Acute Coronary Syndromes

Editorial

Lead Article

Expert Answers to Three Key Questions

Fascinoma Cardiologica

Summaries of Ten Seminal Papers - *M. Faircloth, M. Saha* 183

Bibliography of One Hundred Key Papers

Editorial

Roberto Ferrari, *MD, PhD*
David J. Hearse, *BSC, PhD, DSc*

Modern cardiologists are continuously struggling with new challenges. After having succeeded in steadily reducing the incidence of myocardial infarction, they are now confronted with an increasing incidence of "non–ST-segment elevation acute myocardial infarction (NSTE-MI)." The use of this tongue-twisting clinical description became official in 1996 with its inclusion in the "ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction," which redefined acute myocardial infarction as an "acute coronary syndrome (ACS)" with two presentations: NSTE-MI and STE-MI ([non–] ST-segment elevation myocardial infarction).

Each time the word "syndrome" is used to describe a pathological condition or a disease, it suggests that we know very little about underlying causes and their manifestations. As such, patients with ACS constitute a very heterogeneous group with regard to their clinical history, symptoms, risk level, prognosis, as well as the treatment strategies that should be deployed. Equally vague is our knowledge of the pathogenesis of ACS, which is often described as a continuum of plaque rupture, platelet activation, and thrombus formation.

Such a continuum, however, is of no great help to cardiologists who are faced with the difficult decision as to whether it is best to go for fibrinolysis or primary angioplasty, and how best to control or block platelet activation with agents such as aspirin, glycoprotein IIb/IIIa inhibitors, or clopidogrel. This situation is far from satisfactory and today's cardiologists need to know much more about the etiology and control of the rare, but dangerous "vulnerable" plaque, and how to recognize and differentiate this type of plaque from the "friendly" or stable plaque. This is what this issue of *Dialogues in Cardiovascular Medicine* endeavors to explore.

In the Lead Article, the reader is taken by Marco Valgimigli et al on a journey into the coronary artery in an attempt to detect the fateful vulnerable plaque. This journey is made possible thanks to a gamut of techniques including angiography, angioscopy, ultrasound, elastography, palpography, thermography, optical coherence tomography,

and spectroscopy, to name a few. From this journey a number of pressing questions arise and in addressing these the Expert Answers delve into such vital issues as the role of biomarkers in risk stratification of NSTE-MI (Stefan K. James et al) and the pros and cons of antithrombotic treatments in NSTE-MI (Michel E. Bertrand) and of percutaneous coronary intervention versus fibrinolysis in STE-MI (Alberto Menozzi et al).

This issue of *Dialogues* will have made a major point if the reader recognizes that the interventional cardiologist's focus of interest has now shifted to prevention, rather than intervention alone. One of the most popular strategies is to prevent plaque rupture by using drugs such as statins and angiotensin-converting enzyme (ACE) inhibitors, which can even be delivered locally in order to "stabilize" the plaque. So one might conclude that the challenge of ACS is now characterized by the need for identification of the vulnerable plaque before thrombus formation can occur. In seeking to achieve this, the interventional cardiologist walks hand in hand with the clinical cardiologist, and this exemplary cooperation is tantamount to a new lease of life for our patients.

Acute coronary syndromes: from treatment to prevention

The enduring challenge of vulnerable plaque detection in the cardiac catheterization laboratory

Marco Valgimigli, MD; Gastón A. Rodriguez-Granillo, MD; Pierfrancesco Agostoni, MD; Patrick Serruys, MD, PhD

ThoraxCenter - Erasmus MC - Rotterdam - THE NETHERLANDS

Rupture of vulnerable plaques is the main cause of acute coronary syndromes. Identification of such plaques is therefore essential to develop treatment modalities to stabilize them. Several intravascular technologies are described in this review. The ideal technique would provide morphological, mechanical, and biochemical information; although several imaging techniques are currently under development, none of them provides, alone, such all-embracing assessment. Optical coherence tomography has the advantage of high resolution, thermography has the potential to measure metabolism, and Raman spectroscopy obtains information on chemical components. Intravascular ultrasound (IVUS) and IVUS-palpography are easy to perform, and assess morphology and mechanical instability. Shear stress is an important mechanical parameter that deeply influences vascular biology. Nevertheless, at present, each technique generally only assesses one clinical feature, so that none of them can unequivocally and comprehensively identify a vulnerable plaque nor predict its further development. Thus, the combination of several modalities is required to ensure high sensitivity and specificity in detecting vulnerable plaques.

Keywords: acute coronary syndrome; myocardial infarction; vulnerable plaque; imaging; treatment; prevention

Address for correspondence: Prof Patrick Serruys, ThoraxCenter, Erasmus MC Rotterdam, Room BD 404, Postbus 2040, CA Rotterdam, NL-300, The Netherlands (e-mail: p.w.j.c.serruys@erasmusmc.nl)

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Plaque rupture, platelet activation, and thrombus formation are recognized as key events in the pathogenesis of acute coronary syndromes (ACS). The ability of aspirin to reduce recurrent ischemic events in ACS has been clearly and consistently demonstrated in the last decades, and this has progressively led to an increasing effort to control and block platelet activation when plaque rupture occurs, either spontaneously, during an ACS, or during percutaneous coronary intervention (PCI).

The introduction of potent antiplatelet agents, such as the glycoprotein IIb/IIIa inhibitors, has further reduced the rate of major cardiac adverse events as compared with aspirin and heparin alone, strongly supporting the notion that platelet reactivity is pivotal in the pathogenesis of complications related to plaque rupture, and progressive refinements of antiplatelet treatment will significantly improve outcome in patients suffering from ACS. However, in the last years, focus has progressively shifted from treatment to prevention, mainly driven by a comprehensive approach based on systemic

SELECTED ABBREVIATIONS AND ACRONYMS

ACS	acute coronary syndrome
ANGUS	angiography and intravascular ultrasound
IBIS	Integrated Biomarkers and Imaging Study
IVUS	intravascular ultrasound
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
TCFA	thin-cap fibroatheroma

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therapy, such as use of statins and angiotensin-converting enzyme (ACE) inhibitors coupled with vulnerable plaque detection and "passivation" (the complex process of stabilizing the active plaque at risk of rupture) by means of locally delivered therapy.[1-5]

Before the concept of plaque sealing (by coronary balloon angioplasty or stenting) is tested in terms of efficacy and cost-effectiveness, however, we need to provide clinicians with tool(s) able to consistently and reliably detect vulnerable coronary plaques. The challenge for the future is to identify vulnerable plaques before the thrombus forms. The current review focuses on invasive imaging potentially able to identify hot plaques having recently undergone rupture or prone to rupture.

THE VULNERABLE PLAQUE

A wide variety exists in the structure and function of coronary atherosclerotic plaques. Most plaques may cause no symptoms for decades; however, a few plaques disrupt and cause thrombosis. These rare, but dangerous, thrombosis-prone plaques are termed vulnerable.[6] Thus, a vulnerable plaque is a plaque assumed to be at high short-term risk of thrombosis, resulting in an ACS.

There are three forms of vulnerable plaques, all documented by pathologic studies:

- *Thin-cap fibroatheroma (TCFA):* in about 65% of all symptomatic coronary thrombotic events, rupture of an inflamed TCFA is evident. The major components of such TCFA are: an atheromatous core (usually >40% of the entire plaque), a thin fibrous cap with macrophage and lymphocyte infiltration and decreased smooth muscle cell content, and expansive remodeling.[7]
- *Erosion:* in about 30% of all events, the endothelium overlying the plaque has been found injured at the place where a thrombus has formed. Usually, these plaques are rich in proteoglycans.[8]
- *A calcified nodule:* in 5% of all events, thrombosis covering a calcified nodule suggests that the plaque is heavily calcified, with a calcified nodule projecting into the lumen.[9]

The terms vulnerable plaque, high-risk plaque, and thrombosis-prone plaque can be used identically.[6] Currently, there is no widely accepted diagnostic method to prospectively identify such vulnerable plaques. Many of the imaging techniques used to assess coronary artery disease are able to detect different features of the rupture-prone type of vulnerable plaques.

ANGIOGRAPHY

Coronary angiography has been so far the gold standard to assess the severity of obstructive luminal narrowing. Furthermore, it serves as a decision tool to direct therapy such as PCI or coronary artery bypass surgery (CABG). Using coronary angiography, we can assess the lumen boundaries, but no information is given on plaque burden, plaque delineation, and plaque components. Actually, angiography is able to detect complex lesions, which are considered vulnerable plaques at an advanced stage. Complex lesions have some peculiar angiographic features: intraluminal filling defects (consistent with thrombus), presence of contrast and hazy contour beyond the vessel lumen (consistent with plaque ulceration), irregular margins and overhanging edges (consistent with plaque irregularity and, possibly, fracture) and impaired flow with evident lumen reduction.[10] The presence of multiple complex lesions in patients after a myocardial infarction (MI) has been associated with increased incidence of ACS.[10] However, angiography is a crude technique to assess the presence and burden of vulnerable lesions, as the majority of ulcerated plaques are not big enough to be detected by angiography, but can be well assessed pathologically.[11] Indeed, about 70% of acute coronary occlusions are in areas that were previously angiographically normal, and only a minority occurs where there was severe stenosis.[12,13] Furthermore, we have to take into account that the predictive power of angiography is strongly dependent on the time interval between the angiogram and MI, because both time and interim therapy can influence atherosclerosis. In one study, the angiograms were performed between 1 and 77 months before the event[13] and showed that atherosclerosis can be a rapidly progressive process. Another study evaluated angiograms performed 1 week before acute MI showing that signs of thrombosis and rupture were present in the majority of patients.[14] Thus, patients with silent nonobstructive coronary atherosclerosis harbor vulnerable plaques that cannot be detected by angiograms, but are associated with adverse clinical outcomes. If a disrupted ulcerated plaque is seen on angiography *(Figure 1),* the existence of additional rupture-prone plaques is to be expected. Angiography therefore has a low discriminatory power to identify the vulnerable plaque.

ANGIOSCOPY

Angioscopy uses fiber optics to visualize thrombi and plaque surface *(Figure 2).* Vulnerable plaque features, such as ruptured caps and red discoloration

Figure 1. *Angiography reveals a dissected flap within the lumen, indicating a ruptured plaque.*

(intraplaque hemorrhage), can be detected. In patients with acute MI, angioscopy showed diffuse disease in all the three coronary arteries, with multiple yellow plaques.[15] Furthermore, in a 12-month follow-up study of patients with stable angina, ACS occurred more frequently in patients with yellow plaques than in those with white plaques.[16] These results suggest that yellow plaques, which may be visualized by angioscopy, but not by angiography, may be more prone to rupture than white plaques. However, this technique has several drawbacks. Indeed, only a limited part of the vessel tree can be investigated, due to the size of the device. Furthermore, information about the degree of plaque extension into the vessel wall is not provided. Finally, to enable clear visualization of the vessel wall, the vessel has to be occluded and the remaining blood flushed away with saline, thereby potentially inducing ischemia.

INTRAVASCULAR ULTRASOUND

Intravascular coronary ultrasound (IVUS) provides real-time high-resolution images of the vessel wall and lumen. Depending on the distance of the vessel wall from the catheter, the axial resolution is about 150 microns, the lateral 300 microns. The images appear in real time. Features of the vessel can be detected based on the echogenicity of different tissue types. Small structures can be visualized, however only those sized over 160 microns can be estimated accurately. The normal thickness of the media is about 125 to 350 μm. IVUS provides some insight into the composition of coronary plaques. In IVUS images, calcification is characterized by a bright echo signal with distal shadowing that hides plaque components and deeper vessel structures. In comparative studies between histology and IVUS, plaque calcification can be detected with a sensitivity of between 86% and 97%.[17] The sensitivity to detect microcalcification ranges around 60%.[18] In IVUS images, lipid depositions are described as echolucent zones and can be detected with a sensitivity of between 78% and 95% and specificity of 30%.[19] This sensitivity is dependent on the amount of lipid and can drop down further if the echolucent area is smaller than a quarter of the plaque. Echolucent zones can also be caused by loose tissue and shadowing from calcium, which makes the interpretation of these areas difficult. The sensitivity to differentiate between fibrous and fatty tissue is between 39% and 52%.[20] The detection of vulnerable plaques by IVUS is mainly based on a series of case reports. The main focus of these reports is the detection of already ruptured plaques. To evaluate the role of IVUS in detecting plaque rupture, a study was performed in patients with angina. Ruptured plaques were characterized by a cavity (echolucent area

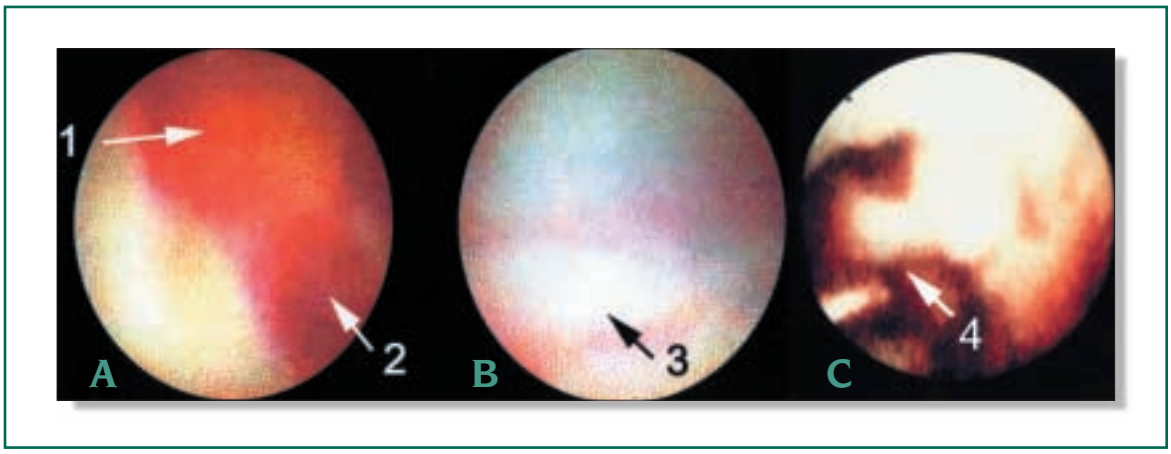

Figure 2. *Angioscopy shows:* ***(A)*** *a red thrombus on a plaque* ***(1),*** *blocking a part of the lumen* ***(2).*** *After removal of thrombus and plaque with atherectomy* ***(B)*** *a white flap is visible* ***(3).*** *Postangioplasty angioscopy* ***(C)*** *can show a dissecting flap* ***(4)*** *within the lumen.*

within the plaque) and a tear of the thin fibrous cap *(Figure 3).* Plaque rupture was confirmed by an injection of contrast medium with subsequent filling of the plaque cavity, seen on IVUS. Ruptured plaques were identified in 74% of patients presenting with unstable angina. Of the patients without plaque rupture, only 18% had unstable angina. The echolucent area (cavity)–to–total plaque area ratio was larger in the unstable group than in the stable group. The thickness of the fibrous cap in the unstable group was also found to be smaller than in the stable group.[21] Other studies have shown that multiple plaque ruptures may be diffusely present in all the coronary arteries of patients with ACS,[22] but not all of them produce symptoms. Indeed, plaque ruptures causing acute symptoms were associated with a smaller minimum lumen area and a greater thrombotic burden.[23] Major limitations of these

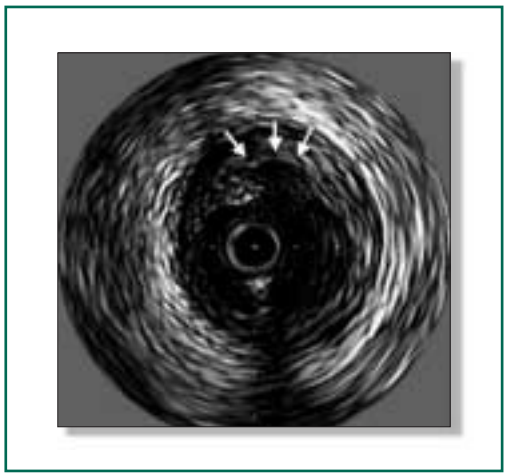

Figure 3. *The intravascular ultrasound cross-section shows an eccentric ruptured plaque with deep ulcus* ***(arrows).*** *A thin flap is still covering parts of the ulceration. Courtesy of Paul Schoenhagen.*

studies are their retrospective nature and the lack of follow-up. Only Yamagishi et al have performed a prospective study with a follow-up period of about 2 years. Large eccentric plaques containing an echolucent zone by IVUS were found to be at increased risk of instability even though the lumen area was preserved at the time of initial study.[24] IVUS assessment of vascular remodeling may help to classify plaques with the highest probability of spontaneous rupture. It has been demonstrated that ruptured plaques are associated with positive remodeling.[25] A number of groups have investigated the potential of ultrasound radio-frequency signal analysis for tissue characterization.[26,27] In particular, virtual histology is the first attempt at detailed tissue characterization. This technique is based on backscatter analysis of the radio-frequency signals produced by the IVUS unit. Spectral parameters derived from the backscatter analysis are used to develop classification schemes, which allow differentiation between four general tissue types (lipid, lipid-fibrous, calcified, calcified-necrotic), validated by ex vivo histology.[28] The value of this technique is being currently tested in several clinical trials.

INTRAVASCULAR ELASTOGRAPHY/PALPOGRAPHY

In 1991, a new technique was introduced to measure the mechanical properties of tissue using ultrasound—elastography.[29] The underlying concept is that upon uniform loading, the local relative amount of deformation (strain) of a tissue is related to the local mechanical properties of that tissue. If we apply this concept to determine the local properties of arterial tissue, blood pressure acts as a stressor. At a given pressure difference, soft plaque components will deform more than hard components. Measurement of local plaque deformation in the radial direction can be obtained with ultrasound. In vitro studies with histologic confirmation have shown that there are differences of strain normalized to pressure between fibrous, fibro-fatty, and fatty components of the plaque of coronary as well as femoral arteries.[30] This difference was mainly evident between fibrous and fatty tissue. Interestingly, these plaque types could not be differentiated by echo-intensity differences on the IVUS echogram. In another in vitro study, postmortem coronary arteries were investigated with elastography and then processed for histology. The sensitivity and specificity of elastography to detect TCFA were, respectively, 88% and 89%. Furthermore, there was a high correlation between the strain in the cap and the amount of macrophages.[31] For intravascular purposes, a derivative of elastography called palpography may be a suitable tool.[32] In this approach, one strain value per angle is determined and plotted as a color-coded contour at the lumen vessel boundary. Since radial strain is obtained, the technique may have the potential to detect regions with elevated stress: increased circumferential stress results in an increased radial deformation of the plaque components. It is feasible to apply intravascular palpography during catheterization procedures. The systemic pressure is used to strain the tissue, and the strain is determined using cross-correlation analysis of sequential frames acquired at different pressures. A likelihood function is determined to obtain the frames with minimal motion of the catheter in the lumen since motion of the catheter impairs accuracy of strain estimation. Minimal motion is mainly observed near the

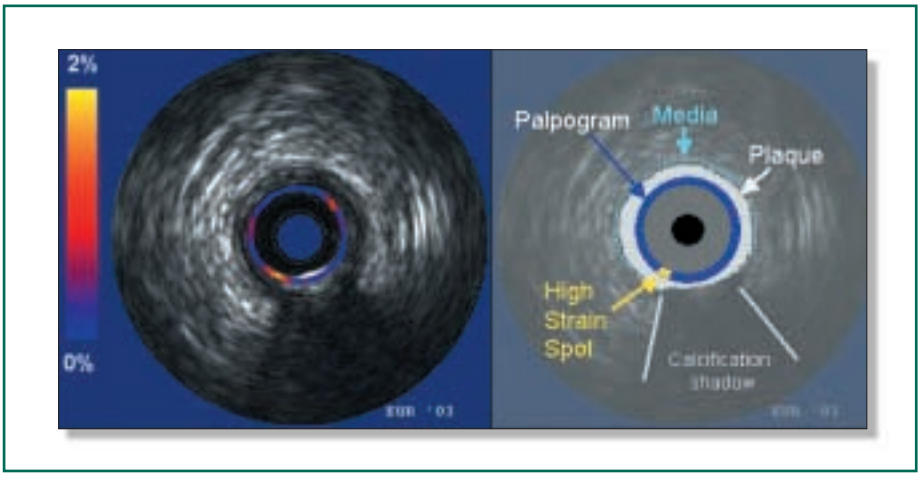

Figure 4. *The palpogram shows an eccentric plaque with a big calcification. On the left shoulder there is a high-strain spot of an otherwise less deformable plaque, probably representing a vulnerable plaque.*

end of the passive filling phase. Reproducible strain estimates are obtained within one pressure cycle and over several pressure cycles. Palpography has been shown to detect, in human coronary arteries, strain patterns typical of deformable plaques *(Figure 4).* Furthermore, the number of deformable plaques per patient correlated positively with the clinical presentation and with the serum level of C-reactive protein.[33] Palpography provides additional information to IVUS. The differentiation between hard and soft tissue may be important for the detection of a vulnerable plaque. Since palpography is based on clinically available IVUS catheters, the technique can be easily introduced into the catheterization laboratory. The clinical value of this technique is currently under investigation in the Integrated Biomarkers and Imaging Study (IBIS).

THERMOGRAPHY

Since atherosclerosis is an inflammatory disease[34] and inflammation determines an elevation in temperature, hypothetically, a temperature rise should be measured at the surface of a plaque. Furthermore, as vulnerable plaque is a very active metabolic area, it has been postulated that even higher temperature could be found due to heat released by activated macrophages either on the plaque surface or under a thin cap. The pioneering paper by Casscells et al reported that carotid plaques taken at endarterectomy have temperature heterogeneity. The temperature difference (measured outside the body, at room temperature) between different areas was up to 2.2°C, and correlated with cell density (mainly macrophages).[35] Stefanadis et al performed studies in human patients with stable angina, unstable angina, and acute MI. Temperature was constant within the arteries of the control subjects, whereas most atherosclerotic plaques showed higher temperatures compared with healthy vessel wall. Temperature differences between atherosclerotic plaque and healthy vessel wall increased progressively from stable angina to acute MI with a maximum difference of 1.5±0.7°C.[36] Furthermore, a high temperature gradient (>0.5°C) between the atherosclerotic plaque in the culprit vessel and the healthy vessel wall was shown to be an independent predictor of adverse events after PCI.[37] These data have yet to be confirmed prospectively in other centers, and the influence of parameters such as coronary blood flow or catheter design has to be studied in the future.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) can provide images with ultrahigh resolution. The technique measures the intensity of back-reflected light in a similar way as IVUS measures acoustic waves. Light is split into two signals: one is sent into the tissue and the other to a reference arm with a mirror. Both signals are reflected and cross-correlated by interfering the light beams. To achieve cross-correlation at incremental penetration depths in the tissue, the mirror is dynamically translated. The intensity of the interfering signals at a certain mirror position represents backscattering at a corresponding depth. Images with an extremely high resolution, ranging from 4 to 20 mm, can be achieved with a penetration depth up to 2 mm. Images can be acquired in real time *(Figure 5, page 146).* Early attempts were made to validate OCT using histology. A lipid pool generates decreased signal areas with poorly delineated borders, a fibrocalcific plaque shows a sharply delineated region with a signal-poor interior, and a fibrous plaque produces a homogenous signal-rich lesion.[38] The first in vivo comparison of OCT with IVUS demonstrated superior delineation by OCT of

Figure 5. *Optical coherence tomography produces high-resolution, real-time, cross-sectional, or 3-D images of tissues at an exceptionally high, histology-like resolution of a eccentric plaque with a thin cap (arrows). Courtesy of Evelyn Regar.*

structural details like thin caps or tissue proliferation.[39] However, OCT has several limitations: the low penetration depth, which hinders studying large vessels, and the light absorbance by blood, which currently needs to be overcome by saline infusion or balloon occlusion with associated potential for ischemia.

SPECTROSCOPY

Using fiber-optic technology, coronary plaques can be illuminated in situ and the reflected light can be collected and launched into a spectrometer. Spectroscopy is based on the property that different chemical compounds absorb and scatter different amounts of energy at different wavelengths, so each tissue, due to its chemical composition (lipid, collagen, calcium, etc), has a unique pattern of light absorbance, leaving a unique chemical (molecular) fingerprint. Different approaches are under development. Raman spectroscopy* uses high-energy laser light, it has a high molecular sensitivity, but its tissue penetration is as low as 0.3 mm. Near-infrared (NIR) spectroscopy (with wavelengths from 750 to 2500 nm) has greater penetration (2 mm), but lower molecular sensitivity and therefore relies on pattern recognition for plaque typing. Intracoronary spectroscopy has not yet been tested clinically.[40]

*based on the the Raman effect, discovered by the Indian physicist C. V. Raman in 1928: when incident photons interact with a molecular system, most are elastically scattered (in a process called "Rayleigh scattering," in which incident photons have the same energy as the scattered photons), while only a small fraction of photons (about 1 in 107) are inelastically scattered ("Raman scattering", in which the energies of the incident and scattered photons are different).

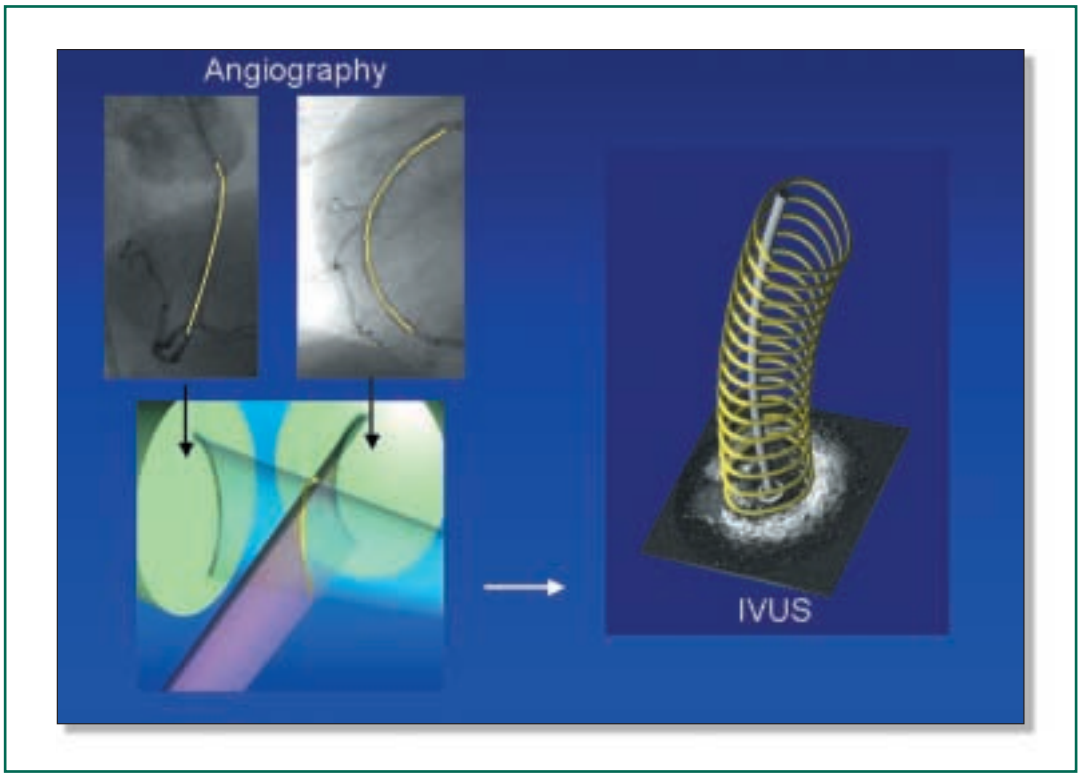

Figure 6. *3-D reconstruction technique combining ANGiography and intravascular ultrasound (IVUS) allowing an exact reconstruction of the vessel shape.*

ANGUS AND SHEAR STRESS

High-resolution reconstruction of three-dimensional (3-D) coronary lumen and wall morphology is obtained by combining angiography and IVUS.[41] Briefly, a biplane angiogram of a sheath-based IVUS catheter taken at end-diastole allows reconstruction of the 3-D pullback trajectory of the catheter. Combining this path with lumen and wall information derived from IVUS images that are successively acquired during catheter pullback at end-diastole gives accurate 3-D lumen and wall reconstruction with resolution determined by IVUS *(Figure 6)*. The use of computation flow dynamics allows calculation of detailed blood velocity profile in the lumen and shear stress on the vessel walls.[42] For this purpose, absolute flow and blood viscosity need to be provided as boundary conditions. From the blood velocity profile local wall shear stress on the endothelium can be accurately derived. Wall shear stress is the frictional force, normalized to surface area, that is induced by the blood passing the wall. Although from a mechanical point of view shear stress is of a very small magnitude compared with blood pressure–induced tensile stress, it has a profound influence on vascular biology and explains the localization of atherosclerotic plaque in the presence of systemic risk factors. Many of these biological processes also influence the stability of the vulnerable plaque, including inflammation, thrombogenicity, vessel remodeling, intimal thickening, or regression, and smooth muscle cell proliferation. Therefore, the study of this parameter as derived by image-based modeling is of utmost importance.

CONCLUSION

Assessment of atherosclerosis by imaging techniques is essential for in vivo identification of vulnerable plaques. The ideal technique would provide morphological, mechanical, and biochemical information; however, in spite of the fact that several imaging techniques are currently under development, none of them provides alone such all-embracing assessment.

OCT has the advantage of high resolution, thermography has the potential to measure metabolism, and spectroscopy obtains information on chemical components. IVUS and IVUS-palpography are easy to perform and assess morphology and mechanical instability. Shear stress is an important mechanical parameter that deeply influences vascular biology. Nevertheless, all techniques are still under investigation and, at present, none of them can completely identify a vulnerable plaque and, most importantly, predict its further development. This is related to fundamental methodological insufficiencies that may be resolved in the future. From a clinical point of view, most techniques currently assess only one feature of the vulnerable plaque. Thus, the combination of several modalities will be of importance in the future to ensure a high sensitivity and specificity in detecting vulnerable plaques. To conclude, a hypothetical clinical decision-making tree is presented in *Figure 7*. If all conditions are satisfied, then it is probably logical to try to treat the vulnerable plaque with a local treatment (plaque sealing) in the attempt to prevent the consequences related to its possible rupture or erosion. In any event, this strategy has never been tested prospectively and it should be never forgotten that the restenosis rate—even in the drug-eluting stent era—is not equal to zero.

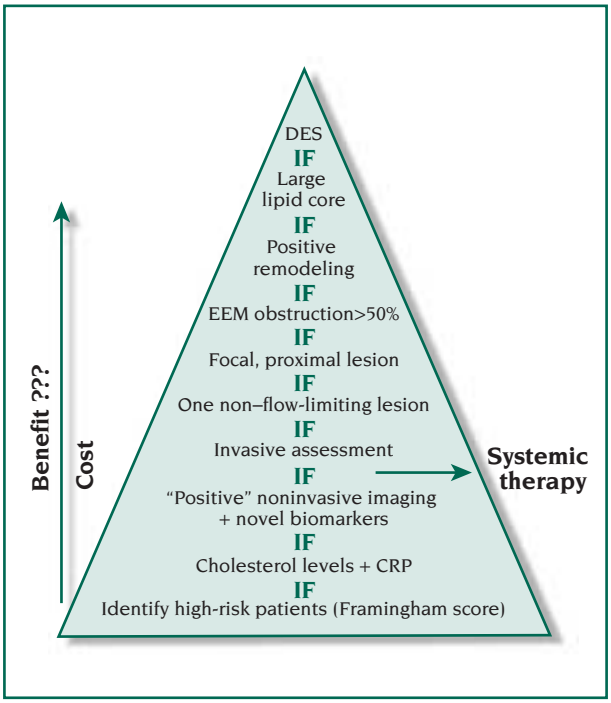

Figure 7. *The hypothetical pyramid of clinical decision-making on how to treat a vulnerable plaque. If all conditions are satisfied, including the fact that a patient is already receiving an invasive procedure due to other flow-limiting lesion(s), the preventive local treatment of a potential vulnerable plaque may be potentially considered. However, it should be always kept in mind that this strategy has never been tested prospectively.*

Abbreviations: *CRP, C-reactive protein; DES, drug-eluting stent; EEM, external elastic membrane.*

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Biomarkers for risk stratification in non–ST-segment elevation acute coronary syndromes: what is their relation to classic clinical characteristics?

Stefan K. James, MD, PhD; Bertil Lindahl, MD, PhD; Lars Wallentin, MD, PhD

Uppsala Clinical Research Center - Uppsala University Hospital - Uppsala - SWEDEN

No single instrument suffices for risk stratification in non–ST-segment elevation acute coronary syndromes. Clinical indicators (age, diabetes, smoking, gender, heart rate, heart failure, renal function, ECG) provide early independent, and complementary prognostic information, as do biochemical markers: troponin T (TnT) has the strongest relationship with subsequent myocardial infarction, while brain natriuretic peptide (BNP) and the aminoterminal portion of its prohormone (NT-proBNP) are the best biomarkers of cardiac mortality, followed by C-reactive protein (CRP). Biomarkers also inform therapy: TnT elevation is an indication for early coronary intervention, glycoprotein IIb/IIIa inhibition, and extended low-molecular-weight heparin, while CRP elevation calls for statin therapy, irrespective of lipid levels.

Keywords: prognosis; myocardial damage; mortality; troponin; myocardial dysfunction; natriuretic peptide; inflammation; C-reactive protein; renal dysfunction; creatinine

Address for correspondence:
Stefan K. James, Department of Cardiology, Thorax Center, Academic Hospital, 751 85 Uppsala, Sweden (e-mail: Stefan.james@akademiska.se)

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Cardiovascular disease is the most common cause of death in the industrialized world. In Sweden, for example, it accounts for 46% of all deaths.[1] In spite of the steady decline in the incidence of myocardial infarction (MI) in recent years, the incidence of non-ST-segment elevation acute coronary syndromes (ACS) has increased considerably. Chest pain—or other symptoms suggestive of ACS—is one of the most common reasons for admission to hospital emergency rooms. These patients constitute a very heterogeneous population with regard to their clinical history and the underlying cause of their symptoms. Consequently, the prognosis is also subject to considerable variation. Early risk prediction is essential for the identification of patients at high risk and for the selection of the most appropriate treatment strategy. Moreover, with early risk-prediction, patients at low risk can be identified and costly and potentially hazardous treatments and prolonged hospital stays can be avoided.

SELECTED ABBREVIATIONS AND ACRONYMS

ACS	acute coronary syndrome
BNP	brain natriuretic peptide
CRP	C-reactive protein
FRISC II	Fragmin and/or Revascularization during InStability in Coronary artery disease II (trial)
GUSTO-IV	Global Utilization of Strategies to Open occluded arteries IV (trial)
MI	myocardial infarction
NT-proBNP	amino-terminal portion of brain natriuretic peptide prohormone
TnT	troponin T

Clinical factors such as advanced age, diabetes mellitus, male gender, heart failure, reduced renal function, and the electrocardiogram (ECG) provide important and independent prognostic information.[2] Due to the heterogeneity of ACS patients and the variable risk and alternative treatment strategies available, there is a need for a better and more individualized method of risk assessment than is offered by traditional clinical factors. With the introduction of rapid, sensitive, and precise immunoassays, levels of serum proteins of myocardial damage, myocardial dysfunction, inflammation, and renal dysfunction have been evaluated to provide easy and ac-

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curate prediction of outcome in patients with non–ST-segment-elevation ACS. Assessment of the biomarkers in large databases has made possible the separate prediction of subsequent death and MI.

MYOCARDIAL DAMAGE

Cardiac isoforms of troponin I and T are expressed solely on myocardial cells and are released from the cytoplasm after disintegration of the cell membrane due to myocardial necrosis. Accordingly, measurable levels of troponin I or T are highly specific for myocardial damage, indicating even microscopic areas of necrosis, irrespective of the cause.[3] The initial rise of troponin concentration occurs 3 to 4 hours after the ischemic injury, with a persistent elevation for up to 2 weeks after the event.

Numerous previous studies have shown that troponin elevation is associated with an impaired outcome in patients with ACS.[4] Troponin elevation has become the cornerstone, not only of the diagnosis of MI, but also of risk prediction and for targeting therapy with low-molecular-weight heparin,[5] glycoprotein IIb/IIIa inhibitors,[6,7] and early revascularization[8] in patients with non–ST-segment elevation ACS. In the Fragmin and/or Revascularization during Instability in Coronary artery disease II (FRISC II) trial including 2329 patients with non–ST-segment elevation ACS,[9] mortality increased stepwise with higher quartiles of troponin T (TnT).[9] Any detectable level of TnT was also associated with an increased risk of MI, probably reflecting a thrombotic coronary lesion with increased risk of subsequent occlusion and/or downstream embolization. Three-vessel and left main disease were also more frequent and absence of any significant coronary stenosis was less frequent in patients with any elevation of TnT. High levels of TnT were also associated with more frequent visible thrombi in the coronary arteries. However, patients in the highest, compared with the two middle quartiles had a lower rate of MI, probably due to a larger proportion of already completed MIs as evidenced by a higher proportion of occlusions of the left circumflex artery in this group. These results were confirmed in the large-scale Global Utilization of Strategies To Open occluded arteries IV (GUSTO-IV) trial in which the results of TnT analysis were available for 7115 (91.2%) patients.[10] Mortality at 30 days markedly increased with increasing TnT quartiles, from 1.1% to 7.4%, the first and the fourth quartile *(Figure 1A)*. The rate of MI at 30 days increased from the first to the second quartile, but did not increase further in the upper two quartiles *(Figure 1B)*. In a multiple logistic regression analysis, TnT quartiles were independently related to both

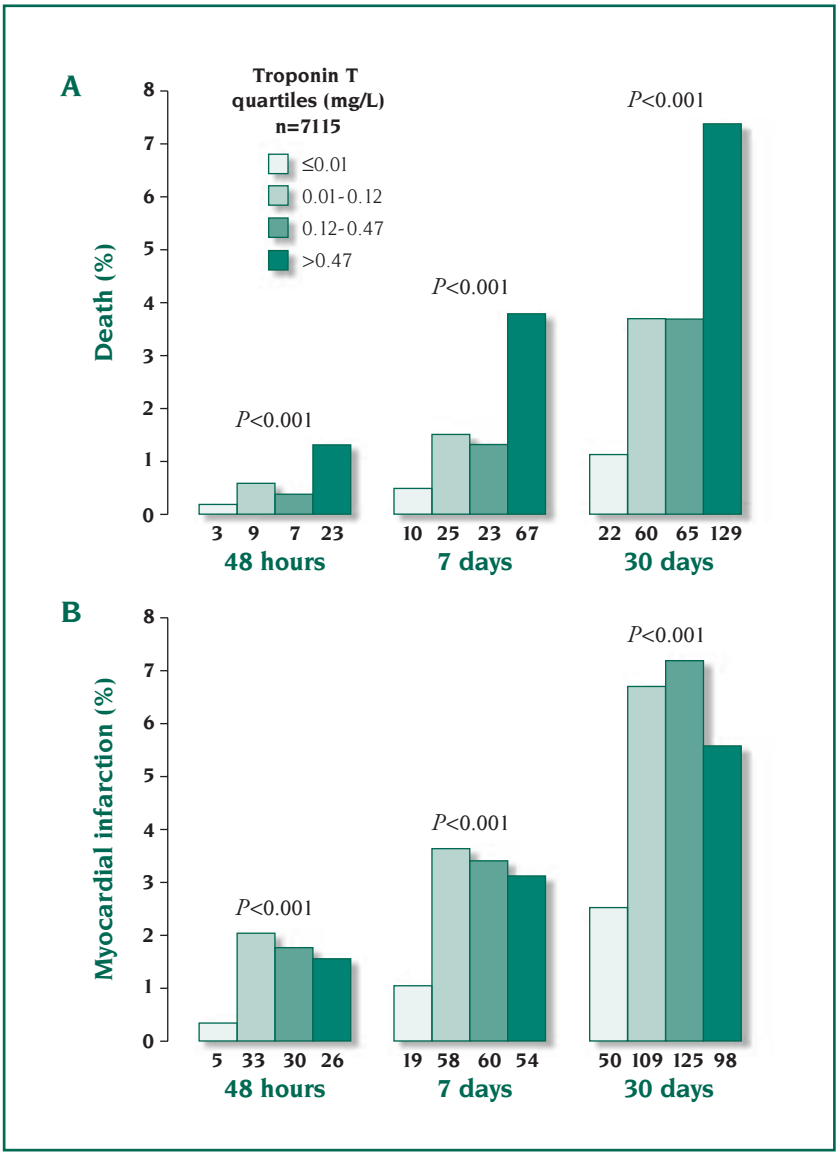

***Figure 1.** Rate of: **(A)** death and **(B)** myocardial infarction, at 48 h, 7 days, and 30 days according to quartiles of troponin T levels. The number of patients who experienced events is given under the bars.*

death and MI at 30 days. Thus, increasing troponin levels are associated with a continuous rise in mortality, whereas any detectable TnT, ie, above 0.01 µg/L, is associated with a raised risk of MI without significantly further risk at higher troponin levels.

The high sensitivity of the troponin assays is of special importance in ACS because of their ability to identify patients with minimal myocardial damage,[10,11] resulting from distal embolization of thrombotic material.[12] However, at the lowest detection limit, the TnT assay has an unacceptable imprecision for the diagnosis of MI. A retrospective evaluation regarding prediction of subsequent cardiac events performed in the FRISC II trial suggested a lower cutoff for TnT (Roche Diagnostics) than the previously established level of 0.1 µg/L. A prospective verification of the cutoff levels 0.03 and 0.01 µg/L was thereafter performed with 7115 non–ST-segment elevation ACS patients included in GUSTO-IV.[13] The cutoff value, with an analytical imprecision corresponding to a coefficient of variation of 10%, 0.03 µg/L, provided a better discrimination between high and low risk: 5.1% vs 1.6%, $P<0.001$ than the previously established cutoff of 0.1 µg/L. However, a cutoff value at the lower limit of detection, 0.01 µg/L, provided the best discrimination; 5.0% vs. 1.1%, $P<0.001$. The lowest cutoff level of 0.01 µg/L also yielded the highest negative predictive value and discriminated best for the combined end point death/MI. Therefore, in a population with suspected ACS, a cutoff level at the lower limit of detection (0.01 µg/L) seems to be the best for selection of patients at low risk of death, both at short and long term. However, for prediction of very high risk among patients with ACS, combination of troponin and other risk indicators might be recommended. In less selected patient populations, the imprecision of the assay becomes more critical and a slightly higher cutoff of 0.03 µg/L, might be more appropriate.

INFLAMMATION

Inflammation plays an essential role in the pathogenesis of atherosclerosis.[14] At every stage of the disease, inflammation is indicated by an increased number of macrophages and lymphocytes secreting cytokines and hydrolytic enzymes.[15] Furthermore, the rupture of a fibrous cap (and thus the initiation of the ACS) involves inflammatory action,[16] as reflected by an increased concentration of activated macrophages and T lymphocytes promoting degradation of extracellular matrix in the unstable plaque.[17,18] Peripheral embolization of thrombotic material causes a secondary acute phase reaction that correlates with the magnitude of the myocardial damage. C-reactive protein (CRP) is an acute phase protein that is synthesized by, and released from, the liver in response to circulating interleukin 6 (IL-6). CRP is an unspecific, but very sensitive, marker of infection, tissue damage, and inflammation, and is associated with an impaired prognosis.[19] Its plasma half-life is short (approximately 19 h) and identical under all circumstances.

The increased inflammatory activity in patients with non–ST-segment-elevation ACS may also, at least partly, reflect an acute phase reaction resulting from myocardial necrosis.[19] In unstable coronary artery disease there is also evidence of widespread inflammation in the coronary arteries, but the actual source of inflammatory mediators remains unknown.[20]

In the FRISC II trial, CRP was shown to provide a strong independent prediction of mortality on long-term (median follow-up on mortality 37 months). In the larger GUSTO-IV trial, CRP analyses obtained at baseline were available for 7108 (91.1%) patients.[10] The rate of the primary combined end point, death or MI, at 30 days significantly increased with increasing CRP quartiles: 7.1%, 7.3%, 8.1%, 10.5% ($P=0.001$). This was due to increased mortality, which had already been noted at 48 h *(Figure 2A, page 156).* At 30 days, mortality increased from 2% in the first quartile to 6.3% in the fourth quartile. However, there was no relationship between the rate of MI and the CRP quartiles at any time-point *(Figure 2B, page 156).* In accordance with previous findings, increased CRP levels during the acute stage of ACS were related to increased mortality in a multiple logistic regression analysis.[21-23] No previous study on inflammatory markers in ACS has included a sufficient number of patients to enable the end points of death and MI to be analyzed separately. In contrast to the well-established relationship between CRP elevation and subsequent coronary events in the chronic phase of atherosclerotic disease, CRP is related to mortality, but not MI, in the acute phase of non–ST-segment elevation ACS.[24] How can this be explained? In the acute phase of ACS, CRP levels are transiently elevated, largely due to an acute phase reaction.[25] Some ACS patients might have an increased hyperresponsiveness of the inflammatory system, which might exaggerate the acute phase reaction and increase the reaction of the immune system.[26] Such a mechanism is supported by the observations of colocalization of CRP and activated complement in infarcted myocardium.[27] CRP may itself contribute to inflammation by activation of complement, which in turn may mediate myocardial damage, induce arrhyth-

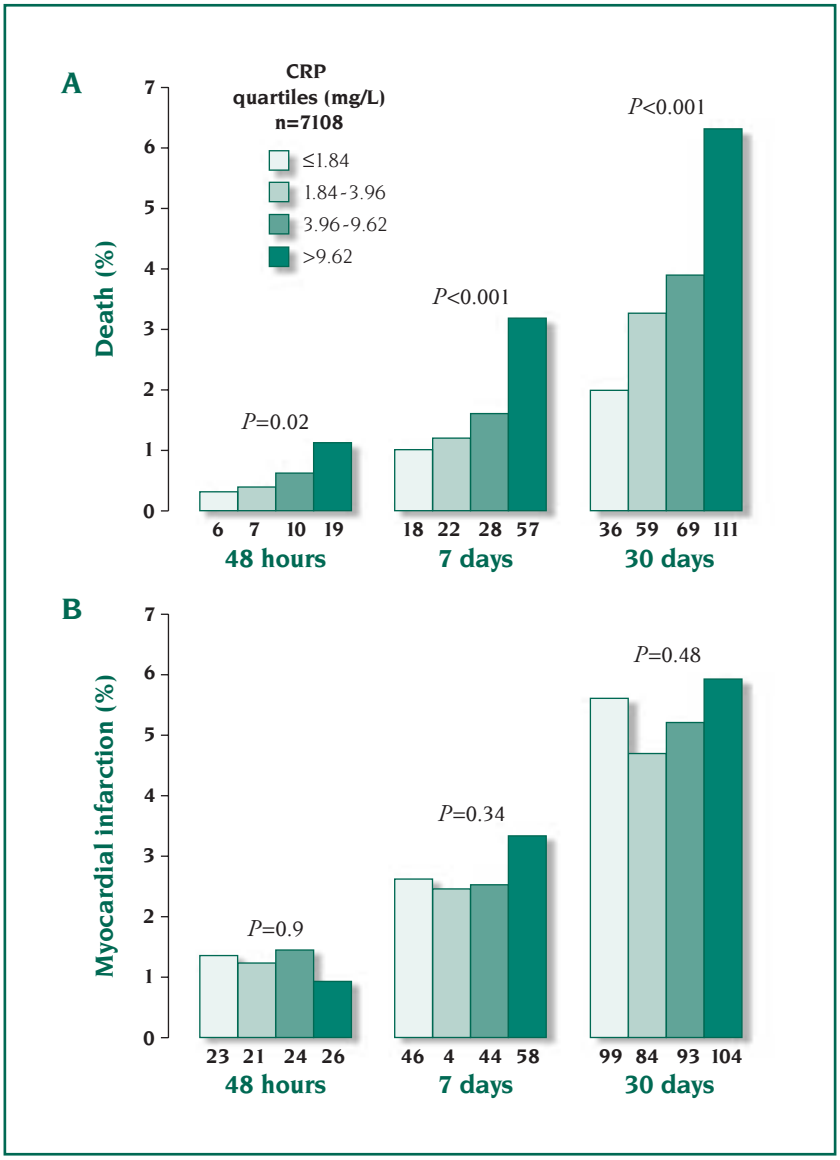

***Figure 2.** Rate of: **(A)** death and **(B)** myocardial infarction, at 48 h, 7 days, and 30 days according to quartiles of C-reactive protein (CRP). The number of patients who experienced events is given under the bars.*

mias, and provoke contractile dysfunction.[27] This is in accordance with the relationship between CRP level and the occurrence of cardiac rupture, left-ventricular aneurysm formation, and mortality after acute MI.[28] Thus, the CRP elevation observed in ACS might indicate a different process from the low-grade CRP elevation that is associated with subsequent coronary events in healthy individuals[24] and in the chronic phase of atherosclerosis after MI.[29] In ACS, as well as in chronic atherosclerotic disease, there is a long-lasting elevation in fibrinogen levels that might indicate that an underlying chronic low-grade inflammatory condition is associated with a raised risk of later MI.[25]

RENAL DYSFUNCTION

Renal insufficiency is associated with a poorer prognosis in a wide spectrum of patients with cardiovascular disease, including ACS.[30] Part of the increased risk associated with reduced renal function is attributable to a large number of coexisting conditions such as greater age, diabetes, and hypertension. However, renal failure itself has consistently been shown to be associated with a worse prognosis.[31] It has been proposed that renal dysfunction is a measure of the extent of vascular damage caused by a variety of insults to the endothelium.[32] In many previous studies, patients with renal insufficiency have been excluded. Hence, the prognostic value of cardiac troponins and brain natriuretic peptide (BNP) in patients with and without renal dysfunction presenting with suspected ACS is an important issue.

In GUSTO-IV, creatinine levels were analyzed and creatinine clearance was calculated for 7703 patients (98.7%). The median level was 66 mL/min with interquartile limits of 51 and 84 mL/min. Mortality increased with increasing quartiles of reduced creatinine clearance. Thus, at 1 year, mortality was 17.7% (n=347), 16.2% (n=162), 4.8% (n=93), and 2.2% (n=43) for the respective quartiles (P<0.001). Also, the incidence of MI at 30-day follow-up increased with increasing quartiles. In a multiple logistic regression analysis that corrected for a large number of risk indicators, creatinine clearance <51 mL/min (first quartile limit) was an independent predictor of the 30-day incidence of MI as well as of 1-year mortality.

Also shown in GUSTO-IV, the prognostic value of TnT was not decreased in patients with impaired renal function.[33] There were 126 (6%) events in patients with abnormal TnT, 140 (8%) events in patients with abnormal creatinine clearance, and 311 (15%) in subjects with both abnormal TnT and creatinine clear-

ance. The highest risk of death or MI occurred in patients with both abnormal TnT and abnormal creatinine clearance, suggesting that abnormal TnT is predictive of outcome in patients with abnormal creatinine clearance. Even after adjusting for multiple significant variables, patients with both abnormal TnT and abnormal creatinine clearance had the highest risk of death or MI. The risk of all-cause mortality among patients with both abnormal TnT and abnormal creatinine clearance was strikingly increased.

Patients with renal dysfunction are at high risk, partly because of the high prevalence of multiple risk factors. In the GUSTO-IV population, a reduced creatinine clearance was significantly correlated with a large number of predictors of a worse outcome, such as diabetes, hypertension, age, heart failure, previous MI,[33] and elevation of CRP, TnT, and NT-proBNP.[31] Still, a creatinine clearance below the first quartile (51 mL/min) was independently associated with mortality as well as subsequent MI in multivariate analyses.[34] Hyperlipidemia (including elevated Lp(a) lipoprotein levels), the insulin resistance syndrome, and hyperhomocysteinemia are factors that contribute to coronary artery disease in patients with renal dysfunction. The chronic anemia and volume overload associated with severe renal dysfunction may be important contributors to an increased vascular stiffness, the development of heart failure, and subsequent mortality. Other specific cardiovascular risk factors that contribute to the vasculopathy induced by the renal disease include secondary hyperparathyroidism, increased sympathetic-nerve activity caused by afferent renal reflexes, elevated levels of oxidized low-density lipoprotein, endothelial dysfunction, and diminished vascular nitric oxide production. Moreover, a reduced secretion of erythropoietin and insulin-like growth factor in patients with renal dysfunction may also specifically contribute to an increased risk of thrombotic cardiovascular events by an inhibition of vascular repair.[35]

MYOCARDIAL DYSFUNCTION

BNP is a neurohormone that is synthesized and released from the cardiac ventricles in response to increased wall tension.[36] By affecting the nephrons, BNP and other natriuretic peptides are involved in the tight regulation of extracellular volume. The plasma level of BNP is increased in patients with heart failure and increases in proportion to the degree of left ventricular dysfunction. BNP levels also increase after MI and in unstable angina pectoris. BNP is produced as a prohormone, proBNP, which is enzymatically cleaved to produce BNP and the amino-terminal portion of the prohormone, NT-proBNP. In ACS, BNP, and NT-proBNP provide independent prognostic information.[37]

NT-proBNP levels were determined for serum samples obtained at randomization from 6809 (87.3%) of the patients in the GUSTO-IV trial with a median time from the onset of the qualifying episode of ischemic chest pain to randomization was 9.5 h (range 5.0 to 16.6 h).[31] The NT-proBNP levels ranged from 5.3 to 35 000 ng/L with a median level of 669 ng/L (interquartile range 237 to 1869 ng/L).

Higher NT-proBNP levels were independently positively associated with age, female sex, diabetes mellitus, angina pectoris, hypertension, previous MI, heart failure, heart rate, and ST-segment depression, but negatively with body weight. NT-proBNP levels were also associated with time from symptom onset, the magnitude of myocardial necrosis, ie, troponin elevation, and with renal dysfunction and inflammatory activity, as reflected by levels of creatinine and CRP, respectively. Part of the relationship with levels of NT-proBNP and low body-weight and renal dysfunction[38] might be explained by an increased sensitivity to volume overload, as BNP levels have been shown to increase in response to volume overload and raised intracardiac pressure, irrespective of the cause. The study demonstrated that levels of NT-proBNP were independently related to clinical factors that indicate any kind of cardiovascular damage or dysfunction, supporting the hypothesis that elevated BNP (or NT-proBNP) is a general indicator of reduced cardiac performance rather than a specific indicator of systolic dysfunction. Moreover, ongoing myocardial damage (ie, minimal troponin elevation), time since start of myocardial ischemia, and damage and the inflammatory response (ie, CRP elevation) were related to the magnitude of elevation of NT-proBNP, further supporting the concept of BNP as a sensitive and rapid marker of reduced cardiac performance.

Mortality was increased in patients in increasing quartiles of NT-proBNP *(Figure 3, page 158).* At 48 h after randomization, the difference in mortality between increasing quartiles was already statistically significant: from 0.2% (n=3), to 1.4% (n=23; P=0.001). The separation of the curves continued throughout the first year after the index event (P<0.001, log rank). Thus, at 1-year follow-up the corresponding mortality rates were: 1.8% (n=31), 3.9% (n=66), 7.7% (n=131), and 19.2% (n=327). At 1 year, mortality increased exponentially across the entire spectrum of NT-proBNP lev-

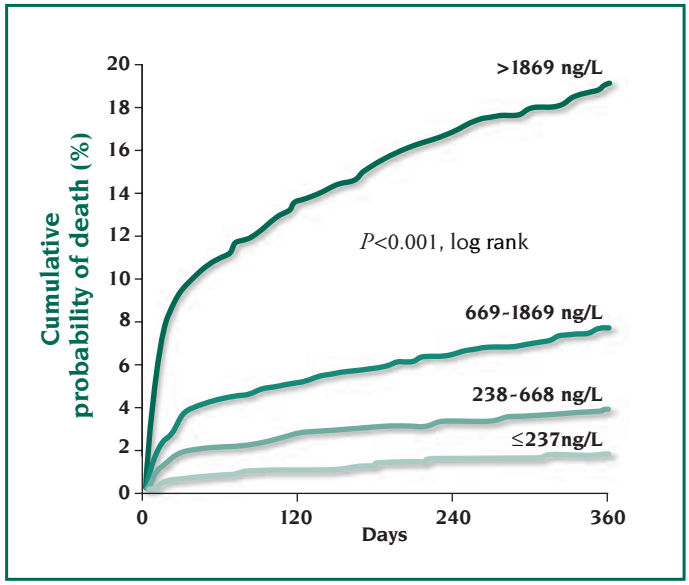

***Figure 3.** Kaplan-Meier curves for the cumulative probability of death during 1 year for patient strata based on quartiles of NT-proBNP (N-terminal pro–brain natriuretic protein).*

els, with a mortality of 0.4% (n=3) in the lowest decile (<98 ng/L) and 27.1% (n=185) in the highest decile (>4634 ng/L) *(Figure 4)*. In a multivariate logistic regression analysis, after adjusting for a large number of predictors of long-term mortality, increasing quartiles of NT-proBNP still independently contributed to the prediction of 1-year mortality *(Figure 5)*.

It has been shown that elevated BNP levels and NT-proBNP levels obtained after the acute phase (median time 40 to 72 h after symptom onset) independently predict mortality in patients with a broad range of ACS.[37] In the GUSTO-IV trial we extended these results to include a considerably larger population of non–ST-segment elevation ACS, obtaining data on NT-proBNP on admission (at a median 9.5 h after symptom onset) in accordance with a previous study from our group in an unselected chest pain population.[39] We were subsequently able to demonstrate that NT-proBNP predicted 1-year mortality in patients with blood samples obtained at <5.0 h (first quartile) as well as >16.6 h (fourth quartile) after symptom onset. The present study also demonstrated that in an ACS population, any elevation of NT-proBNP above the 97.5th percentile (290 ng/L) in an age- and sex-matched population seemed to be associated with an increased risk of death after the index event. Despite the fact that the level of NT-proBNP was independently related to several risk factors, elevated NT-proBNP was the strongest independent indicator of mortality in the multivariate analysis.

In contrast to ST-segment depression and troponin elevation at baseline, and in accordance with previous studies, the risk of subsequent MI at 30-days follow-up was not independently predicted by increasing levels of NT-proBNP. This may be explained by the fact that BNP is a regulatory myocardial hormone that is neither involved in the processes related to the rupture of coronary plaques nor in the formation of coronary thrombi. In contrast, elevated BNP levels have been shown to predict sudden death in patients with heart failure. Thus, the natriuretic peptides released from ventricular myocytes in response to increased wall tension due to ischemia or volume overload might indicate a propensity to develop ventricular arrhythmias, ventricular rupture, or terminal heart failure, rather than MI.

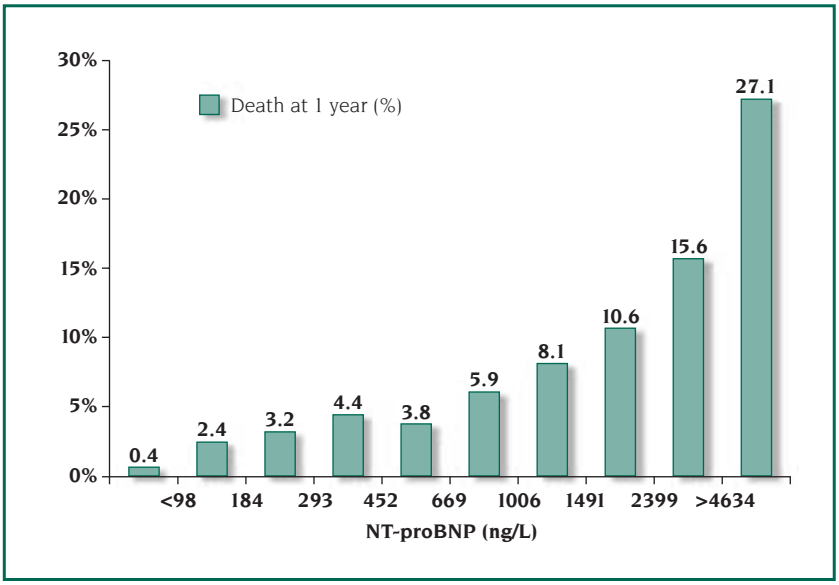

***Figure 4.** Mortality at 1-year follow-up in patients stratified according to their NT-proBNP (N-terminal pro–brain natriuretic protein) levels. The number of deaths in each decile is given at the bottom of the bars.*

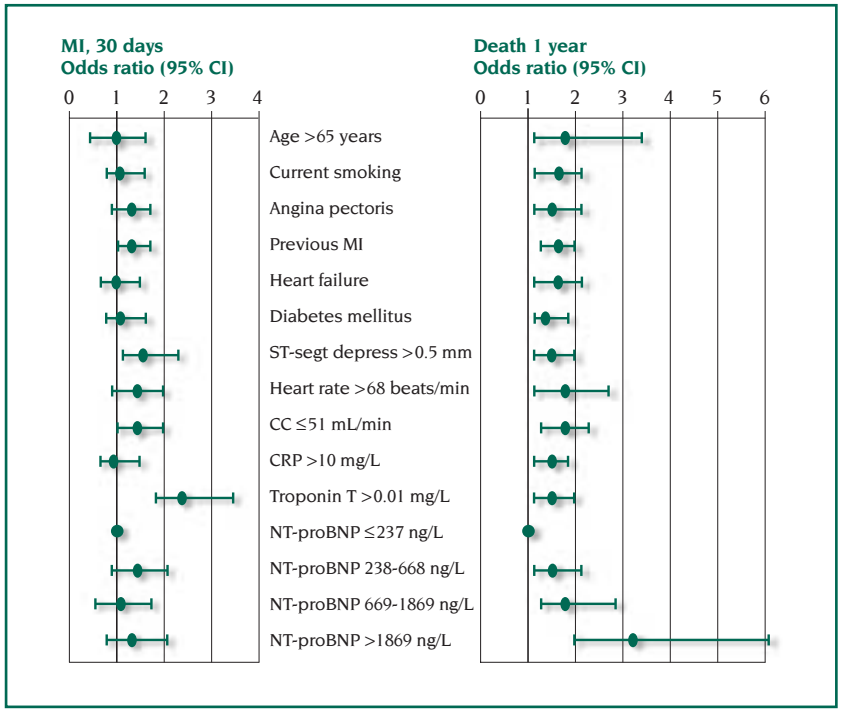

***Figure 5.** Multiple logistic regression analyses for the prediction of myocardial infarction at 30 days and death at 1-year follow-up.*

***Abbreviations:** CC, creatine clearance; CI, confidence interval; CRP, C-reactive protein; MI, myocardial infarction; NT-proBNP, N-terminal pro–brain natriuretic protein.*

CLINICAL CHARACTERISTICS IN RELATION TO BIOCHEMICAL MARKERS

Individual markers

In addition to ST-segment depression on the admission ECG and the aforementioned biomarkers: TnT >0.01 mg/L, CRP >10 mg/L, creatinine clearance <51 mL/min, NT-proBNP >237 ng/L, several clinical characteristics and findings on physical examination were independently related to an increased risk of mortality. The following were also independent predictors of 1-year mortality: heart rate >68 beats/min, age >65 years, male gender, smoking, previous angina, MI, hypertension, present heart failure, and diabetes. From the results of the multivariate analysis, prediction of subsequent MI seems more difficult. Among the independent factors, TnT appears to be an outstanding biochemical factor. ST-segment depression, reduced renal function, and previous MI were also independent predictors of new MI.

Combinations of markers

As TnT, CRP, NT-proBNP, and creatinine clearance were all independent predictors of 1-year mortality, combinations of these markers were evaluated. A very low mortality rate was observed in patients with NT-proBNP levels in the bottom quartile in combination with either creatinine clearance in the top quartile (0.3%) or TnT, CRP, or heart rate in the bottom quartile (1.6%, 1.6%, and 1.8 %, respectively) *(Figures 6 A, B, C, D, page 160).* The highest 1-year mortality, 25.7%, was found in patients with levels of NT-proBNP in the top quartile and creatinine clearance in the bottom quartile. A similar high mortality was found in patients with NT-proBNP in combination with TnT or CRP levels in the top quartiles, 22.3% or 23.4%, respectively. With troponin elevation, the 30-day event rate and 1-year mortality were increased across the entire spectrum of creatinine clearance.[33] Furthermore, the difference became more pronounced as renal impairment worsened. Similarly, elevation of NT-proBNP increased 1-year mortality at every stage of reduced creatinine clearance *(Figure 6 A).* Accordingly, the combination of several of these markers allowed an even better stratification of the future risk of fatal events. The combination of quartiles of increasing NT-proBNP levels and quartiles of decreasing creatinine clearance rates provided the best prediction of long-term mortality. The combination of quartiles of NT-proBNP with quartiles of either CRP or TnT provided a similar prediction of mortality. Interestingly, elevated levels of TnT seemed to contribute to an increased mortality only in patients with NT-proBNP levels in the fourth quartile. Thus, ACS patients without myocardial dysfunction seem to tolerate even moderately large MIs without a lethal outcome. On the other hand, ACS patients with renal dysfunction, myocardial damage, or increased inflammatory activity in addition to any reduction in cardiac performance (as indicated by the release of NT-proBNP) have a high risk of fatal complications associated with their heart disease.

DISCUSSION AND CLINICAL IMPLICATIONS

Which biomarkers or clinical factors should be recommended for the early evaluation of patients with ACS? For the prediction of MI, troponin seems to be the biomarker with the strongest relationship, but reduced creatinine clearance is also independently associated with subsequent MI. However, for prediction

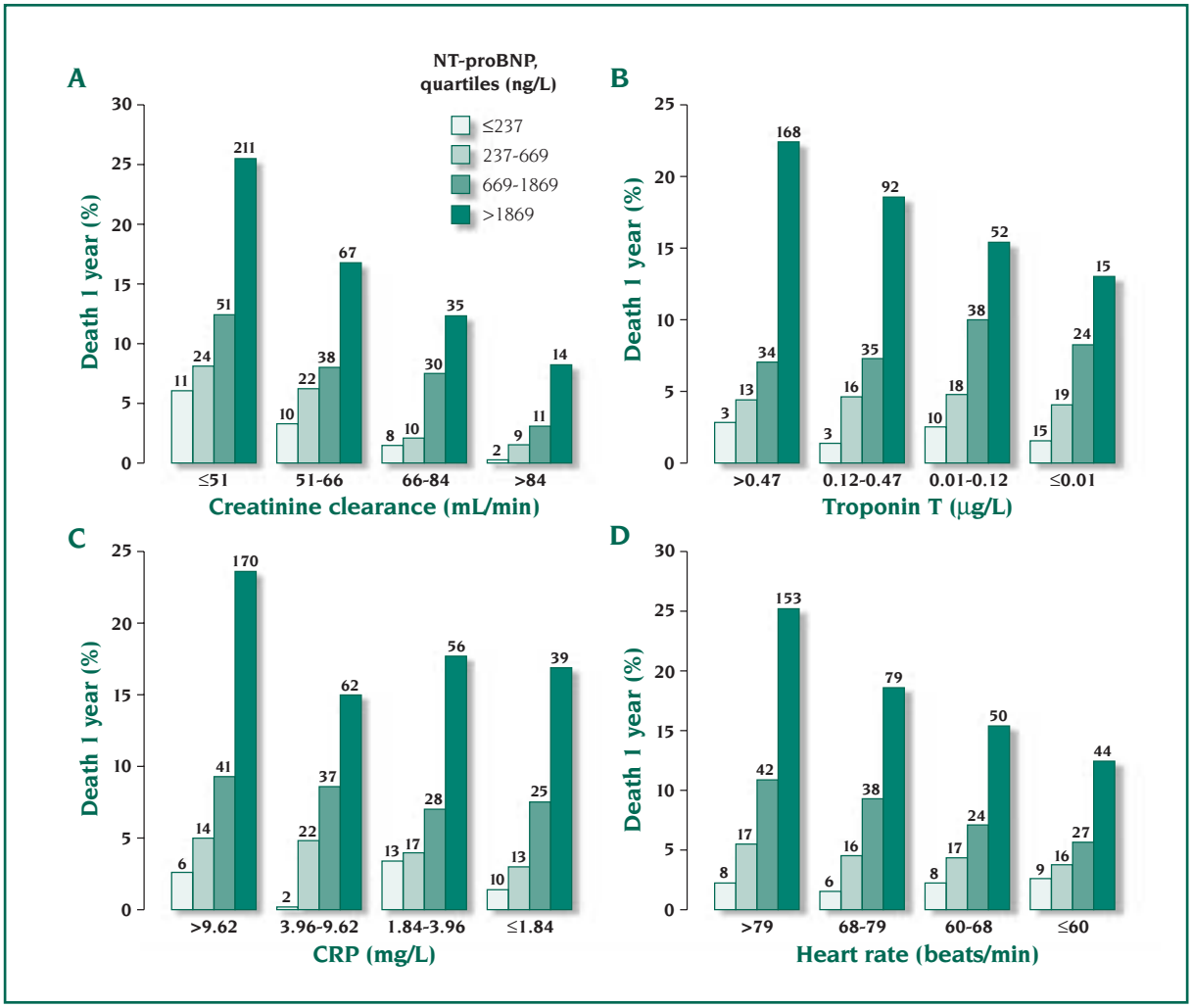

***Figure 6.** Mortality at 1-year follow-up among strata of patients based on quartiles of NT-proBNP (N-terminal pro–brain natriuretic protein) and quartiles of: **(A)** creatinine clearance; **(B)** troponin-T; **(C)** C-reactive protein (CRP); **(D)** heart rate. The number of deaths is given at the top of each bar.*

of mortality, several clinical as well as ECG and biochemical markers seem to be useful. On multivariate analysis, NT-proBNP was the strongest biomarker. By virtue of its being an unspecific marker of reduced cardiac performance, NT-proBNP seems to be very useful for the selection of low-risk patients. A level below the 97.5th percentile of a healthy population (290 ng/L) is associated with very low mortality. In fact, it also seems very unlikely that the patient has any significant heart disease at these low levels. Conversely, patients with elevated NT-proBNP levels are at increased risk of a fatal complication, which may merit further investigation and treatment. It has been shown that carvedilol treatment is particularly effective in patients with heart failure and elevated levels of NT-proBNP. However, it remains to be investigated whether patients with high levels of NT-proBNP might derive a particular benefit from angiotensin-converting enzyme inhibition, early coronary interventions, implantable cardioverter-defibrillators, or other therapeutic modalities. Patients with any detectable TnT elevation are at increased risk of death and derive a particular benefit from early coronary intervention, glycoprotein IIb/IIIa inhibition, and extended low-molecular-weight heparin treatment.[5,8] A moderate reduction in creatinine clearance is independently associated with increased mortality and, although not treatable, should be increasingly recognized as a marker. CRP elevation is particularly useful for the prediction of long-term mortality. Statin treatment has been shown to reduce CRP levels among survivors of MI, and is particularly beneficial for patients with CRP elevation, independently of lipid levels. Furthermore, ST-segment depression on admission is

very useful for prediction of mortality and mortality increases dramatically with decreasing levels of the ST-segment. A large number of clinical factors are predictive of mortality. Among them is heart rate on admission, a clinical variable that is immediately available and probably underutilized. A pulse above 70 (median level) versus below 70 in fact increased mortality during the first year after the unstable episode from 3% to 14 % in the GUSTO-IV trial.

CONCLUSIONS

Patients with non–ST-segment elevation ACS have an increased, but variable, risk of subsequent MI and death. With the markedly improved treatment of these patients, better instruments for selecting high-risk and low-risk patients are urgently needed. Different biochemical markers obtained on admission provide different and complementary prognostic information. TnT is the biomarker with the strongest relationship with subsequent MI. Mortality can be predicted using several clinical and biochemical risk indicators, but BNP (or NT-proBNP) seems to be best biomarker for the prediction of fatal complications associated with heart disease. Classic clinical risk-indicators also provide independent prognostic information and should be used for a very early bedside prediction of risk. The utilization of a multimarker strategy in patients with non-ST-segment elevation ACS in addition to clinical risk indicators, provides early and specific prognostic information. This new multimarker paradigm has the potential to improve and individualize risk assessment and clinical decision-making.

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Non–ST-segment elevation acute coronary syndromes: do the benefits of modern antithrombotic treatments outweigh the risk of major bleeding?

Michel E. Bertrand, MD, FRCP, FESC, FACC

Lille Heart Institute – Lille – FRANCE

Iatrogenic major bleeding occurs in 4% of non–ST-segment elevation acute coronary syndromes (NSTE-ACS), causing increased in-hospital mortality. Prevention requires risk stratification based on advanced age, female sex, a history of bleeding, and renal failure (plasma creatinine, creatinine clearance). Particular caution is required in securing vascular access for percutaneous coronary interventions in high-risk patients. Use of the radial approach and of vascular sealing or suturing devices when performing a femoral approach markedly reduce the incidence of complications. Doses of heparin should be significantly reduced when combined with glycoprotein IIb/IIIa receptor inhibitors, and aspirin should be reduced to 75 to 150 mg/day when combined with clopidogrel. Such precautions should largely eliminate major bleeds in NSTE-ACS.

Keywords: acute coronary syndrome; antithrombotic treatment; hemorrhage; percutaneous coronary intervention; glycoprotein IIb/IIIa receptor inhibitor

Address for correspondence:
Prof Michel E. Bertrand, Lille Heart Institute, boulevard du Professeur J. Leclercq, 59067 Lille, France (e-mail: mbcardio@club-internet.fr)

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Over the last 15 years, the initial clinical presentation of coronary atherosclerosis has markedly changed. Acute coronary syndromes (ACS) are now the most frequent clinical presentation of these patients. The EuroHeart Survey[1] conducted in 2000 reported that, in 55% of cases, the baseline ECG showed non–ST-segment elevation changes (ST-segment depression, T-wave inversion, atypical changes, and even a normal tracing). Thus, this clinical condition (non–ST-segment elevation ACS [NSTE-ACS]), which was initially called unstable angina or non–Q-wave myocardial infarction (MI), is very frequent and is related to plaque rupture, subocclusive superimposed thrombosis, and distal embolization. New advances in antithrombotic treatment and revascularization procedures have markedly reduced the risk of major cardiac events (death, large

SELECTED ABBREVIATIONS AND ACRONYMS

ACS	acute coronary syndrome
ACUTE II	Antithrombotic Combination Using Tirofiban and Enoxaparin–II
A-to-Z	Aggrastat to Zocor [trial]
CURE	Clopidogrel in Unstable angina to prevent Recurrent ischemic Events [trial]
ESSENCE	Efficacy Safety Subcutaneous Enoxaparin in Non–Q-wave Coronary Events [study]
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Use of STrategies to Open occluded coronary arteries [trial]
INTERACT	INTegrelin and Enoxaparin Randomized assessment of Acute Coronary syndromes Treatment [trial]
LMWH	low-molecular-weight heparin
MI	myocardial infarction
NSTE-ACS	non–ST-segment elevation acute coronary syndrome
NSTE-MI	non–ST-segment elevation myocardial infarction
SYNERGY	Superior Yield of the New strategy of Enoxaparin, Revascularization and GlYcoprotein IIb/IIIa inhibitors [trial]
TIMI	Thrombolysis In Myocardial Infarction
UFH	unfractionated heparin

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myocardial infarction compromising left ventricular [LV] function). However, today's powerful antithrombotic therapy is accompanied by an increased incidence of hemorrhagic complications.

The aim of this paper is to describe the magnitude of the problem, to identify patients at risk of major bleeding, and suggest an approach to risk stratification.

LIMITATIONS OF STUDIES OF MAJOR BLEEDINGS IN NSTE-ACS

Modern antithrombotic treatments used in NSTE-ACS include direct or indirect antithrombin inhibitors and antiplatelet agents. A number of multicenter, randomized clinical trials have been implemented in this setting, but information concerning bleeding complications is conflicting, due at least to two factors:

- Most of the clinical randomized trials were performed in selected populations: For example, patients at high risk of bleeding complications, like elderly patients, were in most of the cases excluded from these trials.
- The definitions of bleeding complications in these trials differ to a certain extent, even within the same study, which can lead to conflicting interpretations. For example, in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial,[2] there was an excess of major bleeding in the clopidogrel group in comparison with the placebo group (3.7% vs 2.7%; relative risk [RR]=1.38 [95% confidence interval (CI) 1.13-1.67]; *P*=0.001). However, using the Thrombolysis In Myocardial Infarction (TIMI) definition for bleeding *(Table I),* no difference was found between the two groups (RR=0.94 [95% CI: 0.68-1.30]; *P*=0.70). The same observation can be made if one uses the Global Use of STrategies to Open occluded coronary arteries (GUSTO) definition *(Table I)* (RR=1.12 [95% CI 0.81-1.55]; *P*=0.48) in this trial.
- Another example showing the difficulty of comparisons is that some trials define major bleeding as a drop of 3 g/dL of hemoglobin concentration while other studies define it as a drop of 5 g/dL.

Therefore, it is important to consider incidence and predictors of major bleedings in large registries.

INCIDENCE OF MAJOR BLEEDINGS IN NSTE-ACS

Unfractionated heparin and enoxaparin

All patients with NSTE-ACS receive antithrombin treatment consisting of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), in particular, enoxaparin. A meta-analysis of six randomized trials was recently completed (Efficacy Safety Subcutaneous Enoxaparin in Non–Q-wave Coronary Events [ESSENCE], TIMI 11B, Antithrombotic Combination Using Tirofiban and Enoxaparin–II [ACUTE II], INTegrelin and Enoxaparin Randomized assessment of Acute Coronary syndromes Treatment [INTERACT], Aggrastat to Zocor [A-to-Z], Superior Yield of the New strategy of Enoxaparin, Revascularization and GlYcoprotein IIb/IIIa inhibitors [SYNERGY]).[3] This meta-analysis allowed comparison of UHF and enoxaparin in a total cohort of 21 946 patients. The rate of transfusions within a period of 7 days was 7.2% in the enoxaparin group and 7.5% in the UHF group. As prior antithrombotic treatment before admission was liable to influence the results, when patients with prior antithrombotic treatment were excluded, the transfusion rate was 5.0% and 5.5%, respectively. For major bleedings (keeping the definition given in each individual trial), the rate was 4.7% in the enoxaparin group and 4.5% in the UFH group with all patients included, and 3.8% and 3.4% excluding patients having received prior antithrombotic therapy. Thus, on the basis of the findings from this meta-analysis, it was impossible to establish the predictive factors of bleeding.

GpIIb/IIIA receptor inhibitors

Another meta-analysis, carried out by Eric Boersma et al,[4] included nine randomized clinical trials comparing

- **TIMI** (Thrombolysis In Myocardial Infarction) **definitions:**

  Major bleeding: Overt clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) associated with a drop in hemoglobin of greater than 5 g/dL (0.5 g/L) or in hematocrit of greater than 15% (absolute)

  Minor bleeding: Overt clinical bleeding associated with a fall in hemoglobin of 3 to less than or equal to 5 g/dL (0.5 g/L) or in hematocrit of 9% to less than or equal to 15% (absolute)

- **GUSTO** (Global Use of STrategies to Open occluded coronary arteries) **definitions:**

  Severe bleeding: intracranial hemorrhage or bleeding inducing hemodynamic compromise

  Moderate bleeding: requiring transfusion without hemodynamic compromise

  Mild bleeding: without transfusion or hemodynamic compromise

Table I. *Definitions of bleeding.*

different glycoprotein (Gp) IIb/IIIa receptor inhibitors (tirofiban, eptifibatide, lamifiban, abciximab) vs placebo in patients with acute coronary syndromes. Each group received aspirin and heparin. In other words, the comparison was done between single vs dual antiplatelet treatment (GpIIb/IIIa + aspirin vs aspirin alone). The rate of major bleeding was 2.4% with dual antiplatelet treatment vs 1.4% with aspirin alone (odds ratio [OR]: 1.62 [95% CI: 1.36-1.94]; $P<0.0001$). Intracranial hemorrhage was very rare: 0.09% vs 0.06%.

Thienopyridines

The CURE trial[2] was conducted in a large group (n=12 562) of patients with NSTE-ACS. This trial compared clopidogrel (loading dose of 300 mg followed by 75 mg/d) combined with aspirin, with aspirin alone. It was found that the rate of major bleeding was 3.7% with dual antiplatelet treatment vs 2.7% with aspirin alone. It was also shown that the rate of bleeding complications was markedly increased when high doses of aspirin (>200 mg) were used.[5]

Overall, therefore, the rate of major bleedings in several randomized trials of patients with NSTE-ACS is within the range of 2.4% to 4.7%. The most common sites of bleeding are gastrointestinal (31% to36%), at the arterial puncture site (15% to 25%), and retroperitoneal (3.5% to 6%).

PREDICTORS OF BLEEDING COMPLICATIONS

Most of these trials failed to address the predictors of serious bleedings. The Global Registry of Acute Coronary Events (GRACE) registry[6] is unique in that it took that issue into account. This registry enrolled 24 045 patients between April 1999 and September 2002 with bleeding status identified. The data came from 94 centers in 14 countries worldwide. Major bleedings were defined as life-threatening bleeding requiring transfusions of ≥2 units of packed red cells, or resulting in an absolute decrease in hematocrit of ≥10%, or causing hemorrhagic/subdural hematoma. Here again, the lack of standardized definitions should be pointed out.

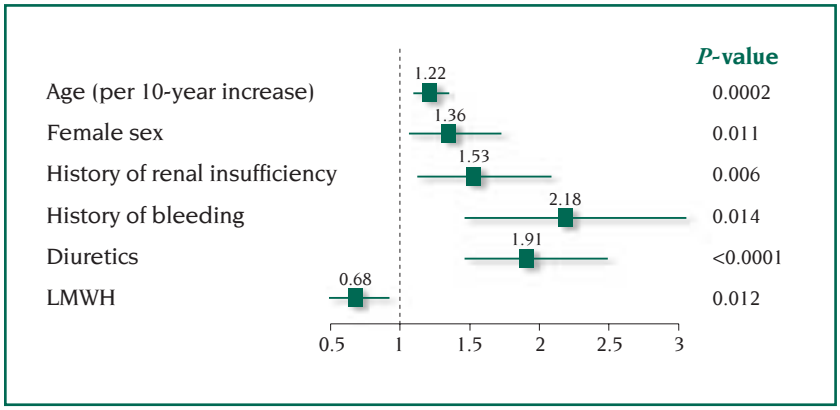

Figure 1. *Multivariate model for major bleeding in NSTE-MI.*

Abbreviations: *LMWH, low-molecular-weight heparin; NSTE-MI, non–ST-segment elevation myocardial infarction.*

Adapted from reference 6: *Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE).* Eur Heart J. *2003;24:1815-1823. Copyright © 2003, Oxford Journals.*

A total of 933 (3.9%) patients experienced major bleeding during hospitalization. This complication was more frequent in non–ST-segment elevation myocardial infarction (NSTE-MI) (4.7%) than in unstable angina patients (2.3%). Patients who had these complications were significantly older (71.1 years vs 66.2 years), females 5% vs 3.3% in males, with lower body mass index (26.2 kg/m^2 vs 26.9 kg/m^2), more peripheral vessel disease (5.5% vs 3.7%), more renal insufficiency (6.5% vs 3.6%), and more frequent history of prior bleeding (11.5% vs 3.8%) when compared with patients without major bleedings. When considering therapeutic interventions, diuretics, vasopressors, GpIIB/IIIa receptor inhibitors, and UHF were associated with significantly more major bleedings. In contrast, administration of LMWH was associated with a lower risk of major bleeding.

After correcting for the influence of other variables, the best predictors of major bleeding were: advanced age; female sex; prior history of bleeding; and renal insufficiency. Among treatments, the pharmacological interventions that were associated with major bleedings after control of variables were: diuretics; inotropic drugs; and GpIIb/IIIa receptor inhibitors. Catheterization and percutaneous coronary intervention were also associated with increased risk of bleeding.

The multivariate regression models of factors associated with high risk of major bleeding are shown in *Figure 1, and Figure 2 (page 166)* for patients with NSTE-MI and unstable angina.

The impact of major bleeding on in-hospital mortality rate is striking: patients experiencing major bleedings have a higher in-hospital mortality rate. This was observed in NSTE-MI and unstable angina

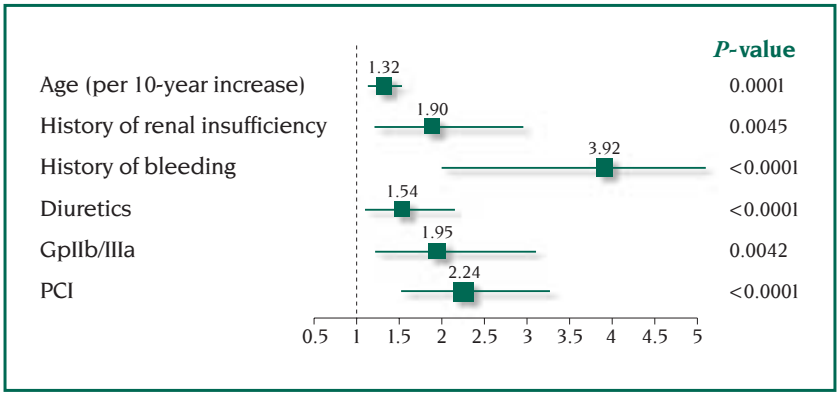

***Figure 2.** Multivariate model for major bleeding in unstable angina.*

***Abbreviations:** GpIIb/IIIa, glycoprotein IIb/IIIa receptor; PCI, percutaneous coronary intervention.*
***Adapted from reference 6:** Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE).* Eur Heart J. *2003;24:1815-1823. Copyright © 2003, Oxford Journals.*

patients. Even after adjustment for comorbidities, major bleeding is strongly associated with a higher in-hospital mortality (OR= 1.64 [95% CI: 1.18-2.28]).

RISK STRATIFICATION

The European Society of Cardiology (ESC) recommendations concerning the management of NSTE-ACS have emphasized the need for risk stratification. Thus, we have to consider the acute risk, which is the thrombotic risk (risk of death and large MI in the acute phase) and the long-term risk. The acute risk includes patients who have recurrent chest pain or ischemia, ST-segment depression or elevated troponins, intracoronary thrombus, and all diabetics. These patients are treated with three antiplatelet drugs (aspirin + clopidogrel + infusion of GpIIb/IIIa receptor inhibitor) associated with enoxaparin and an invasive strategy (coronary angiography within the next 48 h) is indicated. This highly aggressive antithrombotic treatment is necessary, owing to the risk of in-hospital death and infarction, but it induces a risk of serious bleedings. Thus, in patients with NSTE-ACS, advanced age, female sex, history of prior bleeding, are predictive of bleeding and hence should be included in the list of factors denoting high-risk in these patients. Furthermore, the highly aggressive antithrombotic management should perhaps be tempered in these particular groups of patients. In this context, it remains clearly difficult to balance the thrombotic risk against the bleeding risk.

In addition, some of the major bleeding predictors overlap with the markers of long-term risk in NSTE-ACS. This is the case for advanced age, female gender, and renal insufficiency, which are important components of the long-term risk markers such as history of MI, history of coronary artery bypass grafting (CABG), all biological markers (C-reactive protein, interleukin 6, brain natriuretic peptide, soluble CD-40 ligand, etc), and coronary artery disease extension, LV dysfunction, and peripheral vessel disease.

CONCLUSIONS

Major bleedings are relatively frequent in patients presenting with non–ST-segment elevation acute coronary syndromes (≈4%). These events are associated with a higher rate of in-hospital mortality. Risk stratification to identify patients at higher risk of major bleedings is relatively simple. Elderly patients, female sex, particularly women with a low body mass index, prior history of bleeding, and renal insufficiency are predictive of a high risk of major bleeding. Thus, simple baseline characteristics coupled with simple biological assays (creatinine level, calculated creatinine clearance) are able to predict bleeding complications. Patients undergoing percutaneous coronary interventions need special precautions with regard to vascular access. Use of the radial approach[7] even in octogenarians,[8] or of vascular sealing or suturing devices when a femoral approach is performed, should markedly reduce the incidence of these complications.

In addition, when combining GpIIb/IIIa receptor inhibitors with heparin—particularly unfractionated heparin—it is recommended to significantly reduce the doses of heparin. Similarly, when clopidogrel is associated with aspirin as demonstrated in the CURE trial, it is necessary to reduce the dose of aspirin, which should be between 75 and 150 mg/day.

Even though major cardiac adverse events remain a matter of concern in patients presenting with NSTE-ACS, clinicians should now pay special attention to major bleedings, which contribute to the immediate outcome of these patients.

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Should all patients presenting with ST-segment elevation myocardial infarction undergo primary percutaneous coronary intervention?

Alberto Menozzi, MD; Luigi Vignali, MD; Emilia Solinas, MD; Diego Ardissino, MD

Division of Cardiology - Maggiore Hospital - University of Parma - Parma - ITALY

All patients with ongoing ST-segment elevation myocardial infarction (STE-MI) should undergo prompt reperfusion to salvage ischemic myocardium and improve survival. Primary percutaneous coronary intervention (PCI) is considered the treatment of choice with many advantages over fibrinolysis. However, it is sometimes, if it can be performed adequately and in a timely fashion, not available as quickly as necessary to achieve a better result than fibrinolysis. In patients with early presentation (within 2 to 3 hours from symptom onset), fibrinolysis may be a reasonable alternative to PCI, as in such cases the superiority of an invasive strategy is less evident. Fibrinolysis should be preferred in patients without contraindications, in whom the delay of primary PCI exceeds 90 minutes. The best strategy for STE-MI should be evaluated in each patient in relation to clinical and logistic parameters.

Keywords: fibrinolysis; myocardial infarction; percutaneous coronary intervention; acute coronary syndrome; STE-MI; time-to-balloon

Address for correspondence:
Diego Ardissino, MD, Division of Cardiology, Maggiore Hospital, University of Parma, Via Gramsci 14, 43100, Parma, Italy
(e-mail: ardis001@planet.it)

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Patients with acute evolving myocardial infarction presenting with electrocardiographic ST-segment elevation (STE-MI), or with new-onset left bundle-branch block, are highly likely to have a coronary thrombus occluding the infarct-related artery.[1] Given its proven ability to improve survival dramatically,[2,3] all such patients are candidates for early reperfusion therapy in order to restore flow in the occluded coronary artery, and should therefore be rapidly evaluated upon first medical contact in order to ensure the prompt implementation of the best reperfusion strategy.[3] Nevertheless, despite the strong evidence in its favor, reperfusion therapy is widely underused and often not administered soon after presentation.[4]

PCI AND FIBRINOLYSIS: CLINICAL CONSIDERATIONS

Optimal reperfusion should lead to the early, complete, and sustained patency of the infarct-related artery, and thus provide efficacious myocardial reperfusion. The timing of flow restoration after symptom onset is critically important because the sooner it is achieved, the greater the chance of salvaging jeopardized myocardium[5]: reperfusion within 30 minutes of a coronary occlusion can abort an infarction and, within 90 minutes, can salvage approximately half of the myocardium at risk; however, myocardial salvage is generally minimal after 4 to 6 hours of ischemia.[6] The time from symptom onset to reperfusion is therefore a key determinant of infarct size and subsequent short-term and long-term outcome.[7] Accordingly, the international guidelines stress the fact that reperfusion must be implemented promptly by recommending a door-to-needle time of less than 30 minutes before starting fibrinolysis, and a door-to-balloon time of less than 90 minutes before primary percutaneous coronary intervention (PCI).[2,3]

It has been clearly shown that fibrinolytic therapy improves survival in STE-MI patients without any contraindications when it is administered within 12 hours of symptom onset: approximately 30 lives saved for every 1000 patients treated within the first 6 hours, and with an overall 21% reduction in relative mortality.[8] As the mortality benefit of fibrinolytic therapy directly de-

SELECTED ABBREVIATIONS AND ACRONYMS

PCI	percutaneous coronary intervention
STE-MI	ST-segment elevation myocardial infarction

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pends on the time from symptom onset to the start of treatment, its efficacy in terms of survival is maximized during the first 2 to 3 hours,[6] after which the benefit decreases by approximately 1.6 lives per 1000 patients for each 1-hour delay.[3] Mortality in patients treated within the first 2 hours is half that observed in patients treated later, thus leading to the concept of the "golden hour", an early time-window during which the benefit of fibrinolysis is greatest.[6] The benefit of fibrinolysis is extremely time-sensitive not only because of the temporal dependency of myocardial salvage, but also because its efficacy decreases over time as a consequence of the increased resistance of an aging thrombus to lysis.

The limitations of fibrinolytic therapy include its relative and absolute contraindications, as well as an increased risk of bleeding and stroke: intracranial hemorrhages are observed in 0.6% to 1.4% of cases.[8] Furthermore, complete Thrombolysis in Myocardial Infarction–3 (TIMI-3) flow in the infarct-related artery is restored in fewer than half of the patients and, consequently, recurrent ischemia and reocclusion are frequent.

PCI is a very effective means of restoring perfusion in STE-MI patients and, in this setting, is called "primary." Unlike fibrinolysis, primary PCI is suitable for the large majority of such patients and, importantly, has been reported to achieve TIMI-3 flow in the infarct-related artery in more than 90% of cases in a manner that is unrelated to the time from symptom onset. Arterial revascularization after primary PCI is complete and stable, and the rate of reocclusion is low (less than 5% with stenting). However, primary PCI requires a skilled and experienced team, including an interventional cardiologist and supporting staff, working in an appropriate laboratory environment and in a well-defined organizational setting. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that the minimum expertise requirements are at least 200 procedures for the laboratory (of which 36 primary), and 75 for the operator.[3] For these reasons, only a few of the centers admitting STE-MI patients have an on-site catheterization laboratory for emergency procedures operating 24 hours a day, whereas almost all centers are capable of administering fibrinolytic therapy.

Primary PCI and fibrinolysis have been compared in a number of randomized clinical trials, a comprehensive meta-analysis of which has demonstrated the advantage of PCI in terms of short-term mortality (5.0% vs 7.0%; relative risk [RR] 0.70, 95% confidence interval [CI] 0.58-0.85) and nonfatal reinfarctions (3% vs 7%; RR 0.35, 95% CI 0.27-0.45), respectively, corresponding to two and four events avoided per 100 treated patients.[9] A reduction in hemorrhagic stroke (0.05% vs 0.1%; RR 0.5, 95% CI 0.006-0.35) was also reported, but with an increased risk of overall major bleeding (7.0% vs 5.0%; RR 1.3, 95% CI 1.02-1.65) prevalently driven by access-site complications.

Another important factor is that higher-risk subgroups, such as patients with anterior STE-MI or in Killip class >1, receive the greatest survival benefit from an invasive strategy.[10,11] Moreover, primary PCI leads to an absolute 9% reduction in 30-day mortality in patients with cardiogenic shock[12]; and to a dramatic reduction in 1-year death, reinfarction, or stroke in patients aged more than 75 years (13% vs 44%; RR 5.2, 95% CI 1.7-18.1).[13]

An invasive strategy also offers further advantages in terms of early prognostic stratification by means of the immediate assessment of coronary anatomy and hemodynamic data, thus allowing triage to primary PCI, surgery, or medical therapy and a subsequent earlier hospital discharge in comparison with fibrinolytic therapy.[14] Finally, patients in whom a diagnosis of STE-MI is in doubt can take advantage of an invasive strategy in order to clarify the situation without the potential harm of fibrinolysis.

However, primary PCI is not widely used because of its main and evident limitation: it is unavailable or cannot be performed quickly in most centers.

There is a general consensus that, when readily available in centers with the requisite facilities and documented expertise, primary PCI is the preferred approach to reperfusion for all STE-MI patients. However, "readily available" is a somewhat uncertain definition; although the mean delay between PCI and fibrinolysis in randomized studies has been only approximately 40 minutes,[7] and evidence-based data suggest that primary PCI remains superior to fibrinolysis when the added delay is less than 60 to 90 minutes.[15] If the difference between time-to-balloon and time-to-needle is longer than 90 minutes, it is likely that the advantage of primary PCI is totally lost as a result of the prolonged duration of ischemia. Every minute delay may count in terms of survival benefit, as there seems to be a continuous relationship between time-to-balloon and 1-year mortality.[7]

It is not known whether this close relationship only reflects the importance of the time delay or may also be considered an indicator of

the entire process leading to primary PCI, and thus reflect the overall efficiency of the management of STE-MI at a certain site; in any case, it remains the most important performance indicator.

In line with the above data, the international guidelines state that, provided it is immediately available and performed within 90 minutes of the first medical contact, primary PCI should be considered the treatment of choice for all patients presenting with STE-MI within 12 hours of symptom onset.[2,3]

Consequently, a program for the prompt activation of the primary PCI team based on strict performance criteria is needed in order to ensure the efficient implementation of invasive reperfusion (not least because it is often performed outside working hours), and the use of an emergency procedure to treat actively symptomatic and sometimes hemodynamically unstable patients requires skilled and experienced staff. Otherwise, a routine policy of primary PCI without a strict organizational protocol would probably lead to unacceptable delays and suboptimal outcomes.

The choice of the best reperfusion strategy for STE-MI patients in everyday clinical practice should be based on the combined evaluation of clinical and logistic parameters, and each center should develop a plan to offer the best possible treatment to each patient on the basis of its own facilities and organization.

In centers with on-site interventional cardiology facilities, a routine primary PCI program should generally be planned as the preferred approach to STE-MI; but not all laboratories can provide around-the-clock prompt primary PCI, and expertise may be a concern in low-volume centers. In hospitals without interventional facilities, the decision as to whether to use fibrinolysis or transfer the patient elsewhere for primary PCI should be carefully weighed by balancing the pros and cons of each strategy, on an individual basis.

For all of these reasons, and to the best of our knowledge, "it is not possible to say definitively that a particular reperfusion approach is superior for all patients, in all clinical settings and at all times of day."[3]

In clinical practice, the key clinical parameter to consider should be the time from symptom onset to hospital presentation, and the main logistic parameter the expected time from the first medical contact to reperfusion: ie, the added delay in providing invasive rather than pharmacological reperfusion.

The fundamental concept in reperfusion therapy is that time is of the essence because ischemia leading to necrosis is a progressive process. There is therefore a close relationship between the time of presentation after STE-MI and the reduction in mortality that can be achieved by means of either reperfusion strategy. The survival benefit is greater during approximately the first 2 hours after the onset of ischemia because of the greater myocardial salvage that this allows; in this period, the benefit of reperfusion is extremely time-dependent. Myocardial salvage is progressively less from 2 to 6 hours after symptom onset, and in this interval most of the benefit is due to opening the infarct-related artery; however, the duration of this critical period may be influenced by several factors and, in particular, may be extended in the presence of functioning collaterals and ischemic preconditioning.

Finally, between 6 and 12 hours after the onset of ischemia, the possibility of myocardial salvage is definitely reduced and the primary goal of reperfusion becomes that of ensuring the patency of the infarct-related artery. During this late period, the mortality benefit is greatly reduced and the time to treatment is definitely less critical.

Consequently, the delay in implementing a primary PCI in comparison with fibrinolysis has a different clinical impact depending on the time from symptom onset at which the patient is admitted.

RISK STRATIFICATION OF PATIENTS WITH STE-MI

For this reason, STE-MI patients should be immediately stratified on the basis of the time from symptom onset with the aim of providing the best therapy for each case on site or involving transfer. Accordingly, to simplify the discussion, it may be useful to divide STE-MI patients in three main subgroups based on the time elapsed from symptom onset to first medical contact:

- In the case of patients in a very early STE-MI phase (2 to 3 hours after symptom onset), it is extremely important to obtain reperfusion within the shortest time possible in order to maximize the survival benefit. If there are no contraindications and primary PCI cannot be performed within 60 minutes, such patients should undergo fibrinolysis as the preferred strategy because it is particularly effective in the case of fresh-thrombus STEMI and the superiority of PCI is less evident. Moreover, in this early phase, the delay due to referral to a tertiary care center or, possibly, on-site primary PCI may easily outweigh the benefit.
- On the contrary, if PCI can be implemented extremely rapidly and efficiently (especially in the case of

high-risk patients or relative contraindications to fibrinolysis), it should be preferred, and must be considered mandatory in the case of absolute contraindications to lysis even if it entails transportation to another facility.

- Patients admitted between 2 to 3 and 6 hours after symptom onset should preferably undergo invasive reperfusion within 90 minutes because fibrinolysis is less efficient in this time interval. If for logistic reasons they cannot receive primary PCI within the next 120 minutes, and if they have no contraindications, they should be administered fibrinolytic therapy because this may allow at least some myocardial salvage, especially in the case of continued ischemic pain.
- The strategy of choice for patients admitted more than approximately 6 hours after symptom onset is definitely emergency catheterization (possibly followed by primary PCI), because many of them will probably receive more harm than good from fibrinolysis, especially if their chest pain has subsided. In such patients, the further delay due to transportation to another site seems to be justified because myocardial salvage is minimal in this late phase and the ultimate goal is sustained patency of the infarct-related artery and risk assessment. An invasive strategy should also not be denied to latecomers presenting after 12 hours if they still have persistent ischemic symptoms or are in a high Killip class. If primary PCI is not available, the patients admitted approximately 6 to 12 hours after symptom onset with ongoing chest pain and persistent ST-segment elevation may also be considered for fibrinolysis as a last chance of reperfusion. In this case, the benefit should be carefully weighed against the potential harm. There is no evidence that fibrinolysis offers any benefit after 12 hours.

Importantly, STE-MI patients treated with fibrinolysis in a center without catheterization facilities should be considered for immediate transfer to a tertiary care unit in order to ensure a prompt intervention in the case medical reperfusion fails: rescue PCI may be needed by approximately a quarter of these patients.[16]

Research data also suggest that an extensive early invasive strategy in all patients receiving fibrinolytic therapy may further improve outcomes,[17] because adjunctive PCI can sustain the patency of the infarct-related artery and thus avoid the risk of reocclusion and reinfarction.

One probably efficacious solution may be a pharmacoinvasive strategy combining the benefits of the easy and rapid administration of a facilitating drug in order to reestablish flow in the infarct-related artery as soon as possible, and the complete and sustained patency that can be achieved by means of PCI.[18] The apparently promising role of facilitated PCI, as well as the most appropriate pharmacological regimen of achieving facilitation, are currently being evaluated.

CONCLUSION: CHOSING THE MOST EFFECTIVE THERAPEUTIC STRATEGY

In conclusion, to address the question, it can be said that, although a very early and efficient invasive strategy may be preferable for every patient with ongoing STE-MI, obvious logistic reasons prevent the adequate implementation of primary PCI in all patients. Consequently, in clinical practice, primary PCI is not necessarily the best reperfusion choice for every case of STE-MI and three groups of patients may be reasonably or preferably treated with fibrinolysis:

- Patients admitted less than 2 to 3 hours after symptom onset without any contraindications to fibrinolysis in whom primary PCI cannot be performed within 60 minutes (corresponding to a door-to-balloon time of 90 min) by an experienced and skilled team.
- Patients admitted 3 to 6 hours after symptom onset without any absolute contraindication to fibrinolysis in whom the delay in implementing primary PCI due to prolonged transportation or an already occupied laboratory exceeds 90 minutes (corresponding to a door-to-balloon time of more than 120 minutes).
- Patients admitted within 12 hours of symptom onset without any absolute contraindication to fibrinolysis for whom primary PCI is simply not available.

The patients undergoing fibrinolytic therapy (especially those with high-risk STE-MI) should preferably be immediately transferred to a catheterization laboratory in order to allow a rescue intervention in the case of pharmacological failure.

The routine use of adjunctive PCI in patients treated with fibrinolysis aimed at achieving more efficacious reperfusion and obtaining the early and stable revascularization of the infarct-related artery may be effective, but requires further investigation.

A pharmacoinvasive strategy involving facilitation with fibrinolytic and/or antiplatelet agents followed by immediate transfer to a catheterization facility is currently being evaluated, and may become an optimal solution for patients admitted to peripheral hospitals.

In addition to relative and absolute contraindications, and the increased risk of intracranial hemorrhages,

the main limitations of fibrinolysis remain the narrow time-window of efficacy after symptom onset and the high rate of early and late reocclusion with the inherent risk of reinfarction. The first concern may be overcome by using prehospital fibrinolysis to treat patients as soon as possible after symptom occurrence; the second may be prevented by means of adjunctive and novel antithrombotic therapies[19] and a strategy of immediate PCI for higher-risk patients.

Every patient with STE-MI should be individually evaluated and the decision whether primary PCI or fibrinolysis is the preferred option should be taken after carefully balancing the benefit and the risk of both strategy in relation with patient clinical status and available facilities. This evaluation should include and weigh together the following key decisional parameters: time from symptom-onset to presentation, risk related to STE-MI, risk of fibrinolysis, and time delay for implementation of primary PCI; accordingly, the overall management must be tailored in each patient.

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Trails of Discovery

A cornerstone of cardiovascular therapy: the thiazide diuretics

Desmond Fitzgerald, BSc, FRCP, FFPM

Materia Medica - Mere, Nr Knutsford - UK

In this era of molecular biology and the apparently novel subdiscipline of translational medicine, it is perhaps salutary to review briefly the background to the discovery of the thiazide diuretics, which, even 50 years after the initial research leading to their discovery, play a pivotal role in cardiovascular therapy.[1,2] As so often in novel drug discovery, several seemingly unconnected scientific observations coincided to bring about the discovery of the thiazides. The first-generation diuretics were salts of mercury used primarily as topical antiseptics, especially in the management of syphilis, usually in the form of mercurous chloride (calomel). Toward the end of the 18th century, it was observed by astute clinicians that fluid retention secondary to cardiac failure ("cardiac dropsy") responded to calomel. However, it was the careful observations of Jendrassik in 1886 that showed that calomel could promote a diuresis of up to 7 or 8 liters per day, but only if marked fluid retention was already present. Calomel did not promote diuresis in normal subjects.[3] From that time, numerous attempts were made to discover mercurial diuretics that were active orally rather than parenterally. Prolonged administration of mercurial diuretics required daily intramuscular injections and there was the serious risk of mercury poisoning.[4] The alternative orally active diuretic for treating congestive heart failure was theophylline (0.25 g four times daily). Its efficacy depended upon the degree of fluid retention, and tachyphylaxis was observed on long-term treatment. Clearly, there was a need for more effective and efficient diuretics, but there was little scientific evidence at the end of the 1920s to indicate which direction research should take.

Address for correspondence:
Dr J. Desmond Fitzgerald, Materia Medica, Mere Croft, Chester Road, Mere, Knutsford, Cheshire WA16 6LG, UK
(e-mail: des.fitzgerald@tiscali.co.uk)

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EARLY OBSERVATIONS

The events leading to the discovery of the thiazides cover a 30-year period, from 1930 to 1960 (see *Figure 1 page 176,* flowchart), during which important academic and industrial research played a complementary role. There were two pivotal, but seemingly unrelated, scientific discoveries in the early 1930s. Firstly, the demonstration by Gerhard Domagk, working in the laboratories of the IG Farbenindustrie, made the discovery that was to earn him the Nobel Prize in Medicine for 1939, that the red dye Prontosil (sulfamidochrysoidine, or 4-[(2,4-diaminophenyl)azo]benzenesulfonamide), synthesized in 1932, had antibacterial activity when administered to streptococcal-infected mice. Surprisingly it was inactive in in vitro antibacterial studies.[5] Shortly afterwards it was shown that the active metabolite of Prontosil was sulfanilamide by the French group working in Bovet's laboratory in France.[6] Sulfanilamide was found to have potent antibacterial properties in experimental infections in mice.[7] Secondly, Meldrum and Roughton, described the existence of the enzyme carbonic anhydrase in red blood cells and subsequently in the kidney, gastric nucosa, and central nervous system.[8]

In 1937, Southworth published a paper, in which he showed that administration of the first antibacterial sulfanilamide caused a fall in CO_2 combining power of the plasma in 15 patients receiving treatment for infection.[9] The following year, Strauss and Southworth reported on urinary changes due to sulfanilamide treatment in 3 healthy subjects.[10] These were observed over 12 days and given 3 to 5 g of sulfanilamide between days 3 and 6. This paper is perhaps impressive for several reasons:

- The 24-hour urinary volume, pH, and electrolyte changes were recorded over the entire 12-day period.
- Blood CO_2 combining power was measured daily.
- Plasma levels of sulfanilamide were measured, and a relationship demonstrated between drug dose and the increase in urine volume and electrolyte excretion *(Figure 2, page 177).*[10]
- All 3 volunteers developed raised body temperature of between 102 and 103° F, yet the paper does not speculate on the basis of these unwanted effects or that one subject had to stop dosing because of significant side effects.

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Two years later, Mann and Keilin, working in the Molteno Institute, University of Cambridge, published a paper demonstrating that sulfanilamide was a potent inhibitor of carbonic anhydrase.[11] They reported the structure-activity relationships of 16 analogs of sulfanilamide and showed that the amino group of sulfanilamide, which is essential for the antibacterial property, is not responsible for the inhibition of carbonic anhydrase. Furthermore, they demonstrated that sulfonamides, which did inhibit carbonic anhydrase, were highly specific and did not affect other zinc-containing enzymes. Interestingly, the compounds used in this study were supplied by three separate pharmaceutical companies, but it is not clear if the scientists in these companies followed up the clinical implications of these observations.

In 1941, Davenport identified carbonic anhydrase in the kidney.[12] In 1942, Hober reported on the effects of eight sulfonamide analogs on changes in urinary pH in the perfused frog kidney.[13] He concluded that the pH changes due to the sulfonamide analogs could be due to inhibition of carbonic anhydrase, which was involved in the reabsorption of bicarbonate in the renal tubule.

Academic studies	Drug research studies
1933 Meldrum and Roughton describe distribution and properties of carbonic anhydrase (CA)[8]	**1929-35** Gerhard Domagk, of IG Farbenindustrie, Germany, shows that Prontosil (sulfamidochrysoidine), a prototype compound leading to the development of sulfonamide antibacterials, given orally, cures streptococcal-infected mice, but is inactive in vitro.[5] Awarded Nobel Prize in Medicine in 1939
1937 Southworth observes acidosis in Prontosil-treated patients[9]	**1935** Bovet's group identifies sulfanilamide as the active metabolite of Prontosil[6]
1938 Strauss and Southworth show sulfanilamide causes diuresis in volunteers[10]	
1940 Mann and Keilin purify CA and suggest that nonantibacterial sulfanilamide analogs inhibit CA[11]	
1941 Davenport and Wilhelmi identify CA in renal cortex of several species. Propose sulfanilamide causes diuresis by CA inhibition[12]	**1943-50** Sprague and Beyer, of Sharp & Dohme, seek inhibitors of renal excretion of penicillin. Discover probenecid (Benemid), a sulfanilamide analog)[14]
1949 Schwartz shows that sulfanilamide improves heart failure by ↑NA, H_2O loss[16]	**1950** Roblin and Clapp, of American Cyanamid, discover, based on a communication from Schwartz, acetazolamide, an orally active CA inhibitor[18]
1950 Freis initiates clinical research in hypertension[22]	**1950-52** Beyer et al initiate diuretic research on sulfanilamide-induced CA inhibition and improved organomercurials. Clinical target is heart failure and hypertension[15]
1957 Freis shows that chlorothiazide potentiates response of other antihypertensive agents[23]	**1955-57** Novel diuretic action of chlorothiazide discovered[21]
1967 Freis et al show reduction in morbidity by long-term blood pressure control[33]	**1957-62** Numerous thiazide analogs developed
1971 Freis awarded Lasker Prize[33]	**1975** Beyer, of of Merck, Sharp & Dohme, awarded the Lasker Prize for the discovery of the thiazides[15]

Figure 1. *Pathways to the discovery of thiazides. In the 1920s, research was focused primarily on finding potent orally active organomercurial analogs as diuretics, but their therapeutic margin was narrow.*

In 1943, Karl Beyer set up a renal research program in the Sharp & Dohme pharmaceutical company in the United States. The initial purpose of their research was to examine the renal excretion of sulfonamide compounds, because crystalluria, due to sulfonamide treatment, was a common clinical problem. This necessitated studying renal transport mechanisms.[14] At that time, the company was working on analogs of sulfonamides for antibacterial purposes and also on the large-scale production of penicillin G.

The latter is rapidly excreted by the kidney, so studies were performed to find a chemical means of inhibiting its rapid elimination. In 1950, Beyer postulated that two renal enzyme systems were involved in ion transport. These were carbonic anhydrase and an unidentified sulfhydryl-containing enzyme that was possibly inhibited by mercurial diuretics. Initial research success came with the discovery of probenecid (Benemid), a benzoic acid derivative, which markedly inhibited the renal excretion of penicillin G.[14]

STUDIES LEADING TO THE DISCOVERY OF THIAZIDES

Beyer and his chemical colleagues, Novello and Sprague, set up a research program seeking compounds that would inhibit the reabsorption of the cation sodium, resulting in a natriuretic effect. The therapeutic targets were edematous states and essential hypertension. They selected two separate chemical approaches. The priority program was based on analogs of sulfonamides, which were known to inhibit carbonic anhydrase. The secondary target was to discover nonmercurial analogs, which they believed acted by inhibiting sulfhydryl-catalyzed dehydrogenase enzymes in the kidney. Based on their previous experience seeking inhibitors of penicillin excretion by the kidney, they planned to seek compounds that would inhibit carbonic anhydrase in the proximal renal tubule, would be poorly reabsorbed in the distal portion of the tubule and if possible should not act extracellulary, in order to minimize nonspecific systemic toxicity.[15]

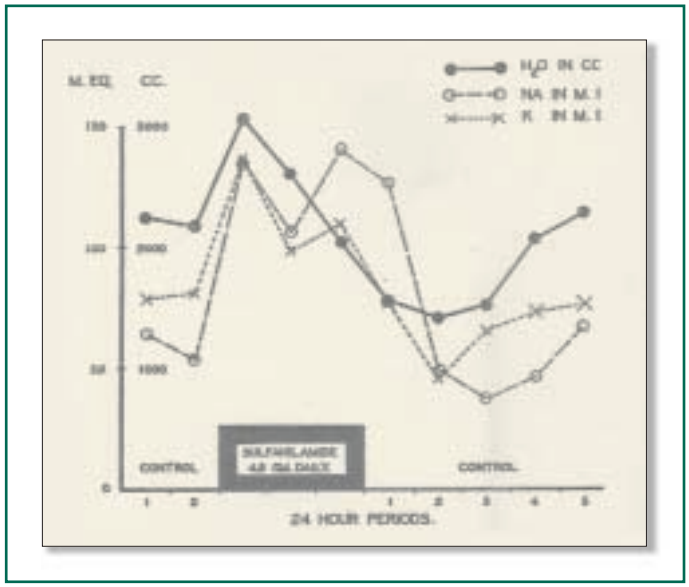

Figure 2. *Urinary output of water, sodium, and potassium in a volunteer given sulfanilamide (0.1 g/kg/day).*

Adapted from reference 10: *Strauss NB, Southworth H. Urinary changes as a result of sulfanilamide administration.* Bull Johns Hopkins Hosp. *1938;63:41-45. Copyright © 1938, The Johns Hopkins University.*

While this initial work was in progress in Sharp & Dohme (Sharp & Dohme merged with Merck in 1953 to become Merck, Sharp & Dohme: MSD), the industrial scientists Roblin and Clapp, working in the American Cyanamid Company, were also seeking novel orally active diuretics based on inhibition of carbonic anhydrase. Their research interest was triggered by the clinical studies of William Schwartz, working as a Research Fellow in the Peter Bent Brigham Hospital, Boston. He had studied the effects of sulfanilamide (4 to 6 g daily) on urinary function in 3 patients with severe congestive heart failure.[16] In his paper, he indicates that his study was prompted by the report by Pitts and Alexander, published in 1945, showing that sulfanilamide administered to dogs increased urinary pH and reduced titratable acidity, probably by inhibiting renal tubular carbonic anhydrase.[17] Examples of the increase in urinary sodium excretion due to sulfanilamide administration are illustrated in a human volunteer *(Figure 2)* and a patient with congestive heart failure *(Figure 3, page 178).* The American Cyanamid scientists prepared analogs of sulfanilamide, seeking potent orally active inhibitors of carbonic anhydrase, based initially on suggestions made by Schwartz, which they acknowledge in their paper published in 1950.[18] One of their analogs proved to be 330 times more potent at inhibiting carbonic anhydrase than sulfanilamide. This compound, subsequently called acetazolamide, was evaluated clinically. Friedberg reported on its effects in 26 patients with heart failure, of which 18 responded with a marked weight loss, diuresis, and improvement in symptoms.[19] However, chronic administration of acetazolamide resulted in a loss of efficacy. Subsequently, a use was found for it in selected cases of epilepsy and glaucoma.

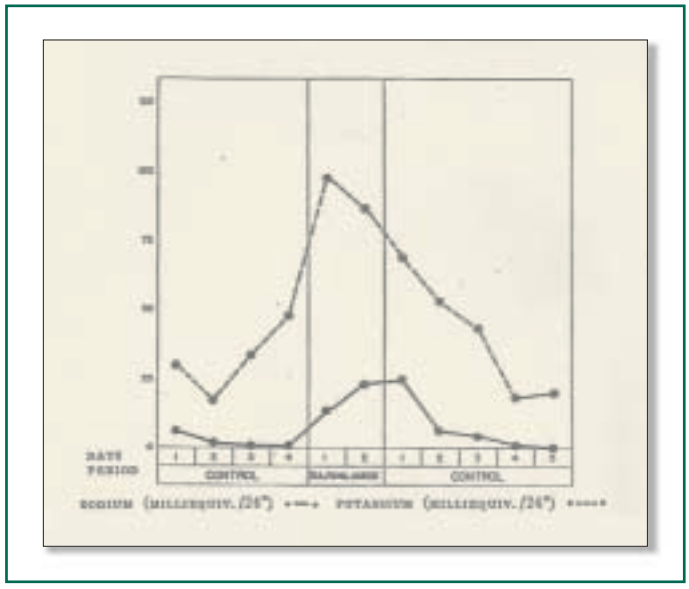

Figure 3. *Effect of sulfanilamide (4 to 6 g daily) on urinary sodium and potassium in a patient with severe heart failure.*

Adapted from reference 16: *Schwartz WB. The effect of sulfanilamide on salt and water excretion in congestive heart failure.* N Engl J Med. *1949;240:173-177. Copyright © 1949, Massachusetts Medical Society.*

In the meantime, the research at MSD progressed rapidly. In contrast to the American Cyanamid approach, which determined the potency of chemical analogs in an in vitro system for detecting inhibition of carbonic anhydrase, Beyer and his colleagues in MSD used the conscious dog in order to determine the effects of compounds on sodium and chloride urinary excretion. In a short time, a lead compound, CBS (*p*-carboxybenzene-sulfonamide), was identified. It was chloruretic, secreted by the renal tubules and rapidly excreted. These findings supported the validity of Beyer's hypothesis. Numerous analogs were evaluated and it became clear that the determinants of diuretic efficacy were not only dependent on the potency of the carbonic anhydrase inhibitors, but also on physicochemical properties of lipophilicity, protein binding, and the handling by the renal tubule.

The chemical synthetic program included the synthesis of cyclized analogs, one of which became chlorothiazide *(Figure 4)*.[20] It's profile in the canine experiments showed a marked (35-fold) increase in sodium and chloride excretion with a lesser (3.8-fold increase) in potassium and bicarbonate excretion. The compound was active orally in the dog, with maximal activity 30 minutes after administration. It soon emerged that the pharmacodynamic profile of chlorothiazide was markedly different to that of acetazolamide and had features similar to organomercurials.[21]

SUBSEQUENT DEVELOPMENTS

Early clinical findings

Since chlorothiazide was active orally and had excellent tolerability, it was rapidly evaluated in both essential hypertension and congestive heart failure. It is salutatory to recall that in the early 1950s, the only agents available to treat hypertension were ganglion-blocking drugs and veratrum alkaloids, derived from natural products. Edward Freis, in his 1971 Albert Lasker Award paper,[22] subsequently describes the evolution of the treatment of essential hypertension between 1946 and 1966. He was among the first investigators to describe the effects of chlorothiazide (1.5 g daily) in reducing blood pressure in patients with moderate-to-severe hypertension. His preliminary conclusion after studying 88 patients and 15 normotensives, none of which received a placebo, was:

- That chlorothiazide is an effective and well-tolerated antihypertensive agent that appears to be specific for the hypertensive state.
- Its mode of action appears to differ from previous antihypertensive agents. It produces significant reduction of blood pressure when used alone and additional reduction when combined with other antihypertensive agents, or when given to sympathectomized patients.
- It does not reduce blood pressure in normotensive subjects.[23]

Other investigators soon confirmed these observations in hypertensive patients[24] as well as showing efficacy in patients with congestive heart failure.[25]

CHLOROTHIAZIDE ANALOGS

Beyer coined the term "saluretic" to distinguish chlorothiazide from previous agents whose characteristics were to cause a marked increase in urine volume, ie, diuretics.[15] The publication of trials of chlorothiazide led to an explosion of medicinal chemistry activity in other pharmaceutical companies. The objective of the research was to identify compounds that would be an improvement on chlorothiazide in terms of potency, specificity, systemic bioavailability, duration of action, and patentability. Chlorothiazide was between 10% and 20% orally bioavailable and was rapidly excreted unchanged in the urine with a plasma half-life of 1 to 2 hours, but a duration of action of 6 to 12 hours. The search for improved saluretics was to an extent con-

founded by the lack of correlation between in vitro tests for inhibition of carbonic anhydrase and the saluretic activity observed in in vivo studies. Detailed analysis of the structure-activity requirements for carbonic anhydrase inhibition was widely available in the literature,[26] but was of little help in making improved saluretics. In assessing the appropriate tests to detect saluresis, Beyer emphasized that the conscious dog model would identify compounds that would be overlooked by animal disease models. He wrote,

> had one employed a model of cardiac decompensation or renal insufficiency adequate to induce fluid retention, the technical difficulty of maintaining a uniform colony of such animals adequate to control and quantify a drug effect on fluid retention might be defeating… Had such other measures been employed as first-line procedures in dogs, both chlorothiazide and ethacrynic acid [see below] may have been missed if they had been administered as a single daily dose, because of their short duration of action.[27]

Within 18 months, the group in the CIBA laboratories in the USA published data showing that hydrochlorothiazide was possibly an improvement on chlorothiazide because it had more than 60% systemic bioavailability, a plasma half-life of 5 to 6 hours and was 10 times more potent. Surprisingly, it underwent enterohepatic recirculation, which may explain its apparent greater potency in human studies.[28] These pharmacokinetic characteristics were brought about by the seemingly trivial substitution of two hydrogens in the heterocyclic portion of the ring system *(Figure 4)*. Subsequently, about 12 thiazide analogs, differing in potency and kinetic properties, were marketed. They all had about the same maximal saluretic effect.

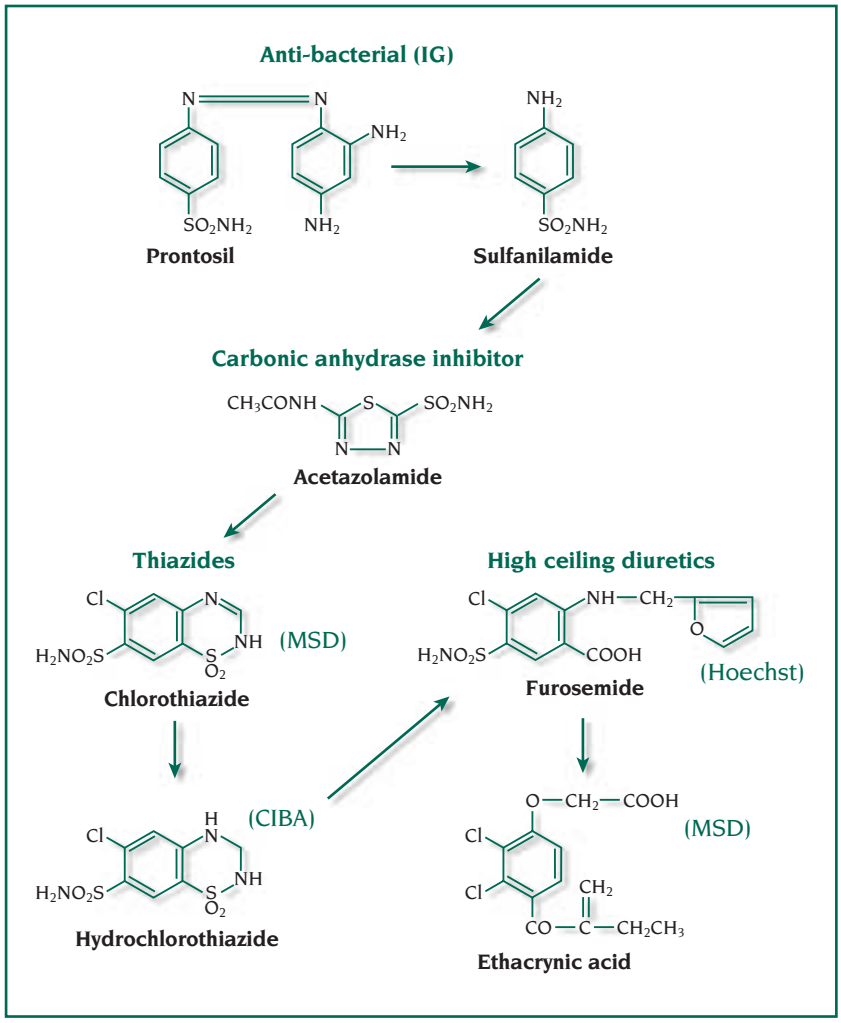

***Figure 4.** Evolution of chemical structures leading to three classes of oral diuretics.*

During the late 1950s, chemists in the Hoechst Company, Germany, initiated a research program to find saluretic agents that could replace their organomercurial compound, mersalyl, which had been used for the previous 30 years before being displaced by the thiazides. The Research Group abandoned their studies to find improved carbonic anhydrase inhibitors and instead set out to find compounds with a higher maximal saluretic efficacy in comparison with thiazides. Muschaweck has described the lengthy chemistry program, which was also based on sulfonamide analogs, specifically sulfamoyl benzoic acids, which they reacted with various amines. This finally led to the identification of furosemide (Lasix), the first compound with a much higher saluretic and diuretic effect.[29] More than 40 years after its discovery, furosemide and other "high-ceiling" diuretics remain the cornerstone of the treatment of congestive heart failure and pulmonary edema, as well as contributing to managing essential hypertension. They differ from the thiazides in primarily inhibiting ion exchange in the ascending loop of Henle and also in the distal tubule. They do not inhibit carbonic anhydrase. Beyer's Group at MSD discovered ethacrynic acid, another high-ceiling diuretic, as part of their program to discover non-mercurial compounds, which were as effective as the organomercurials. Their compound also originated from the sulfonamide analog synthetic program, but the Hoechst Group had priority of discovery with this new class of diuretic.

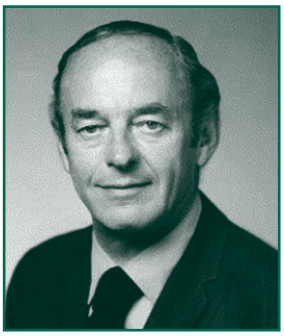

***Figure 5.** Edward D. Freis (1912-2005). All rights reserved.*

Servier's indapamide is also to be cited here. Indapamide's action relies on a thiazide-type renal diuretic effect—although it lacks the thiazide ring of the true thiazides—as well as on specific vasodilator properties that contribute to its antihypertensive efficacy.[30]

DISCUSSION

The discovery of the thiazides provides illuminating examples of the complexity of the relationships between pathophysiology, pharmacology, and clinical science in discovering new medicines. For example, the discovery of the thiazides occurred at a time when the outstanding clinical scientist Professor Edward Freis (Georgetown University, Washington) *(Figure 5)* was already trying to find medical treatments for essential hypertension. The pivotal role of salt and water balance in determining hemodynamic and blood pressure status were recognized, as for example with the adoption of the Kempner salt-free diet, which, while effective, was impracticable.[31] Freis designed the classic first controlled trial in essential hypertension to demonstrate that reducing elevated blood pressure reduced morbidity and mortality in such patients.[32] This trial had several features that were unique at that time, including:

- A trial design requiring double blindness and placebo control.
- The independent assessment of clinical end points by a committee.
- The creation of a data safety monitoring board. As Barry Materson recently said of Freis,

> he designed this study at a time when the conventional wisdom was that it was nonsense and perhaps even unethical to treat patients with hypertension. In essence, he made one of the most important contributions of the century to medical practice.[33]

- The treatment arm of the trial comprised a combination capsule containing a thiazide diuretic (Esidrex), reserpine (Serpasil), and hydralazine (Apresoline) given in a fixed combination 3 times a day (SER-AP-ES).

A subset of the total trial of 523 male patients comprised patients with a diastolic pressure between 115 and 129 mm Hg (73 on active drug, 70 on placebo). Four patients died in the control group of cardiovascular complications, but none in the treated group, while 17 in the control group developed severe nonfatal complications, while only 6 treated patients had these problems.[34] The success of the Veterans Administration trial led to the creation of the National High Blood Pressure Education Program and the award of the Lasker Prize to Freis in 1971.[22]

Sadly, Professor Freis died on February 1, 2005, aged 92 years. The Author met him at a Gordon Conference and asked him how he managed drug-resistant essential hypertension, to which he replied "I don't seem to encounter this very much, I just give them one of those little blue capsules 3 times a day!"

However, it has taken many years for it to be recognized that combination therapy is the best approach to the effective control of raised blood pressure. This has led to the approach exemplified by the modified Cambridge AB/CD rule *(Figure 6).*[35] There have been intensive studies attempting to relate the blood pressure response to different classes of antihypertensive agents to particular genetic polymorphisms, but the present opinion is that single gene effects on antihypertensive drug responses are small.[36] Despite intensive investigation over the last 30 years, there is no final agreement on the mode of action of the thiazides in lowering blood pressure, though their effects in improving the treatment of congestive heart failure are closely related to the reduction in salt and fluid retention. Thiazides

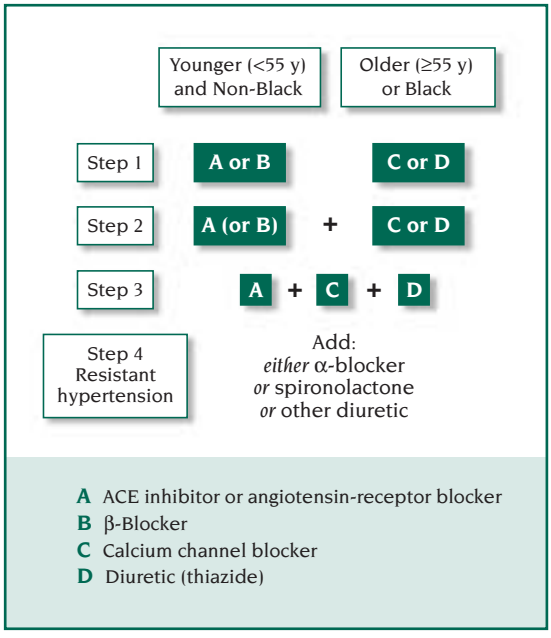

***Figure 6.** British Hypertension Society (BHS) recommendations for lowering blood pressure. Sequential therapeutic regimens recommended for achieving target blood pressure of <140 <85 mm Hg, according to age and ethnic group.*

***Adapted from reference 35:** Schwartz GL, Turner ST. Pharmacogenetics of antihypertensive drug responses.* Am J Pharmacogenomics. *2004;4:151-160. Copyright © 2004 Adis Data Information BV.*

lower the blood pressure during long-term treatment by reducing the peripheral vascular resistance, but how this is achieved is the source of continuing controversy.[37-39]

A second aspect of the complex relationships described above is how research intended to solve one problem—in this instance prolonging the action of penicillin by blocking its renal excretion—led to a research program designed to treat edema and hypertension. However, the feasibility of such research only became possible by the prior serendipitous observations of the effects of sulfanilamide on water and electrolyte excretion in humans.[16] Without the sulfanilamide template, medicinal chemists would have struggled to devise an appropriate chemical synthetic program. The final breakthrough relied on the combination of choosing physiologically based in vivo test systems (the conscious dog) and identifying the difference in pharmacodynamic profile between carbonic anhydrase inhibitors and the urine electrolyte excretory profile of chlorothiazide. In his Lasker Medal lecture,[15] Beyer attributed the success of his group to the following elements:

> (i) The physiological basis for the work and its relevance of the clinical situation seemed sound; (ii) our methodology seemed to be appropriate, adequate and accurate; and (iii) there was a need for many people to work together.
>
> The evidence historically is that these criteria were fulfilled. It attests the reality of what we have fancied to call "designed discovery"—a process whereby clinical need and understanding biological concepts and analogies and chemical ingenuity and perseverance brought together in a stimulating environment can yield a specific result that has been empirically conceived.

This description of designed drug discovery written more than 30 years ago would seem to suggest that the current vogue for creating a subspeciality of "bench-to-bed translational research" was born at least 50 years ago.

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Angiographic progression of coronary artery disease and the development of myocardial infarction

J. A. Ambrose, M. A. Tannenbaum, D. Alexopoulos, C. E. Hjemdahl-Monsen, J. Leavy, M. Weiss, S. Borrico, R. Gorlin, V. Fuster

J Am Coll Cardiol. 1988;12:56-62

This paper is of particular importance because it questions an often-made assumption: are angiographically more severe lesions more likely to cause an occlusion? Or put another way, can one predict the location of a future myocardial infarction from angiographic data?

The study methods are relatively simple. A retrospective analysis of coronary angiograms was performed on two groups of patients, 38 in total, who had all required initial coronary angiography due to anginal symptoms and/or an abnormal exercise test. The distribution of coronary risk factors was equal. Group 1 comprised 23 individuals who had sustained a myocardial infarction following their first angiogram and had required a second angiogram following the infarction due to ongoing symptoms, congestive cardiac failure, or simply "standard practice." The time interval between angiograms was 1 month to 7 years, with a median of 18 months. Group 2 consisted of 15 individuals who had not sustained an infarction, but had developed total occlusion of a coronary vessel subsequent to their first angiogram, the second being performed due to worsening angina and/or worsening exercise tolerance. The time interval between angiograms was 3 months to 9 years, with a median of 33 months. The diagnosis of infarction was excluded in this group by the absence of a typical history, as well as the lack of a new wall-motion abnormality on left ventriculography.

The "before" and "after" angiograms were then compared for each individual using a surprisingly effective solution in an age where electronic quantitative coronary analysis presumably was not available. The images were projected onto a white wall, and after the coronary tree was divided into segments, a consensus of angiographers determined by visual inspection if any segment contained a lesions of >30%. Having confirmed the presence of such a lesion, this was traced onto transparent paper by hand and compared with the corresponding segment of artery in the companion study, and so the amount of stenosis could be quantified with respect to a "normal" segment of artery, which was used as a control in each case.

The results showed a dramatic lack of concordance of angiographic severity of stenosis with subsequent infarction. Indeed, 30% of patients in group 1 had a normal appearing artery in the subsequent infarct-related segment, and most did not have a lesion >70%. Additionally, no arterial segment with >90% stenosis developed Q-wave infarction, but in non–Q-wave infarction, the initial stenosis was higher than in patients with Q-wave infarction. In other words, the severity of stenosis correlates with the type and extent of infarction, in a way that suggests a protective effect of a tight stenosis, perhaps due to the recruitment of coronary collaterals if there is a chronic severe stenosis. The only significant predictor of evolution to infarction of lesions >50% was lesion location in a proximal position. The authors postulate that the proximal lesions may be exposed to a greater degree of shear stress and turbulence than more distal lesions, which may contribute to the time to thrombotic occlusion secondary to fibrous cap rupture. Patients in group 2, by contrast, had a >70% stenosis at the site of subsequent occlusion in 61% of cases.

The study is limited by its patient selection: all patients were required to have at least one angiogram prior to their second (= postinfact or post-aggravation) one, which would exclude most patients with myocardial infarction. Additionally, those with total occlusion, but no symptoms, would not have been restudied. Despite this, however, there is a key clinical message: plaques that appear mild or moderate may be the cause of most infarctions.

1988

Florence Joyner runs the 100 m in women's world record time of 10.49 seconds; the South African government bans antiapartheid film "Cry Freedom"; and the US Navy shoots down an Iranian jetliner over the Gulf, killing 290 civilians

Multiple complex coronary plaques in patients with acute myocardial infarction

J. A. Goldstein, D. Demetriou , C. L. Grines, M. Pica, M. Shoukfeh, W. W. O'Neill

N Engl J Med. 2000;343:915-922

Patients with acute myocardial infarction who have multiple unstable coronary plaques have a poorer prognosis compared with those with a single unstable plaque. This is the fundamental point raised by this article, which would appear to be an intuitive conclusion, but its main interest resides in the authors' discussion of potential mechanisms.

Two hundred and fifty-three consecutive patients with acute transmural myocardial infarction were investigated initially with coronary angiography, having been given standard doses of aspirin and heparin. They were then placed into two groups depending upon the appearance and number of their coronary lesions (single or multiple complex plaques). The definition of a "complex" plaque, therefore, is of central importance, and this includes lesions with thrombus, ulceration, plaque irregularity, or impaired flow. Because of the intrinsic problems associated with such a subjective means of classification, the images were reviewed by two observers (and in almost 7% of cases there was initial disagreement).

The data obtained demonstrated single complex lesions in 153 patients and multiple complex lesions in the remaining 100. Age, smoking, diabetes, hyperlipidemia, and history of myocardial infarction or angina were similarly distributed between the groups. A separate analysis was performed for patients with multiple lesions and those with single lesions.

There were striking differences in the outcome measures between the two groups. Those with multiple complex plaques had a higher prevalence of multivessel coronary disease and poorer left ventricular function. Additionally, these patients were more likely to require early bypass surgery, and, conversely, less likely to undergo percutaneous intervention, although when angioplasty was performed it more frequently involved treatment of multiple vessels. Furthermore, these patients had a higher incidence of acute coronary syndromes and angina in the year following their infarct, as well as requiring further angioplasty. Crucially, at the time of repeat angioplasty, lesions initially identified as being nonculprit required subsequent intervention. The authors indicate that the culprit lesion responsible for the initial acute event was identified in 98% of cases with multiple complex lesions based on ECG changes and regional ventricular wall-motion abnormalities; this figure would indicate a remarkable degree of diagnostic accuracy not always demonstrated in clinical practice!

The authors conclude by commenting that although there is evidence that complex lesions may remain stable over time, their natural history is to progress in the severity of stenosis and become unstable. They speculate that plaque instability that occurs in multiple points in the coronary circulation, or at various times during a patient's life, may represent the consequences of a systemic inflammatory process, and therefore can be modulated by systemic treatments such as aspirin or statins, although no data to support this conjecture were obtained from the study itself.

The limitations of this study are clear, and are made explicit. One is the assumption that plaque instability may be directly inferred from angiographic data alone, ie, complex lesions represent unstable plaques. Secondly, it is arguable that angiography is not sufficient even to reliably identify thrombus or any another manifestation of a pathological process that would allow the distinction to be made between a stable or unstable lesion.

2000

A gene linked to type 2 diabetes is isolated from Mexican-Americans in Texas County who display a high prevalence of the disease; the Olympic games open in Sydney, Australia; and Danish voters vote against joining Europe's common currency

Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro

C. L. de Korte, G. Pasterkamp, A. F. van der Steen, H. A. Woutman, N. Bom

Circulation. 2000;102:617-623

Intravascular elastography is exploited by the authors of this paper essentially with the aim of providing a surrogate for histological analysis of atherosclerotic plaques. They argue that plaque composition can determine clinical syndromes and, therefore, that potentially prognostic data can be obtained using this technique.

Intravascular elastography is a modification of intravascular ultrasound (IVUS), which relies upon the assumption that the composition of a section of arterial wall (in terms of fiber and fat content) will determine its mechanical properties. In particular, when carefully controlled pressures are applied intravascularly (in this case 80 mmHg and 100 mmHg, chosen to reflect physiological coronary pressure), the extent to which a portion of artery distends will be dependent upon its composition, and the change in the radial dimension of the artery can be measured using IVUS. Softer material would therefore be expected to distend more than harder material. The percentage change in size is denoted the "strain" value.

This study examined human femoral and coronary arteries in vitro using this technique. Some aspects of the method require a special mention. The specimens were taken 24 hours after death and stored at –70°C. The experiments were then performed in a water tank at room temperature, having ensured that all side branches that could be responsible for a drop in pressure were ligated. Clearly, these conditions are far from physiological. Furthermore, identification of the precise fragment of artery corresponding to the scanned area was not always possible, and therefore the elastogram could not be validated. Finally, one would expect the precise measurements required to identify differing strain values (as little as 1% to 2%) to be jeopardized when the IVUS catheter is placed in the coronary arteries.

Working within these constraints, however, the results were striking. In all, 125 regions were selected (96 femoral, 29 coronary) from 45 cross-sections in 13 arteries. The strain values obtained were compared with the dominant tissue type as determined by immunostaining. The elastogram could identify regions in the plaque representing differences in strain, and lipid-rich regions demonstrated significantly higher strain values than fibrous-rich regions. Interestingly, although the relationship between plaque type and strain value was maintained in both coronary and femoral arteries, the strain values were different in each.

The technique described therefore appears to be capable of discriminating between tissue types, and thus of predicting the natural history of a plaque. This would make it possible to treat a plaque, perhaps by angioplasty or a pharmacological intervention, before it causes a problem. However, since strain values differ significantly between femoral and coronary arteries, there remains the possibility that they may also differ significantly between individuals, as the data do not include an analysis of the variation of strain within each artery subtype. Consequently, calculation of strain values may demonstrate that different parts of an arterial wall have differing properties with respect to their fibro-fatty composition, but ultimately this information may be pointless without validation against a histological gold standard. This is because the histological data are qualitative, ie, there is no information conveying precisely what quantity of fatty or fibrous tissue corresponds to a particular unit of strain, simply that a relationship exists between the two parameters.

2000

The Russian Orthodox Church canonizes Czar Nicholas II and his family who were executed by Bolsheviks in 1908; the Chilean Supreme Court lifts Pinochet's senatorial privileges, removing the major legal barrier to the trial of the former dictator; and Queen Mother Elizabeth celebrates her 100th birthday

Serum from patients with acute coronary syndromes displays a proapoptotic effect on human endothelial cells: a possible link to pan-coronary syndromes

M. Valgimigli, L. Agnoletti, S. Curello, L. Comini, G. Francolini, F. Mastrorilli, E. Merli, R. Pirani, G. Guardigli , P. G. Grigolato, R. Ferrari

Circulation. 2003;107:264-270

Which factors cause a stable plaque to be transformed into an unstable one is unclear. The presence of multiple unstable lesions in different vessels supports the notion of a generalized inflammatory process. Circulating factors are likely to play a role in this as evidenced by the observation that, following myocardial infarction, patients are at a heightened risk of suffering a further event arising from the offending plaque. This is further supported by the finding of thrombosis in association with plaque erosion, but not rupture, and also the observation that apoptotic endothelium exerts procoagulant activity. Apoptosis might itself by triggered by circulating factors, thus leading to plaque activation.

This study investigates whether serum from 41 patients with an acute coronary syndrome exerts a proapoptotic effect on human umbilical vein endothelial cells (HUVECs) compared with controls (40) and patients with stable angina (32). The role of cytokine activation was assessed by the addition of monoclonal antibodies to tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), and an antioxidant construct of vitamin E (Trulox) was added to the cell culture to assess the contribution of oxidative stress.

Assessment of apoptosis by flow cytometry demonstrated that when HUVECs were cultured with serum from controls or stable angina patients, the rate of apoptosis was low (1.3%±0.8% and 3.3%±1.8% respectively, P=NS). The addition of serum from acute coronary syndrome (ACS) patients increased the apoptosis rate to 14.3%±6%, P<0.001. This group was further divided into unstable angina and acute myocardial infarction, though no difference was observed in the rate of apoptosis, indicating that it is not related to the degree of necrosis. The addition of anti–TNF-α and anti–IL-6 antibodies did not affect the apoptosis rate. The addition of Trulox significantly reduced apoptosis in the cells treated with ACS serum (14.3±6% to 5.5±3.8% P<0.001), indicating that while cytokines do not seem to play a key role in apoptosis, oxidative stress is indeed relevant. Among patients with ACS, an interesting correlation was observed between the rate of apoptosis and the number of complex lesions. Another finding of interest was that when the ACS patients were restudied after 1 year, the rate of apoptosis was similar to that in normal controls.

The apoptotic effect is thus related to plaque activation, as it is not seen in patients with stable angina, and is not present 1 year after ACS. The property that serum from ACS patients demonstrates by inducing apoptosis supports the hypothesis that circulating factors lead to a pancoronary syndrome. A link has been postulated between apoptosis and atheroma denudation and subsequent thrombosis. This might occur by release of prothrombotic apoptotic cell debris causing clotting activation. In addition, activated plaques might release oxidants, stimulating apoptosis, a theory supported by the reduction in apoptosis seen when Trulox was administered.

The factors present in serum during ACS that trigger this increase in apoptotic activity remain unclear. CD4 T cells develop cytotoxic properties by oxygen radical production. C-reactive protein (CRP) has been shown to sensitize endothelial cells to this process, further linking immune activation and plaque rupture. The authors were perplexed by the apparent lack of effect exerted by TNF-α, given that in heart failure, it is associated with apoptosis.

2003

Fossil evidence of a four-winged dinosaur, *Microraptor gui* is found in China that may explain the evolution of birds and flight; France announces it will use its veto power in the Security Council to thwart the US push for action against Iraq; and Prime Minister Ariel Sharon and his Likud Party resoundingly defeat the Labor Party in the Israeli election

Characterizing vulnerable plaque features with intravascular elastography

J. A. Schaar, C. L. de Korte, F. Mastik, C. Strijder, G. Pasterkamp, E. Boersma, P. W. Serruys, A. F. van der Steen

Circulation. 2003;108:2636-2641

In this paper, the authors' aim is to demonstrate a way of reliably assessing the future risk of rupture of an atherosclerotic plaque. Given this bold premise, one would expect numerous practical and theoretical difficulties, and indeed these are all laid bare in the discussion. However, the methods are elegant and may serve as a platform for further investigation.

Two modalities are used to obtain such prognostic data: ultrasound and histopathology. More specifically, a modification of intravascular ultrasound (IVUS) called elastography is used to determine the distensibilty or "strain" of a portion of a coronary vessel in a postmortem specimen by applying a known pressure within the vessel. The subtle changes in the radial dimension of the vessel are used to calculate the strain as a percentage. In theory, areas with greatest strain correlate with "vulnerable" areas of the vessel wall that are more prone to plaque rupture, as these potentially have different mechanical properties due to their unique composition of macrophages, collagen, and smooth muscle cells relative to "normal" vessel. However, in order to determine the predictive value of strain, a histopathological sample was also taken from precisely the same portion of vessel as the elastogram so that a direct comparison could be made between the two. By this latter method, a vulnerable plaque was defined as having more than 40% atheroma covered by a cap of no more than 250 mm with moderate-to-heavy macrophage infiltration. Therefore, a secondary aim of the study was to determine which anatomical features were responsible for generating these high-strain areas.

Based on a histological comparison as a gold standard, intravascular elastography had a sensitivity of 88% and specificity of 89%, and, correspondingly, those plaques deemed to be vulnerable by histology had statistically thinner caps. As expected, vulnerable plaques had a demonstrably higher strain value compared with stable plaques. Additionally, there was strong positive correlation between the strain value and amount of macrophages, but an inverse correlation with smooth muscle cells. These findings are of particular interest because of the unprecedented relationship being drawn between histological/anatomical characteristics and mechanical properties—it could be hypothesized, therefore, that macrophages induce a weakening of the arterial wall, whereas smooth muscle cells may be a strengthening factor. No statistically significant correlation could be made with collagen.

As outlined above, the authors do not hold back in describing the limitations of this study. The primary criticism is that these experiments were performed within the limits of a very precise set of pressure and temperature parameters in vitro, and the tissue mechanics may well be entirely different in vivo. Furthermore, the term "vulnerable plaque" implies that the fate of the plaque was known—this is not the case, as indeed all the individuals from whom the specimens were taken died from noncardiac causes, and the vulnerability has been inferred from previous experiments. Hence, the definition of this term determines the results obtained.

Despite these shortcomings, the potential advantages of this technique include the relative accessibility of IVUS in clinical practice, as well as having a tool to monitor the natural history of a plaque, with potential modifications by therapeutic measures. On the other hand, many individuals may find having an elastogram to monitor their plaque progression to be excessively invasive!

2003

Rev Canon V. Gene Robinson is consecrated as bishop of the Episcopal Church of New Hampshire, becoming the first openly gay man to hold such a senior position; movie star Arnold Schwarzenegger is sworn in as governor of California; and former military dictator General Efrain Rios Montt is soundly defeated in the Guatemalan presidential election

Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions

R. Virmani, F. D. Kolodgie, A. P. Burke, A. Farb, S. M. Schwartz

Arterioscler Thromb Vasc Biol. 2000;20:1262-1275

Virmani et al present their reinterpretation and refinement of the American Heart Association (AHA) classification of atherosclerotic lesions. This classification arose from Davies' observations in studies of postmortem hearts from patients with coronary artery disease. Apart from having a forgettable numerical scheme rather than a descriptive one, the current paradigm suggests that there is an orderly progression of disease. It proposes that there is a stepwise advance of atheroma until mature lesions rupture, causing infarction. In this model, stable lesions with fibrous caps containing smooth muscle overlie a lipid-rich core. When rupture occurs, it exposes the thrombogenic material within the plaque, which causes platelet aggregation and coagulation, leading to further propagation of thrombus and, ultimately, vessel occlusion. On this basis, vessel wall irregularities seen at postmortem or angiography are interpreted as ruptured plaques. Such rupture is seen as the critical event leading to coronary artery death.

Limitations of the current scheme include its basis on postmortem evidence. However, the lack of prospective human studies, or of a useful animal model, precludes any alternative. Animal models of lipid-laden macrophages within a well-developed cap have been designed, though these do not mirror the clinical situation well.

Recent studies of sudden death have demonstrated other deficiencies in the above paradigm. These studies have shown thrombus without plaque rupture, but in the presence of superficial erosion only. Of two recent papers, only one has demonstrated significant inflammation at the site of erosion, indicating that while this may be important, it is not an essential event in the buildup to thrombus formation. The AHA classification does not include death with severe plaque burden, but without occlusion. It also suggests that a significant degree of luminal occlusion by the plaque is necessary before rupture may occur. However, there is now evidence that 50% of cases of sudden death with thrombus in the vessel occur with lesions of less than 75% cross-sectional area (50% diameter).

The authors have described a new classification, which is based on the AHA scheme, but is descriptive in its nomenclature, and avoids implications of mechanism. They have moved away from a stepwise progressive disease to a series of processes in which progression may be in one of many directions. For example, thrombus may form on a calcified nodule or a ruptured thin-cap fibrous atheroma, or on erosions of fibrous atheroma or intimal thickening. In particular, they highlight specific morphological events that appear to be highly important in the final stages of atherosclerosis, leading to acute thrombosis. They hope that this scheme will identify appropriate targets for the development of diagnostic procedures or interventions.

The classification is based upon histopathological findings, and, as such, it is difficult to usefully summarize the criteria for each class without losing important detail. The key events described are erosion, rupture, and thinning of the fibrous cap, and the development of a procoagulant and thrombotic environment. The factors that influence the state of the fibrous cap are not clearly known, but are clearly of great importance, and a scheme that allows more targeted study of this is likely to be useful. The authors accept that this might not be the ultimate classification, but that it at least opens the door to a new method of determining future research strategies.

2000

Research demonstrates that thalidomide may have potential therapeutic roles in the treatment of AIDS, leprosy, and some cancers; virus "I love you" crashes e-mail systems and destroys data on hundreds of thousands of computers worldwide; and Chen Shuibian, member of the Democratic Progressive Party, is inaugurated as the new president of Taiwan, ending 50 years of rule by the Nationalist Party

Widespread coronary inflammation in unstable angina

A. Buffon, L. M. Biasucci, G. Liuzzo, G. D'Onofrio, F. Crea, A. Maseri

N Engl J Med. 2002;347:5-12

The hypothesis that inflammation of a vulnerable plaque leads to its rupture has become increasingly accepted over recent years, and has spawned research into means of detecting such plaques and stabilizing them. It is unclear whether such inflammation is widespread throughout the coronary circulation or confined to a single lesion. Postmortem findings of multiple fissured plaques and the presence of diffuse coronary thrombus suggest the former.

Activated monocytes and neutrophils have been detected in the coronary sinus, but not the aorta, of patients with unstable angina. Using an alternative method of detecting activated neutrophils, others have demonstrated that they are found in the peripheral blood of patients with unstable, but not stable, angina.

In this study, the investigators assessed neutrophil activation by assay of myeloperoxidase (MPO) in the culprit vessel of patients with unstable, stable, and variant angina (the latter with demonstrable coronary spasm) and in patients with normal coronary arteries investigated for other reasons. Patients with recent infarcts and receiving nonsteroidal anti-inflammatory drugs were excluded.

Blood from the femoral vein, aorta, and the great cardiac vein (GCV)—which drains the left anterior descending coronary artery (LAD), but not the right coronary artery (RCA) territory—was sampled for MPO measurement, levels of which fall as neutrophil activation, and thus inflammation, increases.

Levels of MPO in GCV blood were found to be lower in unstable patients than all other groups. In keeping with previous research, CRP levels were significantly higher in the unstable angina group than in the others, and significant correlations were found between CRP and MPO in both the aortic and GCV samples.

The finding that MPO levels from the GCV were lower in patients with unstable lesions in both the RCA and the LAD demonstrates that the coronary inflammation is widespread.

The authors state that these findings cannot be comfortably explained by ischemia-reperfusion since one would expect similar findings in the group with coronary spasm, which was not the case.

Many previous reports have recorded instances of multiple fissured plaques at postmortem, and of active inflammatory infiltrates in atherectomy studies, respectively. These results imply either simultaneous mechanical stress, which appears unlikely, or an inflammatory process, which may be either multifocal or generalized. Such a process then leads to vasoconstriction and a prothrombotic state. The mechanism by which neutrophils become activated remains unclear.

Other studies have demonstrated that 70% of patients with severe unstable angina are found to have elevated levels of CRP, and of these, approximately 20% will continue to have elevated levels at 6 months, associated with a higher event rate. Intriguingly, patients who suffer myocardial infarction without prior unstable angina have lower rates of elevated CRP, which suggests that the mechanism of vasoconstriction and thrombosis is not the same in all cases of acute coronary thrombosis. However, this study clearly challenges the theory of there being a single vulnerable plaque, but rather suggests that there is a more generalized inflammatory process throughout the coronary vasculature.

2002

Alexandros Yiotopoulos, a mathematician and the leader of the November 17 terrorist group, is arrested; former Yugoslavian president Milosevic is diagnosed with a serious heart condition delaying his war-crimes trial at The Hague; and Ted Williams, the legendary Boston Red Sox baseball player, dies in Inverness, Florida, aged 83

True 3-dimensional reconstruction of coronary arteries in patients by fusion of angiography and IVUS (ANGUS) and its quantitative validation

C. J. Slager, J. J. Wentzel, J. C. Schuurbiers, J. A. Oomen, J. Kloet, R. Krams, C. von Birgelen, W. J. van der Giessen, P. W. Serruys, P. J. de Feyter

Circulation. 2000;102:511-516

ANGUS is an intriguing acronym resulting from the bold fusion of "angiography" and "IVUS" (intravascular ultrasound). In this paper, the investigators hope to convince the interventional cardiology community that this is a new method for imaging coronary vessels. Intuitively, the benefits of ANGUS over IVUS are clear—the former offering a three-dimensional (3-D) representation compared to the 2 dimensions of the latter, and therefore allowing a more immediate understanding of the coronary anatomy. However, in order to achieve this goal, a number of relatively complex concepts need to be grasped, with a background of some rather daunting mathematics.

The authors begin by describing the basic requirements for constructing a 3-D image of the coronaries. A biplane x-ray imaging system was required to construct a virtual "calibration cube," within which the 3-D position of any marker could be reconstructed. Taken further, a 3-D IVUS pullback trajectory could then be derived from successively reconstructed transducer positions using the IVUS catheter itself as a reference or "backbone," to produce a catheter "core line," which was used to represent the trajectory. The IVUS images were acquired after detection of an R-wave on the ECG, after which an automated stepping motor would pull back the IVUS catheter by increments. Following this, the IVUS cross-sections would be repositioned upon the reconstructed trajectory. This repositioning involved 3 steps: firstly, the transducer locations on the trajectory would need to be reconstructed; secondly, the center of the IVUS image was positioned at a reconstructed transducer location; and finally, the image would have to be rotated around the trajectory to account for the changing orientation of the vessel. These final steps necessarily involved some complicated computational procedures that are explained in some detail.

ANGUS was initially validated against an in vitro model, followed by an in vivo trial involving 16 patients seen 6 months after the implantation of a Wallstent, with all 3 major epicardial vessels studied (left anterior descending, circumflex, and right coronary artery). Analysis of the results indicated that the 3-D reconstruction was surprisingly accurate for both distance and diameter measurements, when validated against the angiographic silhouette (including the visualization of stented portions), with clear clinical implications.

However, there are some notable limitations. Firstly, a biplane imaging system is required and the quality of the x-ray images has to be good enough to allow a 3-D reconstruction to be made. Hence, there would be obvious problems in applying ANGUS to patients who are obese and often have poor angiographic data as a result. Secondly, the IVUS system used was sheath-based, which allowed for an accurate construction of the core line, but devices without this feature would require new methods. Next, one of the main reasons why a "core line" trajectory could be obtained was because the sheath position was stable within the vessel; it is possible that within larger vessels there could be a greater degree of movement, and therefore error. Conversely, in the presence of tight stenosis, friction with the sheath could introduce rotational error. Finally, side branches are not taken into account during the reconstruction.

Hence, the benefits of ANGUS make it a technique worthy of further investigation, but combining two imaging modalities that each have their own flaws may expose a potential to accruing a greater number of errors than each component individually.

2000

Two hundred people from North and South Korea meet relatives on the other side of the border for the first time in 50 years; Indonesia's disgraced former dictator Suharto is charged with embezzling $400m of state funds; and Sir Alec Guinness, the versatile British stage and film actor, known for his gifts of mimicry and characterization, dies

Incidence of high-strain patterns in human coronary arteries: assessment with three-dimensional intravascular palpography and correlation with clinical presentation

J. A. Schaar, E. Regar, F. Mastik, E. P. McFadden, F. Saia, C. Disco, C. L. de Korte, P. J. de Feyter, A. F. van der Steen, P. W. Serruys

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The thrombosis that occurs in acute coronary syndromes may be superimposed on a variety of underlying coronary pathologies, including ruptured thin-cap fibroatheroma. Plaque rupture may occur when the cap is weakened by the ingress of inflammatory cells such as macrophages, which produce metalloproteinases. Plaque rupture is particularly likely in places with high mechanical stress, which is caused by the pulsatile nature of blood pressure.

In this paper, the authors describe intravascular palpography, which is a relatively newly developed technique. It measures vessel wall strain with radiofrequency ultrasound signals according to the principle that the strain of the tissue is a function of its mechanical properties. A color-coded display is combined with intravascular ultrasound (IVUS) images to show the position of areas with high strain. A typical strain pattern has been described that was highly sensitive and specific for thin-cap atheroma when tested in postmortem coronary arteries. This study sought to determine the frequency with which this pattern could be found in patients undergoing intervention for unstable and stable angina and acute myocardial infarction.

This study recorded palpograms of culprit vessels in patients with stable and unstable angina and of nonculprit vessels in patients with acute myocardial infarction. In each group, the left anterior descending coronary artery (LAD) and right coronary artery (RCA) were studied with equal frequency, whereas the circumflex artery currently presents technical difficulties and was not studied. The main parameter recorded was the number of lesions with the typical pattern of a vulnerable plaque. In stable patients, 0.6±0.6 such lesions were found compared to 1.6±0.7 in unstable angina (P=0.002) and 2.0±0.7 in acute myocardial infarction (P<0.0001), with no significant difference between the latter two groups. A similar number of lesions were found in the LAD and RCA. C-reactive protein (CRP) levels followed a similar pattern, and there was good correlation between the CRP level and the number of vulnerable plaques (R^2, 0.65; P<0.0001).

This study thus provides the first evidence that the high-strain pattern observed in postmortem specimens can be detected in a clinical setting. The frequency of such findings alters with the nature of clinical presentation. This supports the hypothesis that acute coronary syndromes are part of a multifocal inflammatory process. The number of lesions found is similar to the number of thin-cap fibroatheroma lesions found in postmortem studies, and it is these lesions that the authors imply their technique identifies.

The authors accept that this study provides no data on which to base decisions regarding intervention, and that prospective studies following the natural progression of the lesions identified by this technique are required. In addition, the practical difficulties that might be caused by combining IVUS with this second modality might limit its uptake unless it shows substantial utility as a clinically useful predictor of future events by reliably identifying the "vulnerable plaque."

2004

The Cassini space probe enters orbit around Saturn and returns stunning photographs of the planet's ring system; an interim cabinet of 36 Iraqis assumes power from the Iraqi Governing Council led by Prime Minister Iyad Allawi; and French president Jacques Chirac hosts world leaders to commemorate the 60th anniversary of the Allied landings in Normandy

CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: report from the laboratory science discussion group

G. L. Myers, N. Rifai, R. P. Tracy, W. L. Roberts, R. W. Alexander, L.M. Biasucci, J. D. Catravas, T. G. Cole, G.R. Cooper, B.V. Khan, et al

Circulation. 2004;110:e545-e549

In light of the increased understanding that inflammation plays a key role in the development of atherosclerosis, the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) reviewed the data regarding inflammatory markers. The paper discusses the potential measures and assesses which might be usefully employed as clinical predictors of cardiovascular disease.

Cytokines and chemokines such as tumor necrosis factor and interleukins present practical obstacles. They require enzyme-linked immunosorbent assay (ELISA) techniques for measurement and, due to the short half-lives of these factors, samples must be frozen rapidly after they have been obtained. Commercial assays have been designed to measure the high levels seen in acute inflammation, and are not sufficiently sensitive to measure the lower levels associated with ischemic heart disease pathogenesis in "apparently well" individuals. Soluble adhesion molecules including soluble intercellular adhesion molecule–1 (sICAM-1), soluble vascular cell adhesion molecule–1 (sVCAM-1), and selectins may all have possible future utility in this regard, but share the practical difficulties with assays described above for cytokines.

There has been more success in utilizing acute phase reactants as predictors of future risk, like fibrinogen and serum amyloid A (SAA). Since fibrinogen is a component of the clotting pathways, functional assays tend to be more commonly used, though they require swift measurement after taking the sample. Immunoassays are more stable, but less commonly used, and there are no standards to allow comparison of results from different assays. SAA presents similar problems, and the presence of different phenotypes adds further to this, though it is likely that these problems will be surmounted in the near future.

The most investigated of all the potential markers is C-reactive protein (CRP). A many hundredfold rise in the level of CRP is seen in response to inflammation, injury, or inflammation, and the stability of the protein makes its measurement more practical. In subjects without acute inflammation or infection, the levels recorded using high-sensitivity assays of CRP (hsCRP) are correlated with future risk of cardiovascular events. There is variability of measurements between manufacturers of assays, and this requires harmonization according to global standards. Factors that increase the suitability of hsCRP as a biomarker include its remarkable freedom from variation across racial groups and gender. It is little affected by age, and seasonal variation follows no particular pattern, which might otherwise confound results. Samples are better taken during fasting conditions, as turbid serum will reduce accuracy of the assay.

High measures that suggest acute inflammation (>10 mg/L) should be excluded, and the test repeated once further investigations and treatment as appropriate have been performed. There is a degree of intraindividual test variability and it is recommended that two samples should be taken at least 2 weeks apart, and the mean result used for risk prediction. Subjects may be divided into tertiles of future risk (low <1 mg/L, medium 1-3 mg/L, high >3 mg/L).

In conclusion, hsCRP remains the only practical marker of inflammation at present. Other analytes hold promise, though the lack of suitable commercial assays and the absence of standardization will continue to prevent their application in the clinical setting.

2004

A tsunami originating off the island of Sumatra kills nearly 140 000; the Bill and Melinda Gates Foundation is to donate $42.6 million to a nonprofit drug company attempting to produce an inexpensive malaria treatment; and President Jacques Chirac inaugurates the world's highest bridge, the Millau Viaduct, spanning the Tarn valley in southern France

Acute Coronary Syndromes

Bibliography of One Hundred Key Papers

selected by **Marco Valgimigli, MD; Gastón A. Rodriguez-Granillo, MD; Pierfrancesco Agostoni, MD; Patrick Serruys, MD, PhD**

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