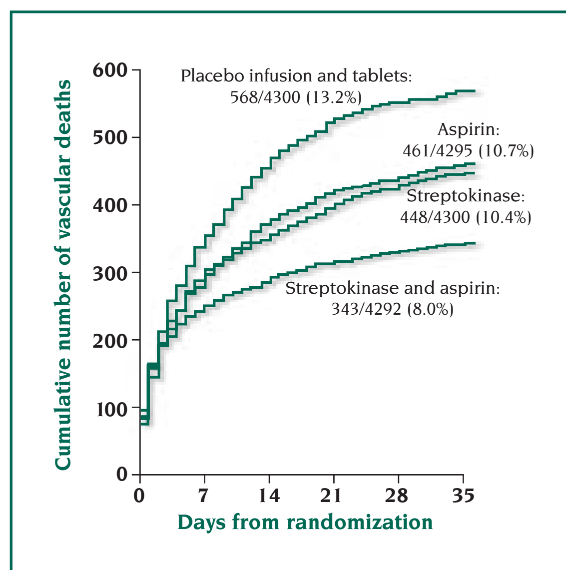

Figure 7. *Second International Study of Infarct Survival (ISIS-2) trial of streptokinase and aspirin. Cumulative vascular mortality on days 0-35 of patients allocated to active streptokinase only; active aspirin only; both active treatments; and neither.*

Reproduced from reference 21: *ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2.* Lancet. *1988;2: 349-360. Copyright © 1988, Elsevier Ltd.*

Following these trials, fibrinolytic therapy, together with aspirin, became widespread and was incorporated into the guidelines for the management of myocardial infarction produced by the American College of Cardiology and the European Society of Cardiology.

Percutaneous coronary intervention

Although Grüntzig of Zürich had pioneered angioplasty in 1977, he and others were, for many years, hesitant about utilizing this technique in patients with acute myocardial infarction. More recently, a number of well-conducted clinical trials have demonstrated that percutaneous clinical interventions are at least as effective, if not more so, than fibrinolytic treatment in preventing death and morbidity after myocardial infarction, and have fewer major side effects, notably stroke.

Other advances

A number of drug therapies have been tried out in the acute phase of myocardial infarction. Although some benefit has been claimed for the calcium channel blockers verapamil and diltiazem, other drugs in this class have proved disappointing, as have hyaluronidase, a combination of glucose, potassium, and insulin, and a variety of antiarrhythmic drugs. On the other hand, angiotensin-converting inhibitors have been found to be of value at this time, especially in patients with evidence of heart failure or poor left ventricular function.

CONCLUSION

Since the introduction of the CCUs, the in-hospital fatality of myocardial infarction is reported to have fallen from about 25%-30% to 5%-10%, although this apparent success

may be partly spurious as modern methods of diagnosis detect more small, low-risk, infarcts. In view of the relatively low mortality, at least in younger patients, it is doubtful if much further improvement in the management of patients who are admitted to hospital with acute myocardial infarction can be anticipated.

The large number of deaths from myocardial infarction outside hospital remains challenging, but perhaps not adequately appreciated. Data from three British cities in the 1988 UK Heart Attack Study showed that of 3523 heart attacks, 1172 (33%) of patients died outside hospital and an additional 12% in hospital.[26] Although patients with infarction are being treated earlier than previously, one can only expect a major impact on this problem by prevention, which might be achieved by improved diet, less smoking, and the better treatment of hypertension, diabetes and the other precursors of coronary heart disease.

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