Unstable Angina in 1998

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Summary

Unstable angina (UA) and non-Q-wave myocardial infarction (NQWMI) are acute coronary syndromes with repeated, severe ischemic events of short duration. These events are mainly due to a rapid decrease in coronary blood flow, and to a rapid, reversible reduction of the arterial lumen in localized areas. Episodes often are a mixture of thrombus formation due to platelet aggregation and localized spasm, leading to vasocostriction. Due to the short interval (minutes) of ischemic events, usually no or minimal irreversible myocardial damage takes place.

The main goal of treatment is to prevent progression of this unstable situation into a myocardial infarction. In the majority of cases, this is possible with adequate treatment of vasodilatory substances like nitrates, long-acting dihydropyridines like amlodipine and betablockers. In addition heparin and particular antiaggregatory drugs inhibiting platelet activation by blocking the GPIIb/IIIa receptor, the common pathway for platelet aggregation, are applied to prevent thrombus formation. This, in the majority of cases allows a passivation of the acute situation, leaving time to undertake possible further steps as coronary angiography, eventually followed by PTCA of the culprit lesion or, in advanced cases of CAD, by CABG with complete revascularization.

Introduction

This syndrome has a long history, and there are multiple denominations like acute coronary syndrome, acute coronary insufficiency, preinfarction angina, intermediate coronary syndrome, impending myocardial infarction, rest-angina, and the latest and most commonly used term “unstable angina” (UA) in contrast to “stable angina”. The title of the article, “unstable angina in 1998”, indicates that this presentation will deal mainly with the most recent advances in this field, concerning both diagnosis, treatment strategy and briefly new treatment possibilities (8, 53).

Firstly, we have to discuss the question, why it is so important to distinguish between unstable and stable angina? An important factor is that the pathophysiological and clinical course of the two types of angina differ considerably. In unstable angina, especially when we are not presented with a “non-Q-wave myocardial infarction” (NQWMI), that means when ischemia is still reversible, and there is no definitive irreversible myocardial damage, prognosis is considerably better than in the presence of an already starting acute myocardial infarction. UA has to be regarded as a transition stage between silent CAD and the beginning of an acute myocardial infarction with all its consequences.

Therefore, the definition of this syndrome is as follows: UA is an acute syndrome of early manifestation of coronary artery disease (CAD) with clinically silent and manifest ischemic events, leading to transient, yet still reversible wall motion changes, a stage shortly before the development of irreversible myocardial damage. Clinically, three different types of events can be distinguished in UA. Braunwald, in 1989 (2), defined the following three classes: Class I: New beginning of severe, progressing angina, occurring for the first time in life, patients with new angina at exertion (> 3 episodes per day); chronic stable angina with sudden acceleration, without pain at rest; angina lasting less than 2 months; Class II: Angina at rest, yet subacute, patients with one or more episodes per day during the last 2 months, yet not during the last 48 h. Class III: Angina at rest, acute, patients with several episodes per day during the last 48 h. In addition, he added UA with regard to special clinical situations as causes. Class A: Secondary unstable angina: extracoronary disease leading to angina (reduction of MVO2, increase of Ó2 demand) due to anemia, fever, infections, hypotension, hypertension, tachyarrhythmias, hypoxia in lung disease etc. Class B: Primary UA; patients with UA without extracoronary diseases. Class C: Postinfarction angina, patients with UA during the first 2 weeks after documented myocardial infarction. Patients can be combined with Class I to III. As UA happens during the preinfarction period, the main goal of treatment consists in the prevention of an acute myocardial infarction or, in the presence of a NQWMI, in the prevention of a transition to a QWMI, with irreversible myocardial damage. For the heart this is especially important as the heart is not able to replace dead myocytes. The number of myocytes is determined at birth.

Diagnosis

The diagnosis of UA is primarily a clinical one (3, 4), based on the recognition of typical symptoms, as mentioned above. The diagnosis must be based on an exact history regarding typical signs of CAD, including the above mentioned criteria. The physician confronted with such a patient must follow its clinical course very closely and start medical treatment as early as possible, before sending the patient to a hospital. If chest pain and typical signs of ischemia, documented by ECG cannot be controlled within a short time, i.e. in less than 2 h, the patient should be hospitalized, preferably in a hospital able to perform invasive diagnosis and treatment, if necessary.

Pathophysiology

In order to understand the special diagnostics, the physician must have a basic knowledge of the pathophysiology of UA (15-17, 20, 34, 38). In the great majority of patients, the underlying changes are of atherosclerotic origin, pure spasm (Prinzmetal angina) is rare. This presentation will therefore concentrate on organic changes in the
coronary artery system. Today, the pathophysiology of UA is well known and therefore will be mentioned only briefly in this article. Atherosclerosis usually starts with endothelial injury, caused by various events, lipid infiltrations, ulceration of small plaques (4, 16), followed by ruptures of soft plaques; this leads to exposure of subendothelial layers of matrix proteins, collagen, fibrinogen, fibronectin, von Willebrand factor (31), exposed to flowing blood. Platelets adhere to this layer through specific receptors as GP (glycoprotein) Ib (22, 23) and integrin, leading to platelet activation and aggregation, especially through activation of the fibrinogen receptor of GpIIb/IIIa, (32) enabling the binding of fibrinogen; this then leads to the formation of thrombi of various sizes. The process is often supported by functional changes, especially local vasoconstriction, platelet-dependent, mediated by leukotrienes, serotonin and thromboxane A2 as well as thrombin-dependent vasoconstriction, further enhancing the decrease in lumen size of the coronary vessel. The formation of fresh thrombi most often leads to considerable luminal reduction, a drop in oxygen delivery, followed by ischemia (silent or manifest), yet without irreversible myocardial damage. Hence, these episodes are transient, and occur most often at rest, where the transition from a pain-free to a painful stage is due mainly to additional, reversible attacks of vasoconstriction, but also to thrombus formation. Vasoconstriction (5) seems to be due to endothelial dysfunction or to deep arterial damage with plaque disruption, caused by vasoconstriction in the area of the culprit lesion; it can also be provoked by endothelial injury, acetylcholine and by vasoconstrictor mitogens like leukotrienes and serotonin (62). If one thinks in teleological terms, the whole process put into action during plaque rupture is — as it were — a misunderstanding by nature. The thrombus formation initiating the cascade of plugging is a necessary mechanism correcting severe local vascular damage during rupture of the vessel wall followed by life-threatening bleeding. This necessary and healthy mechanism here leads to an unnecessary plugging of the vessel lumen, due to overreaction of specific blood clotting mechanisms.

**Definition of High and Low Risk Patients**

In the following chapter the most important steps to be undertaken by the physician confronted with a patient developing UA are discussed. As mentioned before, the first step is to establish a correct diagnosis as quickly as possible. As said earlier, this depends mainly on the patient’s history and the acute clinical signs. If the patient has already previously suffered from manifest episodes of CAD the diagnosis is relatively easy.

In case of first attacks of angina, however, one has to analyze exactly the number of attacks per hour and days, their intensity and duration, to find out whether they occur at rest or also during exercise, the latter being the exception in UA. Non-invasive clinical tests are mandatory, especially ECGs at rest, also a 24 h ambulatory ECG (44, 45), and — if feasible, when resting ECG is still normal — an ECG under exercise. ECHO-tests are only valid if done during the anginal attack, as in early anginal episodes the myocardium is usually still normal in the absence of ischemic attacks. — Repeated blood tests include cardiac enzymes (CK-MB), and troponin T or I plasma levels (29, 37). The most important thing, however, is to always include UA in the differential diagnosis of acute chest pains. It can occur in all age groups, in young, so called healthy people, and in elderly ones who so far had been free of any signs of CAD.

If the diagnosis is definitely positive, the physician today is often in a dilemma. On one hand he should try and undertake everything to prevent a myocardial infarction, on the other hand, he should act reasonably, and this means he must make a decision whether he should send the patient immediately to a hospital familiar also with invasive treatments, or whether he can treat the patient at home, especially elderly patients. This raises the question whether treatment at home of patients with UA is still permitted today?

The opinions and guidelines on this problem are controversial especially for mild, low-risk cases. Fuster, Theroux and Braunwald (3, 53), as well as the task force of the ESC (48) in low-risk patients with new onset of exertional angina and minor exacerbation of chest pain during exercise, promptly relieved by nitroglycerin, recommend a “home treatment” with the necessary drugs (nitrates, aspirin, opioids, morphine, furosemid). Close follow-up and further investigations are, however, necessary. This group of patients with only exercise-induced pain is however rare, as was said before. Hospital treatment includes mainly high-risk patients with angina at rest and abnormal ECG signs during anginal attacks. The critical question remains, however, the definition of a low-risk or high-risk patient. The low-risk patient has a low likelihood of CAD, no family history, a new onset of the disease, mainly effort angina, a low UA score (1 to 2/6), a normal resting ECG, normal blood tests, especially CK-MB and troponin T and I, both being normal at admission and after 8 and 12 h, and an echocardiogram without any regional dysfunctions, no perfusion defects, no hypertension yet a normal pressure.

The high-risk patient in contrast has a documented history of prolonged pain at rest, recurrent angina (silent or manifest) mainly at rest, a UA score of 5-6, an ECG with ST-segment shifts during angina at rest and during mild exercise (both ST-depression and elevation), elevated CK-MB and troponin values, eventually perfusion defects and transient LV dysfunction.

Patients with pain at rest, or even silent ischemia at rest, should be hospitalized, especially if the diagnosis of UA or NQWMI has been clearly established by positive ECGs at rest and the above mentioned blood tests (1, 30). Most studies recommend that patients with ruled-out diagnosis of myocardial infarction yet prolonged pain, should be observed in the emergency room, and should have a 24 h ECG, as well as the above mentioned enzyme studies at admission and 8 and 12 h later to rule out myocardial damage. Patients with repetitive pain, ST-segment changes, especially ST-elevation, troponin T and I levels elevated, should undergo close monitoring and treatment in a CCU; hence they should be sent to a hospital with the availability of invasive studies and a possible treatment. It should be mentioned that mortality of UA is highest at the time of hospital admission and decreases over the next two months. Patel et al. (46) studied 212 patients with UA, average age 59 years, recruited within 24 h of an anginal episode. Death, myocardial infarction and/or revascularisation were assessed for 2.6 years. Risk of death was highest in the first 6-8 weeks after admission. Prognosis was best in patients with normal ECGs. Transient ischemia or hypertension predicted best an increased risk of death or myocardial infarction. In 14 patients, ST-segment monitoring provided the only evidence of recurrent ischemia and 72% of these patients suffered adverse events.

**Clinical Trials**

At this point of our analysis of UA, after discussing the diagnosis of UA, and the risk strategy, in 1998, when invasive treatment is quickly at hand, the question arises whether a more thorough investigation is necessary, e.g. the demonstration of the coronary artery system by angiography in order to evaluate the need for PTCA or CABG to prevent an acute myocardial infarction with a possible fatal outcome.
This question is difficult to answer as there have only few studies been performed comparing medical treatment of UA with invasive treatment, especially CABG. This is the National Cooperative Study in 1977 (27) and the Veterans Administration Cooperative Study in 1987 (35). Similar survival rates with the two therapies have been observed in both studies. In the former study mortality at one year was 8% in surgical patients and 7% in medically treated ones. In the Veterans Administration study the results at 2 years were 11.7% and 12.2%. There was, however, considerable cross over from medical treatment to surgery, 19% at 1 year for the National Cooperative Study, and 34% at 2 years for the Veterans Administration Cooperative study. In this study, a subgroup of patients with triple-vessel disease, followed over 5 years showed a significantly better survival for surgical patients, 89%, than for medically treated ones with 75% (p = 0.02). Mortality in patients with ejection fractions between 30% and 49% was reduced from 27% to 14%.

More important are studies comparing medical treatment with PTCA. The first study was the TIMI 3 B trial (1994) (56), with an early invasive (PTCA or CABG) and early conservative patient group, including a total of 1473 patients with UA or NQWMI. Patients in the early invasive arm underwent coronary angiography within 24-48 h after randomization followed by PTCA or CABG. In addition, patients were treated with t-PA or placebo. Ninety-eight % of patients randomized to the early invasive group had cardiac catheterization versus 69% in medically treated ones. Angioplasty was performed in 64% and surgery in 49%. There were no differences in the primary endpoints, death, myocardial infarction or a positive exercise test after 6 weeks. Primary endpoints were reached in 18.1% of conservatively treated patients and in 16.2% of invasively treated ones (p = ns). Death or myocardial infarction occurred in 7.8% and 7.2% of patients at 6 weeks and 12.2% and 10.8% after one year (p = ns). Hence, there was no difference between the two treatment groups concerning major events. It should, however, be mentioned that 64% of patients randomized to medical treatment crossed over to invasive treatment because of recurrent angina or positive exercise tests. Hence, the disadvantage of this study is the relatively large number of patients, who crossed over to surgery. The advantage was a significantly shorter hospitalization and less antianginal treatment in the surgical group. – Opposite results were found in the VANQWISH-study (59) (the Veterans’ Affairs NQWMI Strategies in Hospitals). This study included 820 patients randomized either to early aggressive strategy, with early catheterization and possible invasive treatment versus early conservative strategy, with standard medical therapy and a predischarge stress test. Here, the incidence of death and myocardial infarction was with 3.3% versus 7.8% at discharge, significantly lower in the conservatively treated group; after one month it was 5.7% versus 10.4% and after one year 18.5% versus 24%. Revascularisation rate at 1.5 years was 44% in patients with early aggressive management and 33% in those with early medical treatment (p = ns).

These two studies are at first glance conflicting; the TIMI 3 B trial shows no significant difference between the early conservative and early invasive treatment groups over one and more years; the VANQWISH-study demonstrates a slightly better early outcome with initial conservative treatment, at least in the first year. Unfortunately, both studies again had a large crossover rate from conservative to invasive, 64%, but also 44% of patients randomized to surgery changed to medical treatment. These large crossovers, to a certain extent, invalidate the data. At least they indicate that many patients with early conservative treatment, 50%, later still become candidates for invasive corrections, PTCA or CABG. Early angiography in patients with a history of prior revascularization (17), repeated prolonged anginal attacks refractory to medical therapy, or depressed left ventricular function (26) seem to be recommendable for surgery. In these patients, myocardial infarctions often become impending, and the risk is rapidly increasing, due to underlying thrombotic formations which cannot be corrected medically.

From the above mentioned studies one can conclude that for a large majority of patients with the diagnosis of UA or NQWMI, the short-term prognosis is a good one, provided adequate and immediately starting medical treatment is available (39, 40). The course over the first 6 days often decides whether invasive treatment will become necessary (7). Intensive treatment with aspirin, anticoagulants, GPIIb/IIIa inhibitors (lamifiban, tiroliban, abciximab), heparin, eventually hirudin, often reduces or even stops ischemia within days.

Nevertheless, the risk of recurrence is high after UA and NQWMI, even when medical therapy with the above mentioned drugs is closely followed. Several studies mention rates of death and myocardial infarction after 4-6 weeks of 8% and 14% and of death, myocardial infarction or refractory ischemia of 15-25% (7, 28, 29, 40, 46, 55-57, 58, 63). The period of high risk includes several months after UA, requiring a close follow-up, especially in patients without angiography, where the extent of CAD is unknown. In case of repeated episodes of UA, coronary angiography and possible invasive treatment are mandatory and should be performed rather early in time. The term “plaque passivation” (22), intending to prevent reactivation and recurrence of platelet aggregation and thrombus formation, addresses this problem.

**Modern Treatment of UA**

The last part of this presentation briefly addresses treatment of UA, especially the most recent progresses. In the last years new drugs for antithrombotic treatment with the aim of “plaque passivation” and prevention of recurring ischemic events were introduced. As these new techniques will change the treatment of UA to a great deal, this selection concentrates mainly on them.

**Nitroglycerin**

Nevertheless, the standard treatment of UA still has its place and should not be abandoned: vasodilatation, prevention of vasoconstriction is best done by nitroglycerin, applying a long-acting form orally or better, applied as infusion. Nitroglycerin also prevents ischemia (silent and manifest) and reduces elevated blood pressure. Due to tolerance, application has to be on an intermittent basis. Nitroglycerin can be combined with betablockers, lowering the angina threshold, especially in the presence of an increased heart rate and/or blood pressure.

**Calcium Antagonists**

Calcium antagonists improve coronary blood flow by vasodilatation, and reduce blood pressure; especially active are long-acting forms such as amlodipine, with a half-life of more than 24 h or nifedipine GITS (Gastrointestinal system); however, the latter still has inconsistent blood levels although to a much lesser degree than the short-acting calcium antagonists, like the nifedipine capsule; these should not be used anymore for UA, unless for acute control of high blood pressure.

**Aspirin**

The classic drug for antithrombotic therapy is still aspirin (9, 12, 51, 52). Aspirin inhibits cyclooxygenase and by this, the metabolism of arachidonic acid to prostaglandin-endoperoxid and prostacyclin and
finally to TxA2, a potent platelet agonist. One should, however, remember that platelet aggregation can be initiated by several substances, like thrombin, collagen, ADP, and adrenaline, each of these substances interacting with specific receptors on the platelet surface, ultimately activating the fibrinogen receptor function of GPIIb/IIIa, the final common pathway for platelet aggregation. Hence, it is important to know that this receptor function of GPIIb/IIIa (15) is activated by several signal transduction pathways, and therefore, the inhibition of any of these drugs alone has only a modest effect on platelet aggregation, as several other pathways bypass cyclooxygenase.

For all these reasons, in the eighties aspirin became a standard drug also for treatment of UA (13, 41, 51, 61). Several double-blind studies, performed already in the eighties, first by Lewis (33), then by Cairns (9), Theroux (55) and others demonstrated in patients with UA a significant reduction of the incidence of myocardial infarctions or death by 51%, 52%, 62% and 72% (p = 0.012-0.0005).

The dose of aspirin ranged from 75 to 1300 mg per day, treatment duration from 9 days to 24 months.

### Heparin

Also heparin (24) in the unfractionated form (UFH) is widely applied in UA since several years. Its efficacy is documented in several studies (14, 42); it is administered as an i.v. bolus followed by an infusion with PTTs of 65-90 s. A study by Theroux et al. (55) in 479 patients showed a significant reduction in myocardial infarctions from 11.9% to 0.8% (RR-93%) (p < 0.001) and in refractory ischemia from 22.9% to 8.5% (RR-63%) (p = 0.002). Oler et al. (42), in a meta-analysis of 1315 patients demonstrated a 33% reduction in death and myocardial infarctions in patients on UFH and ASA versus ASA alone. The combination of aspirin and heparin (55) brought a further decrease in the rate of myocardial infarction or death in patients with UA or NQWMI within the first five days by 36%. Low-molecular-weight heparin (14), introduced more recently, has a better bioavailability, induces less platelet activation, can be applied subcutaneously and therefore is often preferred to UFH inspite of a higher bleeding rate.

For the FRISC study (21), analyzing low-molecular-weight heparin during UA, showed daltaparin superior to placebo. The ESSENCE study with 7081 patients, analysing the efficacy and safety of subcutaneous enoxaparin (14) in NQW coronary events at 30 days demonstrated a 20.4% reduction rate of death and myocardial infarction and a 15% decrease in rate of death and myocardial infarction and refractory ischemia for enoxaparin given for an average of 2.6 days (4 h to 7 days) as compared to standard heparin. At 8 days events were 13.4% for UFH and 10.6% for LMWH (p = 0.02). Hirudin, on the other hand, seems to be associated with a relatively high risk of bleeding (24).

### Thienopyridines and GPIIb/IIIa Antagonists (Table 1)

More recently, 3 classes of substance became important as antiplatelet drugs, the mimetics of prostacyclin, the thienopyridines (ticlopidine, clopidogrel), and most importantly the fibrinogen receptor blocking agents, the GPIIb/IIIa antagonists. This presentation – only concentrates on the last group.

The typical examples of the thienopyridines are ticlopidine and clopidogrel (6). Both interfere specifically with the ADP receptor on
the platelet surface and by this stop platelet aggregation and the transformation of GPIIb/IIIa into its high affinity state. But, like aspirin, these two drugs interfere with only one of several pathways. The precise mechanisms are not yet clear. Nevertheless, in a study with 625 patients with UA, ticlopidine 250 mg twice daily showed a 46% reduction in the combined endpoints of vascular death and fatal and nonfatal myocardial infarction at 6-month follow-up. Important is the observation that the effects of ticlopidine on platelet aggregation become manifest after 2-4 days only. Hence, it cannot be applied as an immediately effective antiaggregatory drug in the first hours of UA.

The inhibitors of GPIIb/IIIa (15, 32, 52), which directly block the final common pathway for platelet aggregation, are the most promising of the 3 groups of these drugs. Several drugs based on this molecular pathway shall be mentioned, also the most important clinical studies. The earliest study was done with integrilin (eptifibatide), a synthetic cyclic peptide of seven amino acids, which specifically blocks the GP IIb/IIIa receptor. It was tested in the PURSUIT-trial with 10,948 patients (10). Integrilin significantly reduced the number of ischemic events, the duration of ischemia as well as the risk of death and myocardial infarction after 96 h by 16.5% (p = 0.001), at 30 days to a lesser degree, from 15.7% to 14.2%, a risk reduction of 9% (10). The PRISM-PLUS trial (47), applying tirofiban, the first non-peptide GPIIb/IIIa receptor antagonist undergoing clinical evaluation, compared tirofiban alone with tirofiban plus heparin and with heparin alone, all patients receiving also aspirin. Included were 915 patients with UA or NQWMI, undergoing a 48 h infusion period; after that patients underwent coronary angiography (90%) and continued with the drug. In case of PTCA, study drugs were prolonged up to 24 h. Primary endpoints were at 7 days, secondary at 30 days. At 7 days the combination of tirofiban and heparin significantly reduced the risk of death and myocardial infarction from 8.3% (UFH alone) to 4.9% (T+H), i.e. by 41% versus heparin alone (p = 0.04); at 30 days tirofiban and heparin reduced the risk of refractory ischemia, myocardial infarction or death from 11% to 8%, that is by 22% versus heparin alone; after PTCA from 10.2% to 5.9% (-27%). Of the 773 patients treated with heparin and tirofiban 3.9% experienced myocardial infarctions versus 7% of the 797 patients with heparin alone. The risk of myocardial infarction or death was 8.3% in the heparin group and 4.9% in the combined group (p = 0.006). Major bleedings were insignificantly higher in the tirofiban plus heparin group (1.4 vs 0.8%) (p = 0.23). It should be mentioned that the tirofiban-alone-arm was dropped early due to excess mortality, without, however, any excess of myocardial infarction or refractory angina. Similar results were also observed in the RESTORE-trial (randomized efficacy study of tirofiban on outcome and restenosis) (49), evaluating the effect of tirofiban in patients with acute ischemic syndrome undergoing angioplasty. The risk of an event at the second day was reduced by 38% with tirofiban plus heparin (p = 0.005) and by 27% after 7 days (p = 0.022); it was insignificant at 30 days (p = ns).

The PRISM-trial (platelet receptor inhibition ischemic syndrome management) (60) for ischemic symptoms showed no excessive mortality with tirofiban alone versus heparin alone, yet a significant risk reduction of death, myocardial infarction or refractory ischemia during the 48 h drug infusion by 36%. The EPILOG-EFFICAY-TRIAL (evaluation in PTCA to improve long-term outcome by c7E3 GPIIb/IIIa receptor blockade) (19) applied ReoPro (abciximab), which not only blocks the GPIIb/IIIa receptor, but also inhibits the vimentin receptor (alpha n, beta 3) with the aim to reduce bleeding. It included 2792 patients with UA or NQWMI, referred for urgent PTCA, who applied ReoPro and heparin, the latter with standard and low doses. There were 3 arms: UFH plus abciximab as bolus and infusion, LDH plus abciximab as infusion, and UFH alone. At 30-day endpoints, death, myocardial infarction or urgent intervention showed a reduction from 11.7% with heparin alone to 5.2% (LDH) and 5.4% respectively with abciximab and heparin (p = 0.001). At 6-month endpoints there were 25.8% in the heparin group and 22.3% in patients with abciximab plus UFH (RR-14%) (p = 0.04). Major bleedings were 3.1%, 2.0% and 3.5%. Hence, the effect of ReoPro was still present after 6 months, but clearly attenuated as abciximab was no longer applied.

The CAPTURE-trial (11), applying abciximab in 1265 patients with refractory UA, on nitrates, aspirin and heparin prior to percutaneous interventions, had two treatment groups, one with ReoPro as bolus followed by infusion over 18-24 hours before PTCA and a placebo group. Endpoints were death, myocardial infarction or urgent revascularization. The final analysis at 30 days on 1265 patients showed a reduction of death, myocardial infarction and urgent revascularization from 15.9% (placebo) to 11.3% in the abciximab group (RR 29%) (p <0.012). Death was reduced from 1.3% to 1.0% (p = ns), myocardial infarctions from 8.2% to 4.1% (RR-50%) (p = 0.002), the need for urgent revascularization from 10.9% to 7.8% (RR-28%) (p = 0.054).

The PARAGON-trial (43, 54) belongs to the most recently published studies (1998). It analyzes the different doses of lamifiban, a platelet IIb/IIIa antagonist, alone and in combination with heparin. 2282 patients were randomized to lamifiban low dose (1 µg/min) with and without heparin versus high dose (5 g/min) with and without heparin or to placebo and heparin. All patients received aspirin. The primary endpoint of death or myocardial infarction at 30 days occurred in 11.7% of patients with standard therapy, 10.6% in those with low-dose and 12% in those with high-dose lamifiban, hence, no significant differences were found (p = 0.668). At 6 months, endpoints were lowest for all those patients assigned to low-dose lamifiban (p = 0.027) versus those on high-dose lamifiban plus heparin (p = 0.450) (low-dose lamifiban 13.7%, high-dose lamifiban 16.4%, UFH 17.9% alone). There was more bleeding in patients with high-dose lamifiban (12.1% versus 5.5%; p = 0.002) and a similar rate of ischemic events. Low-dose lamifiban and heparin had similar bleeding rates (0.8% and 0.5% respectively, high-dose 2.4%). There were also fewer ischemic events at 6 months (12.6% versus 17.9%) (p = 0.025).

Concluding Remarks

Early diagnosis and start of treatment are mandatory, therefore UA and NQWMI should always be on top of the differential diagnosis of chest pain, occurring suddenly. There is no doubt that for a large number of patients with silent CAD, myocardial infarction could be avoided, if the correct diagnosis of UA were made early, in the beginning of the development of this syndrome. Here, the way how medicine is performed can indeed be life-saving. Because, as the most famous internist of the last century, William Osler, already said 100 years ago: Medicine is an art, but it must be based on science!

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