UNSTABLE ANGINA, MYOCARDIAL INFARCTION, HEPARIN AND DEATH: MEDIUM DOSE HEPARIN (NOT EXCEEDING 20,000 UNITS/DAY) IN THE TREATMENT OF PATIENTS WITH ACUTE CORONARY EVENT—FIRST YEAR AND LONG-TERM COMPARATIVE MORTALITY*,†

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In the treatment of acute myocardial infarction (MI) and unstable angina pectoris (UAP), where heparin has been used it has generally been given as an introductory agent to the oral anticoagulants, in high dosage, and with disputed results (1). Indeed, controversy in the medical literature about the value of "anti-coagulants" in the management of coronary heart disease (CHD) has persisted for almost 40 years. Nevertheless, they still are more extensively used in the treatment of acute coronary event (2) and in long term management (3) than is generally realized, especially by their detractors. Favorable results continue to appear (4). However, what we wish to present here is statistical evidence for the effectiveness of heparin, not oral anticoagulants (OAC), in the treatment of acute coronary event (ACE), both during the acute phase and in the subsequent long run management of the patient.

The plan of treatment we have used evolved in the early years of an observation period extending from 1955 to 1975. In the course of this we have accumulated experience with 42 ACE patients followed for an average of 5 years. Before the development of a subcutaneous injection technique which permitted self-administration for indefinite periods (5), we had been favorably impressed with the use of intramuscular heparin given as 5,000 units every six hours, both as an introduction for oral anticoagulants and as carried on for as long as it could be tolerated (not more than 2–3 weeks at most) before resorting to OAC at all. After subcutaneous injection techniques made resort to intramuscular injections unnecessary, we continued to use 20,000 units as our top heparin dosage for CHD patients and continued it for 3–5 weeks or longer after

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acute coronary events. We stepped down the dose by 5,000 unit decrements for longer term use in accordance with reduced risk and clinical improvement. We were ready to increase the dose to the medium range very promptly for any recurrent ACE or other high risk complication of CHD.

On the basis of our experience we are convinced that medium dose heparin is as effective for mortality reduction in ACE as higher doses would be, that it is more effective than lower doses, and that all the dosage ranges we have used are remarkably safe for long-term administration. Medium dosage for acute MI had been used in only one three week study (6) up to 1981, when a seven day clinical trial in patients with UAP (7) reported favorable results: facts that render the substance of this report of particular importance clinically.

Table 1 lists the actions of heparin that appear to have pertinence to our favorable results. In particular the last six items call attention to recent investigations that have disclosed or defined actions of heparin which could not have entered into our original rationale but which further emphasize the potential usefulness of medium dosage. They suggest explanations for the favorable effects of heparin in "intractable" angina, congestive failure resistant to standard medical management, and the vascular complications of coronary disease, both cerebrovascular and peripheral. Selected references are provided in the table (8–23) but the literature is too extensive to cite in detail.

TABLE 1
Actions of Heparin with Relevance to CHD (Ref)

1. Anticoagulation: Prevention of experimental coronary thrombi (8)
2. "Clearing" of plasma. Relief of post fatty meal angina (9)
3. Anti-inflammatory, anti-allergic, anti-trauma effects (10)
4. Reduction of platelet adhesiveness postoperatively (11)
5. Hypoaldosteronism induced by medium dosage (12)
6. Preservation or restoration of vascular wall negativity (13)
7. Antithrombotic properties further defined:
   Accelerates antithrombin-heparin cofactor (AT III)'s action:
   AT III also blocks activated Factor X (and IX, XI, XII) (14)
   Low and high AT III activity chains, respectively high and low in molecular weight (15)
8. Reduced blood viscosity in postoperative and CHD patients (16)
9. Affinity for vascular endothelium, 100-fold that of plasma (17)
   Pool behavior: better filling via s.c. than i.v. injections (18)
10. Inhibition of vascular smooth muscle proliferation after injury in rats (19)
    Heparin-like substance secreted by vascular endothelium in tissue culture (20)
11. Prostacyclin-mediated increase of coronary flow in CHD patients, inhibited by aspirin (21)
12. Antithrombotic effects of medium dosages reassessed:
    Fully equivalent to OAC in rabbit model (22)
    As effective *vs.* recurrent phlebitis, without bleeding (23)

The degree of antithrombotic effect achievable by medium daily dosage of heparin appears to be effective in the reduction of mortality in ACE and attended with remarkably few serious hemorrhagic complications. By reserving this dosage for periods of high risk or seeming intractability, patients can be persuaded to continue self-injection schedules indefinitely, provided attention is periodically paid to alterations of injection technique and dosage level which minimize local hemorrhage at injection sites. The latter have never required more than brief intermission of heparin in our experience. There is a wide assumption that patients cannot be kept on long-term heparin because of difficulties attending self-injection—not the case in our experience or that of others.*

Material and Methods

Patients with ACE were recruited for this heparin series from the referral cardiovascular practice of one of us (JJS) at the Hospital of the University of Pennsylvania. Out of a total series of 115 CHD patients, observed from 1955 to 1975, 42 were started on heparin because of ACE, and 73 for CHD with other severe manifestations or complications. Experience with the total series has been reported in abstract (24). *No* exclusions were made because of associated factors such as history of prior MI, obtained in 10 patients, coexisting hypertension (15 patients), diabetes (8 patients), or cancer (3 patients), and in this sense the ACE group is a consecutive series. Diagnostic criteria for acute MI were persistent pain with no early relief by nitroglycerin, sequential ST-T abnormalities in the ECG with Q-waves, and elevation of serum enzymes (SGOT and later others) in the 17 patients ultimately so diagnosed. The remaining 25 patients diagnosed as UAP (synonymous with intermediate coronary syndrome) had pain relievable by sublingual nitroglycerin and isosorbide dinitrate but occurring at rest and repeatedly. ECG abnormalities (primarily RST depression and T-wave inversion) tended to be transient. New Q-waves did not develop acutely. There were no more than minimal increases of enzymes, usually none.

The age range was 34 to 85 years. Mean age of the 31 males was 61.0 years, substantially lower than the average of 66.6 years for the 11 females.

Subcutaneous medium dose heparin was started immediately in divided doses, usually 5,000 units every six hours, and continued until clinical improvement for a sufficient period of time led us to consider the initial high mortality risk substantially reduced: the usual course for those who

* We are grateful for the counsel and encouragement of Dr. Harry F. Zinsser, whose larger favorable experience with subcutaneous heparin in coronary disease at the Graduate Hospital has been invaluable to our work.

survived the first month (25). Dosage was then usually lowered by steps of 5,000 units to 10,000, to 5,000, and sometimes intermitted. All patients were continued on sublingual isosorbide dinitrate with additional sublingual nitroglycerin as needed. They were not kept at complete bed rest ordinarily and were allowed up progressively as their conditions seemed to permit it.

All the acute MI patients and 19 with UAP received 20,000 units of heparin from the start. One UAP patient received 15,000 units and five only 10,000 units but two of these latter developed recurrences of severe unstable angina within 4 and 6 months and were placed on 20,000 units of heparin. Oxygen, anti-arrhythmic agents, hydrochlorothiazide and Henle loop diuretics (when these became available) were used as needed, as well as digitalis, although we did not give this agent when in doubt.

During the hospitalization, and always by the time of discharge, the patients were instructed in self-administration. Once they were sufficiently proficient in this the frequency of injections was reduced to not more than two/day without changing the total 24 hour dosage. We never had more than 10,000 units of heparin (0.5 cc. of 20,000/cc aqueous solution) administered at any single injection and not more often than every 12 hours. The technique of injection was taught to patients *before* the technique of withdrawing heparin from the vial and measuring the dosage. After cleansing the skin with alcohol and spreading it with two fingers of one hand, the patient being in a semirecumbent position if possible, the syringe was inserted vertically and the heparin slowly injected without aspiration. Gentle pressure was made after withdrawing the needle, but no massage of the site. Any part of the anterior abdomen and as far laterally in the flanks as the patient could reach were suitable for injecting. In loading the syringe, after air had been evacuated to provide correct measurement, a small amount of air (0.1–0.2 cc.) was pulled into the syringe (with the needle pointing downward) and made to rise to the top of the heparin bolus so as to follow it down the needle track as the injection was made. It was necessary to review these techniques many times and periodically advise and commiserate all the patients in regard to local hematoma formation. This varied considerably with the skill and experience of the injector. Most patients, however, became quite proficient, preferring to inject themselves rather than have a member of the family do it. We regularly used 20,000 units/cc aqueous heparin (porcine origin). Suppliers such as large hospitals, which can obtain special rates from the drug houses are important.*

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* The Pharmacy Service of the Hospital of the University of Pennsylvania has provided heparin to our patients at low rates, without which it would have been very difficult to carry on. We are especially grateful to Freddy Grimm, D. Pharm. of the Out Patient Division.

The total follow-up for each patient ("exposure") was divided into separate heparin dosage periods. These were grouped into therapeutic sequences of steady or descending dosage levels, beginning with the initial event and ending either with a new event that led to an increase of dosage and a new sequence, with death, or with the cut-off date for the statistical evaluation. This we set as of May 1975. The exposure was continued to drop out, to the cut off date, or to the anniversary date (from entry) in any year in which death on heparin treatment occurred, whichever occurred first. This is in accordance with the actuarial convention that a full year of exposure is counted for the year in which death occurred, even if the death occurred early in the follow-up year. Both non-cardiovascular and cardiovascular deaths were included. If a patient came under other medical management and heparin was never increased or resumed in the face of a clear indication, this event was designated a dropout from heparin therapy. Any subsequent experience was considered as dropout exposure, distinct from the heparin treatment experience. Deaths after dropout were excluded from the heparin experience (see below). None of the patients reported here dropped out when on 15,000–20,000 units/day, but after they had improved enough to be on 5,000 units/day or intermitted heparin.

First-year exposure and total exposure were crucial to the calculation of standard or expected deaths to compare with observed deaths on heparin treatment. The *first basis for comparison* was what we shall refer to as mortality in the "general population". For each patient the probability of death over his or her exposure to risk was calculated by matching sex, race and attained age at each follow-up year to mortality rates in the 1969–71 U.S. Life Tables (26). The individual probabilities were then added to give the matching number of expected deaths for the ACE patients (or any other subgroup), and the significance of the difference estimated by the chi-squared test.

The second comparison basis involved the use of first-year mortality rates in several series of patients hospitalized after acute MI (27–33). To make the conditions in the post-MI series as comparable as possible to the heparin patients, deaths before hospitalization have been excluded but all other deaths in the first week or month following onset of MI have been included. These series were chosen to permit calculation of rates by sex and age under 65, or 65 years and up, since rates are about three times higher for older patients. Our series contained 45% patients age 65 and up, an unusually high proportion of older patients compared with most follow-up studies of patients with acute MI. Appropriate rates were then applied to the 42 ACE patients, divided by age and sex, to obtain an estimate of first-year predicted deaths on the basis of the averaged experience of 2 to 4 series in each age-sex group. This comparison was made only for first-year rates, not for the total experience.

Mortality in the first year after MI is higher than in subsequent years, especially when the early deaths from hospitalization to the end of the first month are included (25).

Results

Only two of the 42 ACE patients died in the first year while being treated under our heparin regimen. As shown in Table 2 the two observed deaths were higher than the 1.29 deaths expected from age/sex/race matched U.S. population rates but the difference was not statistically significant.

The comparison with mortality predicted from age/sex-specific rates for the post-MI series from the medical literature is shown in Table 3. There were 13.04 deaths predicted for our 42 ACE patients, given the age and sex distribution in the table. It is evident that there is not much sex difference in the average post MI rates, but mortality is much higher in

TABLE 2

First Year Mortality in Heparin-Treated Patients with Acute Coronary Event: Comparison with U.S. Population Matched by Age, Sex and Race

	No. of Patients	No. of Deaths Observed	No. of Deaths Expected*	Significance of Difference† p value
Actue MI	17	1	0.49	
UAP (Intermediate Cor. Syn.)	25	1	0.80	
Total Acute Coronary Events	42	2	1.29	NS

* Basis of expected deaths: U.S. Life Tables 1969–71

† p value by chi-squared test. NS—not significant

TABLE 3

First Year Mortality in Heparin-Treated Patients with Acute Coronary Event: Comparison with Post MI Rates Matched by Age and Sex

	First-Year Post-MI Mortality*	No. of Patients	No. of Deaths Observed	No. of Deaths Expected*	Significance of Difference† p value
Male under 65	15.6%	18	0	2.81	
Female under 65	16.1	5	0	0.80	
Male 65 up	47.1	13	1	5.12	
Female 65 up	55.1	6	1	3.31	
Total	(31.0)	42	2	13.04	<0.01

* Basis of post MI rates: 328 deaths in 2100 patients, 4 series M < 65; 24 deaths in 149 patients, 2 series F < 65; 138 deaths in 293 patients, 4 series M 65 up; 125 deaths in 227 patients, 3 series F 65 up.

† p value by chi-squared test.

the older patients as noted previously. The difference between the two observed deaths and the predicted value of 13.04 is statistically significant, $p < 0.01$, despite the small size of our series. In spite of the uncertainties inherent in the use of "historical controls" we would like to emphasize the consistency in the mortality rates in the quoted series for each age/sex group. Followup was obtained within our 1955–1975 observation period in all but one of these comparison series. Our study was never conceived as a clinical trial. Since our statistical analysis is based on mortality observed in a series of patients and related to age, sex, race and follow-up duration, comparison must be on the basis of appropriately matched external controls. We believe the matching is appropriate, and consider it highly unlikely that the small number of first-year deaths observed in our 42 patients subject to the high mortality risk of ACE is either a random fluctuation or due to an unusual proportion of cases of mild severity.

The favorable nature of our first-year experience was maintained in our long-term experience with the 40 survivors, as given in Table 4. Total exposure generated by observation of our 42 ACE patients was 204.8 patient years, distributed as shown. There were seven deaths observed subsequent to the first year, with 5.92 expected deaths, giving totals of 9 and 7.21 deaths, respectively, when the first year's experience is added. The excess of observed deaths over deaths expected from U.S. population rates is slight and not statistically significant, so long as the patients continued on the heparin regimen.

Nevertheless, 11 of the ACE patients became dropouts from our heparin treatment plan after an average of 4.1 years of treatment. Through follow-up after dropout we have determined that 9 deaths occurred in an exposure of 18.0 patient-years, six of these being in the first year following the new event that marked the dropout. Consequently the dropout experience shows a very high mortality, in marked contrast to the benign earlier course of these same patients in 45.2 years exposure to risk while

TABLE 4

Long-Term Mortality in Heparin-Treated Patients with Initial Acute Coronary Event: Comparison with U.S. Population Matched by Age, Sex and Race

Follow-up	No. of Patients	Exposure Patient Yrs.	No. of Deaths Observed	No. of Deaths Expected*	Significance of Difference† p value
First year	42	42.0	2	1.29	NS
1 year and up	40	162.8	7	5.92	NS
Total Experience with heparin	42	204.8	9	7.21	NS

* Basis of expected deaths: U.S. Life Tables 1969–71.

† p value by chi-squared test. NS—not significant.

on heparin. In our view this high post-dropout mortality is a reflection of the high risk to which they were exposed because of the severity of their disease, and another piece of evidence supporting the effectiveness of our regimen of long-term heparin, with its emphasis on medium dosage in critical situations.

Discussion

Two other great advantages of the heparin management were reduction in morbidity and functional disability in our ACE patients and many of the other patients in our total series of 115 patients (24). Despite the nuisance of the injections, our patients were convinced that they lived better because they could carry out their normal activities without development of increasing heart size or congestive failure and with satisfactory control of any episodes of anginal pain with nitroglycerin. The incidence of new events continued to be low. There was indeed an impressive correlation with heparin dosage level in this regard. No new cardiovascular events occurred on 20,000 or 15,000 units, three occurred on 10,000 and five on 5,000 or intermitted heparin. All these events were comparatively mild and there was clinical improvement when the heparin dosage was increased. These phenomena are better dealt with when the whole series of patients is considered as in the abstract aforementioned (24).

The need for hospitalization was infrequent, except for surgical procedures or other indications not related directly to coronary disease or its complications. The availability of additional diagnostic studies was always explained to patients, but they were not prescribed as routine measures. The absence of results of coronary angiography, ventriculography and rhythm monitoring means that we generally cannot present such information as evidence of the severity of our patients' CHD. A striking and consistent phenomenon was the disappearance of intellectual curiosity in our patients regarding the severity of their disease when they were doing well clinically, *i.e.*, carrying out the activities they considered most important in life with only occasional follow-up advice. The average frequency of follow-up visit was about once in three months, but the patients could always obtain advice by telephone.

In the extensive medical literature on heparin in cardiovascular disease very little has been published about the effects of medium doses. Griffith et al (6) gave 10,000 units twice daily by subcutaneous injection to patients with acute infarction over a three week period with slightly lower mortality and fewer hemorrhagic complications than a comparison group treated with oral anticoagulants. However, higher doses of heparin were considered preferable, medium dosage having been chosen as a compromise of efficacy *vs.* safety. Yet to our knowledge no direct comparison of

20,000 units with higher or lower doses has been carried out by any other group than our own. There has been no long-term use reported after Griffith's paper on osteoporosis (35) but most of his patients were receiving 10,000 units per day. A recent and highly pertinent study has been reported by Telford and Wilson (7) using medium dosage but as four intravenous doses of 5,000 units every six hours. This was a randomized double-blind study with 100 patients diagnosed as UAP receiving heparin for one week, and 114 matched patients receiving placebo instead of heparin. About half of each group also received Atenolol. There was no difference related to the use of Atenolol but there were notable differences related to the use of heparin: only three patients developed a transmural MI during their week on heparin, significantly fewer than the 17 who received no heparin ($p = 0.024$). None of the patients in the heparin group died within 8 weeks of onset, but five of the other group died (coumadin was given to patients under 65 after the first week). Despite its very short-term nature this study also tends to support the benefit of 20,000 units/day heparin in the management of UAP, one type of ACE. None of our 25 patients with UAP developed a transmural MI in their initial therapeutic sequence.

In addition to evidence on the efficacy of long-term heparin in the treatment of CHD another important consideration is its safety. Hemorrhage is the obvious first concern—serious internal hemorrhage either spontaneous or due to trauma—because of excessive anticoagulation. The incidence of major hemorrhage with higher doses than 20,000 units/day is similar to the incidence found with oral anticoagulants. Such hemorrhage was never seen in our patients, in whom 20,000 or 15,000 daily doses were always administered in at least two divided doses. Medium and low doses of heparin appear to be safe with respect to the risk of major hemorrhage. Minor hemorrhage or hematoma at the injection sites is a common but relatively minor problem. With the technique we used and taught the patient for subcutaneous injection the incidence was kept below 20% and never was troublesome enough to require discontinuance of heparin. In 1965 two articles and an editorial (35) in the JAMA highlighted the risk of osteoporosis and pathological fracture in patients receiving heparin, generally in single doses of 20,000 units or more daily, over long periods of time. The use of long-term heparin in any but low doses was apparently discouraged by these reports. Although we have been watching carefully for evidence of osteoporosis, we never found it with the heparin plan we used.

The very rare but serious complications of severe thrombocytopenia—not ordinarily manifested by hemorrhage, but by arterial thrombosis, embolism, skin necrosis or disseminated intravascular coagulation (36, 37)—had not been defined till after our cut-off date. We did have to stop

heparin in a single noncoronary patient in 1979 because of a cutaneous infarct (38). With this exception, and a single patient who developed a subdural hematoma following severe head trauma for which he failed to discontinue heparin (successfully evacuated without residua), we have experienced no major complications up to or since 1975 in patients treated under the heparin plan described here.

The reader is referred back to Table 1. The dozen heparin actions—selected from a much larger variety (39)—that may have pertinence to CHD and its vascular complications make it unlikely that our findings will have a single or simple explanation. Our continuing experience since 1975 has been at least as favorable. We feel strongly that enlargement of this experience by other cardiovascular physicians and research workers is very much in order: such investigation should be practicable, safe and likely to throw more and more light on the ways in which heparin produces its remarkable effects on the natural history of coronary disease.

Although more than 30 years of experience with very low ("mini") dose heparin (20,000 units twice weekly) have been encouraging and carry fascinating implications (40), the urgent need is for critical attention to the top medium dosage of 5,000 units sc four times a day—recently called a "magic number" (41) and perhaps better referred to as the strategic heparin dosage with the widest spectrum of safe actions.

Summary and Conclusions

1. Forty-two coronary disease patients of diverse age groups were followed over a period of 205 patient years after being given medium dose heparin for acute coronary event (myocardial infarction or unstable angina) and continued on flexible dosage schedules with increases for any new events.
2. Self-administered long-term heparin over long periods of time is attended with no serious complications. An annoying, sometimes deterrent complication was subcutaneous hemorrhage at injection sites. This could be obviated in almost every instance by proper instruction and supervision.
3. The one year mortality was compared with the U.S. general population (weighted for age, sex and race) and was found to be not significantly higher.
4. The over all mortality (first year plus remaining years) was also not significantly higher than the U.S. general population.
5. Since virtually all follow-up studies of acute coronary event have shown mortality markedly greater than the U.S. general population, based on U.S. Census data, these findings are unexpected and striking.
6. The average first year mortality rates for several series of medically

treated acute MI patients were applied to the numbers of patients in our series, categorized by age and sex. The number of deaths thus calculated was significantly higher than the number of deaths actually observed in our series.

7. We believe that for unstable angina patients several weeks of medium-dose heparin are superior to oral anticoagulation. Heparin treatment has proved an effective and safe treatment that does not interfere with other modalities but may make some of them unnecessary. For acute myocardial infarction the sooner medium-dose heparin is started the better.
8. We believe that long-term heparin treatment is beneficial, and may save patients from unnecessary tests, expenses, and interruption of life. It should surely be used as an option for maximal medical care before considering surgical intervention and its precursor invasive studies.

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DISCUSSION

Dexter (Boston): Well, Pete, this is very nice. You probably all know that Pete and I were classmates in college and therefore he can do no wrong as far as I'm concerned. However, I have a couple of questions to ask because this is a very controversial subject. What did you do statistically with the dropouts? This is a thorny problem because you put the dropouts from the heparin group into the untreated group, and that puts your statistics very much askew. I've never known quite what to do with dropouts. What did you do with them?

Horwitz: I didn't mean to be casual about the drop-outs. But I did think that a detailed dissertation would be tedious. I told you that they were taken out of the group. The drop-outs were those who went along with heparin but later discontinued it permanently. Patients who dropped out but then came back were all included in the series. Incidentally, nobody dropped out permanently because of blue belly from local subcutaneous hematoma at the site of injection.

Dexter: The other point I wanted to raise was this: you said that the differences were not statistically significant, but almost so. Am I right?

Horwitz: No, I said there was no statistically significant difference between our acute coronary event patients and the general U.S. population. These figures derived from the 1969–71 United States Life Tables which are published by the National Center for Health Statistics and derive from United States Census figures. The U.S. population is not "normal" in the sense that a preferred risk group of insurance patients might be. They represent roughly how long each of us is likely to live once we attain a certain age, depending on our sex, race and the general incidence of disease in the U.S. population as a whole. They are pretty close to what we would be inclined to call "normal". They should, of course, be quite different from the mortality of coronary disease patients, as they are in the comparison series of past myocardial infarction patients we surveyed in this study. Our patients showed an insignificantly higher mortality than the U.S. population, but quite a significantly lower mortality than the medically treated post myocardial infarction series.

I'm sure I did not make this clear, otherwise any classmate of mine would have understood.