Intracranial Bleeding, Fibrinolysis, and Anticoagulation: Causal Connections and Clinical Implications

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“A drug can be an inert substance, a poison, or a therapeutic agent dependent upon how it is used and the dosage in which it is given.”

Erik Jorpes
Paraphrasing Paracelsus

The TIMI-9A and GUSTO-IIA trial preliminary reports, in this issue of Circulation by highly experienced and respected investigators, show unexpectedly high rates of intracranial bleeds (ICBs) associated with administration of two plasminogen activators (streptokinase [SK] and tissue-type plasminogen activator [TPA]) and two intravenously administered anticoagulants (heparin and hirudin). Another report in this issue by equally outstanding researchers shows an increased risk of ICBs with hirudin compared with heparin, in combination with TPA, and no ICBs with TPA in combination with heparin. Cognizance by clinicians of these important observations, however, is not sufficient, particularly in a climate in which simplistic interpretations can inhibit illumination of mechanisms responsible and uncritical extrapolations can compromise patient care. By contrast, elucidation of specific causal connections will undoubtedly result in greater efficacy and safety in the use of anticoagulants accompanying coronary thrombolyis.

Incidence of ICBs in Perspective

Before coronary thrombolysis became a mainstay of primary treatment for myocardial infarction, strokes occurred in approximately 1% of patients with infarcts. Approximately 0.4% were attributable to hemorrhage. Subsequently, in tens of thousands of patients treated with fibrinolytic agents as well as anticoagulants, the overall stroke incidence was virtually identical to that seen with anticoagulants alone but the incidence of ICBs was slightly higher (0.4% to 0.7%).

In their review of studies involving 36,002 patients, Drs Tiefenbrunn and Ludbrook concluded that “any increment in intracranial hemorrhage that might be ascribed to... a lytic agent... is small and offset by a decrease in...”

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was crude but effective. As Dr Alvin R. Feinstein\textsuperscript{a} notes, modern trials are frequently flawed by the failure to address "basic scientific challenges in data … and reasoning." Their fidelity to "quantitative models, derived from non-clinical domains, (does) not … meet the main challenges of clinical judgement." Dr Califf\textsuperscript{10} a leader in both GUSTO-I and GUSTO-IIA, has highlighted specific and important limitations, including restricted focus on particular questions; enrollment of unrepresentative, homogeneous subsets of patients; enrollment of only a small fraction of those eligible; rapid evolution of treatment that often renders even the most recent data from large trials irrelevant; and performance of the research in centers with specific characteristics and consequently limited applicability to diverse practice settings. He concluded that randomized controlled trials are encumbered by "difficulty in generalizing their results … and … rapidly changing technologies and therapies" such that clinicians must rely on "additional considerations and information."\textsuperscript{10}

Dr. Rahimtoola\textsuperscript{11} considered clinical trials in depth in a previous contribution to Circulation. He noted the "unbounded enthusiasm for these trials" and questioned the "unproven premise that randomized clinical trials (are) the best … or … only correct way to evaluate new therapies." He emphasized "the importance of hypotheses not tested" and the need to avoid "inappropriate conclusions and extrapolations" because of "problems in study design, data analysis, and presentation." We have recently observed that "valid conclusions are not necessarily ensured by a large sample size, even with an unequivocal end point such as mortality."\textsuperscript{12}

In the context of these acknowledged limitations of the applicability of clinical trial results to practice, how can the astute clinician benefit from the TIMI-9A, GUSTO-IIA, and HIT-III observations? The first step is to identify the causal connections accounting for the high ICB rates observed. "Consideration of causal connections … should help to avoid both unrealistic expectations and deprecation of general relationships otherwise obscured by observations in specific subsets of patients."\textsuperscript{13} By hewing to causal contiguity, the astute clinician can avoid "throwing out the baby with the bath water," i.e., rejecting fibrinolysis with conjunctive anticoagulation, a treatment of proven benefit, rather than refining the conjunctive anticoagulation regimens appropriately.

Mortality associated with infarction has been reduced markedly by coronary thrombolysis with conjunctive anticoagulation. Thus, although the TIMI-9A and GUSTO-IIA results underscore risks inherent in using anticoagulants and fibrinolytic drugs together, it must be recognized that coronary thrombolysis is not monotherapy and that conjunctive anticoagulation is invaluable. Delineation of optimal dosage and duration of conjunctive anticoagulation is therefore essential. Failure to implement conjunctive anticoagulation at all would be a disservice.

**Importance of Conjunctive Anticoagulation**

Effective coronary thrombolysis depends on prompt induction of a favorable balance between fibrinolysis and ongoing thrombosis. Paradoxically, occult thrombosis is exacerbated by plasmin generated by all clinically available fibrinolytic agents. Without conjunctive anticoagulation, the time to recanalization is prolonged; the incidence of early thrombotic reclosure is increased; and net clinical benefit, which is dependent on prompt and sustained recanalization, is compromised. Vigorous anticoagulation with intravenous agents is particularly essential with relatively clot-selective fibrinolytic agents such as TPA because of their modest generation of fibrinogen degradation products (FDPs), moieties with anticoagulant properties. However, it also applies to nonselective fibrinolytic agents, including SK.\textsuperscript{12,14}

Although fibrinolytic drugs can induce ICBs, particularly when doses are excessively high,\textsuperscript{15} and although the risk can be increased by aggressive conjunctive anticoagulation, the benefits of conjunctive anticoagulation far outweigh the risks.\textsuperscript{8} Accordingly, clinical investigators have been "stretching the envelope" to identify optimally effective conjunctive anticoagulants and regimens, including those applicable to direct-acting antithrombins. A particularly promising example of a direct-acting antithrombin is hirudin. It facilitates thrombolysis in laboratory animals. In patients, it appears to induce a higher incidence of recanalization with TPA, a lower incidence of reocclusion, a lower incidence of in-hospital death or reinfarction, and no difference in spontaneous hemorrhage compared with heparin, as judged from results in the "TIMI-5 Trial\textsuperscript{16} and pilot studies.\textsuperscript{17} The adverse experience with hirudin given in a particular regimen in TIMI-9A, GUSTO-IIA, and HIT-III should not dampen enthusiasm for direct-acting antithrombins per se. Instead the experience highlights the importance of delineating critical risk factors in patients, improved monitoring of conjunctive anticoagulation, and delineation of the optimal duration and dosage of specific anticoagulants. The very late occurrence of ICBs in TIMI-9A and the apparent lack of benefit of heparinization when continued for more than 48 hours\textsuperscript{18} support the view that, pending acquisition of additional information, the duration of anticoagulation should be curtailed to 24 to 48 hours in the absence of specific indications for sustaining it further.

**Interactions Between Platelets and the Coagulation and Fibrinolytic Systems**

Biochemical systems activated in the setting of pharmacologic fibrinolysis and their interactions are complex. Pharmacologic activators of the fibrinolytic system given intravenously invariably induce at least some plasminemia. Accordingly, paradoxical procoagulant activity occurs that is due to plasmin-induced activation of factors X, XII, and V, the IXa/VIIa complex, and prothrombin.\textsuperscript{19} Generation of thrombin is central not only to coagulation but also to activation of platelets. Patients given plasminogen activators exhibit high concentrations in plasma of markers of thrombin activity including fibrinopeptide A (FPA), cleaved by thrombin from fibrinogen,\textsuperscript{20-22} thrombin-antithrombin complexes (TATs); and prothrombin fragment 1.2 (F1.2), a byproduct of thrombin generation from prothrombin. Plasminogen activators may attenuate effects of heparin by depleting the heparin cofactor, antithrombin III (ATIII).\textsuperscript{23} The thrombin generation they induce is amplified profoundly because of thrombin activation of factors V and VIII and the genesis of thrombin by the factors Va- and VIIIa-dependent coagulation cascade. Thus, the procoagulant effects of plasminogen activators must be offset by prompt and adequately vigorous conjunctive anticoagulation.\textsuperscript{24-32}

Additional interactions that can contribute to an unfavorable imbalance between thrombosis and fibrinolysis include platelet release of plasminogen activator inhibi-
or type-1 (PAI-1) that can attenuate activity of endogenous plasminogen activators well after an administered pharmacologic fibrinolytic agent has been cleared from the circulation.33 Conversely, degradation of von Willebrand factor (vWF) by plasmin may exacerbate bleeding,34 particularly when heparin is present, because of its direct inhibition of both platelets and vWF.35 The FDPs elaborated by plasmin can attenuate activation of platelets36,37 and inhibit procoagulant protein interactions.

An alternative type of interaction, activation of the fibrinolytic system by antithrombotic agents, may occur in some patients. For example, aspirin can activate plasmin38 in addition to inhibiting platelet aggregation and reducing thrombin generation by acetylating prothrombin and platelet surface membrane macromolecules.39

Factors Influencing Activity of the Anticoagulants Used in TIMI-9A, GUSTO-IIA, and HIT-III

Heparin binds to ATIII, inducing a conformational change that accelerates inactivation of thrombin and factors Xa, IXa,40 and VIIa.41 It can impair platelet function directly or indirectly by inhibiting thrombin and its generation and by inducing thrombocytopenia. Heparin also increases capillary permeability and bleeding time.39,40 Properties of a given lot of heparin depend on the extent of sulfation and the frequency distribution of contained components of particular molecular weights. Low-molecular-weight heparins inhibit factor Xa without necessarily prolonging activated partial thromboplastin times (aPTT) or inactivating thrombin.40 Clinical effects depend on hepatic function, which, in turn, influences synthesis of ATIII, other heparin cofactors, and procoagulants. Clearance of heparin from the circulation is mediated initially by endothelial cell–binding sites and binding to plasma proteins, including acute-phase reactants and vWF (with consequent inhibition of platelet function). Subsequent clearance depends on renal function. Thus, bioavailability of heparin in response to a fixed dose varies markedly from patient to patient and in the same patient over time, as does the anticoagulant response. Only approximately one third of the molecules of heparin administered exhibit potent anticoagulant properties; they may be cleared differentially.26

Hirudin, a uniquely powerful direct-acting antithrombin, forms an essentially irreversible complex with thrombin by binding both at catalytic and substrate (fibrinogen) recognition sites (anion-binding exosite) of thrombin. Hirudin can reduce activation and adhesion of platelets by inhibiting thrombin,42 thereby profoundly depressing platelet function,43 and can displace factor Xa from endothelial cells, thereby exerting anticoagulant effects that far outlive its presence in the circulation.44 Inhibition of thrombin can mask accumulation of plasmin-induced procoagulants (eg, factor Xa) giving rise to “rebound” clotting, with elaboration of prothrombin F1.2 reflecting markedly accelerated generation of thrombin as the antithrombin activity dissipates.45 This phenomenon lends impetus to the development of novel anticoagulants, including inhibitors of factor Xa or the VIIa/tissue factor complex, analogs of activated protein C (a naturally occurring anticoagulant, which, when activated by the thrombomodulin–thrombin complex in association with protein S, inactivates coagulation factors Va and VIIa in a negative-feedback fashion), and inhibitors of factors Va and IXa.

Differences in sulfation, the distribution of molecular weights, or both in heparin used in specific studies can result in marked differences in activity. Because GUSTO-IIA used a single lot of heparin,2 results may have been atypical. The actual interval over which bolus injections are administered (generally not defined) and the dose and duration of infusions (high and more prolonged in GUSTO-IIA than in GUSTO-I)26 can modify efficacy and the risk of bleeding markedly. Verification of the comparability of these variables in diverse studies requires the assay of blood to determine actual concentrations of heparin and markers of the adequacy of anticoagulation in vivo (such as FPA). Reliance on the aPTT is potentially misleading because of the dependence and nonlinearity of the sensitivity of the assay to heparin on the concentrations of particular plasma proteins in the sample and because of the variability of results with different reagents and, hence, in different laboratories.

Similar considerations apply to hirudin. Different recombinant and desulfatohirudins may differ functionally from each other and from the native protein. Fragments liberated differentially by proteolysis of each secondary to plasminin may alter platelet function and binding of fibrinogen to thrombin or displace factor Xa from thrombogenic surfaces. Levels of antibodies induced in different patient populations may vary and may modify the intensity or duration of anticoagulation induced.46

One spurious conclusion that could be drawn from GUSTO-IIA, TIMI-9A, and HIT-III is that a particular anticoagulant (eg, hirudin) is intrinsically hazardous rather than that a given duration of infusion or dose is excessive for particular subsets of patients. Because the ICB rates with hirudin and heparin in TIMI-9A were not significantly different, it appears likely that characteristics of the patients studied contributed to bleeding. By contrast, the complete absence of ICBs with heparin and TPA in HIT-III differs strikingly from the 2.7% ICB rate with hirudin and TPA. Thus, anticoagulation with hirudin in all three studies1,3 may have been excessive, despite the 33% lower dose of hirudin used in HIT-III. Regardless, generalized rejection of hirudin is presently not warranted.

Patient Characteristics and Other Variables That May Have Contributed to the ICB Rates With Both Heparin and Hirudin in TIMI-9A and GUSTO-IIA

The diversity of factors that can influence the efficacy and risks of coronary thrombolysis implies that patient characteristics may have contributed to the high incidence of ICBs encountered in TIMI-9A and GUSTO-IIA. unrecognized, modest impairment of renal function may have increased adverse effects of the anticoagulants by diminishing clearance. Impaired liver function, perhaps because of occult heart failure or exacerbated by beta-blockers that diminish hepatic blood flow, may have altered the concentrations of circulating vWF and several clotting factors, including factors V and X. Lower vitamin K intake or a higher use of aspirin, NSAIDs, beta-blockers, or nitrates before enrollment may have increased the susceptibility to hemorrhage. The doses of aspirin used (325 mg in TIMI-9A compared with 250 mg in HIT-III) and the prolonged anticoagulation in TIMI-9A and GUSTO-IIA (96 and 72 hours, respectively, compared with 48 hours in GUSTO-I) may have added to the risk.
ICBs in the setting of fibrinolysis appear to be attributable largely to the susceptibility of cerebral vasculature in specific patients, including those with occult amyloid deposition in vessel walls, to injury by proteolytic agents such as plasmin. ICBs do not occur in normal animals given even massive amounts of plasminogen activators, despite marked depletion of fibrinogen (eg, 10 mg/kg TPA as a bolus) (B.E.S., 1994, unpublished observations), nor when profound depletion of fibrinogen is induced in animals or human subjects by cobra venom (ancred). Subtle differences in the extent and severity of cerebrovascular disease in patients in TIMI-9A and GUSTO-IIA compared with those in other studies may account for the high incidence of ICBs. A high frequency of hypertension, advanced age, and female gender in these two studies, all known risk factors for ICBs after fibrinolytic drugs, support this possibility. Of interest, TIMI-9A patients who had major hemorrhages had significantly lower body weights than those who did not, just as was the case in the TIMI-II trial. In addition, patients in the GUSTO-IIIA trial (who had a high incidence of ICBs) were significantly older than those in GUSTO-I (who did not).

Because enrollment could be late in TIMI-9A and GUSTO-IIIA (up to 12 hours after the onset of chest pain), ongoing thrombosis, which is known to be maximal at the time of onset of infarction and is known to decline rapidly, is likely to have been less intense than in patients in many other studies. Unopposed effects of anticoagulants may have therefore been more intense and have predisposed the patients to hemorrhage. The prolonged duration of anticoagulation (96 hours in TIMI-9A and 72 hours in GUSTO-IIIA compared with 48 hours in GUSTO-I) would compound the predisposition. The late occurrence of hemorrhage and ICBs in TIMI-9A and GUSTO-IIIA is consistent with late enrollment and its influence on the intensity of ongoing thrombosis.

The fibrinolytic system is modulated by PAI-1, α2-antiplasmin, and other inhibitors. Thus, decreased PAI-1 could predispose patients to ICBs by accentuating and prolonging the intensity of fibrinolysis. Accordingly, the fraction of patients with high concentrations of triglycerides or occult carbohydrate intolerance or insulin resistance, all of which influence PAI-1 levels— in TIMI-9A and GUSTO-IIIA—is relevant. Similarly, the incidence and effect of diabetes are important because of its association with occult cerebrovascular disease that can predispose patients to ICBs.

Effects of SK are influenced markedly by antibodies present in most patients. Thus, titers present at the time of treatment require definition. Differential activation of platelets by epinephrine in different settings and its determinants (including stress induced by hospitalization and participation in specific studies) can alter the balance between thrombosis and thrombolysis even when aspirin dosing is comparable.

Effects of plasminogen activators on the fibrinolytic system depend critically on the actual rate and duration of their administration. Even with nominally identical regimens, the actual intervals over which fibrinolytic drugs are administered and the actual rates of infusion and “deceleration” of dosing may vary between studies, potentially substantially altering the incidence of untoward events. Comparability can be ensured only by quantitative determinations of the activity of the fibrinolytic system in vivo with markers such as n-dimer reflecting plasmin-induced cleavage of cross-linked fibrin and of the activity of the coagulation system in vivo with markers such as FPA.

Both the TIMI-9A and GUSTO-IIIA investigations were terminated prematurely because of a high incidence of hemorrhage with heparin and with hirudin. As the investigators note, adverse events occurred in elderly patients who had high aPTTs. However, the high values were temporally dissociated from the hemorrhages. aPTT values are actually a reflection of the concentration of anticoagulant in the blood sample being assayed rather than a criterion of the adequacy of anticoagulation in vivo. Furthermore, elevations are not linear with respect to the concentration of anticoagulant in the sample, in part because of considerable and variable binding of an anticoagulant such as heparin to acute-phase reactants and also because of sensitivity of the assay to heparin being influenced by concentrations of factor VIII and other plasma proteins. Thus, although the aPTT results imply that too much anticoagulant was present in the blood when it was sampled, they do not provide a quantitative index of the magnitude of the excess nor do they imply that the induction of adequate anticoagulation in vivo with the same agent would have been deleterious. Furthermore, ischemic strokes with secondary bleeding into zones of infarction can be mistaken easily for primary ICBs in patients in whom anticoagulants were administered with fibrinolytic agents. Accordingly, optimal interpretation of the results in TIMI-9A and GUSTO-IIIA requires unequivocal demonstration that the ICBs were primary hemorrhagic strokes. If so, it is essential to delineate their temporal relationship to the status of activity in the coagulation and fibrinolytic systems in vivo as well as to the prevailing concentrations of plasminogen activators. (ICBs in the TPA-treated patients occurred generally at a time when TPA would have been gone from the circulation.) Persistence of SK-plasminogen complexes, FDPs, or both may have contributed to the extraordinarily high ICB rate seen with SK and hirudin (3.6%) in GUSTO-IIIA.

**Clinical Implications**

The major determinant of a favorable outcome after coronary thrombolysis is the rapidity of induction of sustained recanalization of the infarct-related artery. Concomitant, vigorous anticoagulation is needed for both optimal rapidity of recanalization and prevention of early thrombotic reocclusion. Although the aPTT and activated clotting times (ACTs) are used extensively to monitor anticoagulation in this setting, their results do not reflect the adequacy of suppression of coagulation in vivo. Accordingly, increasing attention is being paid to monitoring activity of the coagulation system in vivo with assays of FPA, F1.2, and TATs; platelet function in vivo by assay of proteins released with activation (eg, β-thromboglobulin and platelet factor IV) and changes in the conformation of surface glycoproteins (GPs) such as GPIIa/IIIb by flow cytometry; and bleeding time. Limitations of aPTT values are evident in the TIMI-9A data. Patients with major hemorrhage had abnormal values but only with respect to the 12-hour aPTTs. Elevated aPTTs occurring at this interval after administration of fibrinolytic drugs can reflect fibrinolysis and consumption of factor V and other proteins by plasmin rather than the extent of anticoagulation in vivo or even the concentration of anticoagulant in the sample. Regardless, ICBs occurred much later (89 hours after enrollment with heparin and 62
hours after enrollment with hirudin), at a time when aPTT values were not higher than those in patients without hemorrhage. Thus, the aPTT is far from ideal as a tool for titrating conjunctive anticoagulation.

When delineating the specific causal connections that may account for the high incidence of ICBs in TIMI-9A and GUSTO-IIA, biochemical characterization of the heparin used would be helpful, as would analyses of blood samples, presumably already in data banks, for levels of heparin, hirudin, hirudin-thrombin complexes, FPA, TAT, F1.2, d-dimer, potentially concomitant medications (salicylates, NSAIDs, nitrates, and β-blockers), PAI-1, markers of platelet activation in vivo, and individual, activated coagulation factors. Thorough subset analysis to delineate characteristics of patients prone to adverse effects is needed. Detailed characterization of age, gender, and body weight, renal function, hepatic function, previous infarction, hypertension, diabetes, insulin resistance, and occult cerebrovascular disease (patients with transient ischemic attacks were not excluded in TIMI-9A and GUSTO-IIA—only those with a stroke in the past year were excluded) is needed. The ICB incidence should be defined also with respect to the actual rates of fibrinolytic drug administration, time of day of treatment (in view of the diurnal variation of PAI-1, platelet activation, and other modulators of fibrinolysis and thrombosis), time of treatment onset, actual doses of aspirin and anticoagulants administered, and duration of anticoagulation.

The clinical community should not overreact to some assertions that will undoubtedly be made as a result of the TIMI-9A and GUSTO-IIA observations. If it does, many patients who should be treated with thrombolytic agents and conjunctive anticoagulants will not be, and may will be treated only after unifiable delay or without sufficiently vigorous anticoagulation. Clinicians will eagerly await elucidation of the factors that led to the atypically high ICB rates observed and use the forthcoming information to refine and improve conjunctive anticoagulation further. In the interim, assays that are already available can delineate the adequacy of anticoagulation in vivo and identify patients who may be responding anomalously. In view of the late occurrence of ICBs in TIMI-9A and GUSTO-IIA and the lack of proof that protraction of anticoagulation with heparin beyond 24 hours is beneficial, the duration of anticoagulation with heparin should be limited to 24 to 48 hours in the absence of specific indications for continuing it longer. One such indication is failure to suppress ongoing thrombosis, reflected by persistent elevations of FPA, TATs, or F1.2.

We do not yet know how long it takes for the infarct-related artery to lose its thrombogenicity (“passivate”). However, the adequacy of anticoagulation and the lack of recurrent thrombogenicity when anticoagulants are discontinued or when doses are tapered may be ascertained by sequential assay of markers such as FPA, TATs, and F1.2, particularly in the context of mechanistic studies that are progressing that are delineating their behavior in specific settings.22,25,54–58 Pending acquisition of additional data, the occurrence of ICBs in two studies1,2 with 12-hour time to enrollment windows, their absence with TPA and heparin with a 6-hour window,3 and the clear dependence of the benefit of coronary thrombolysis on the rapidity of recanalization59 should encourage clinicians to implement coronary thrombolysis in patients who can be treated within 4 to 6 hours after the onset of infarction. The absence of ICBs with the use of TPA and heparin in HIT-III, in which the enrollment window was 6 hours, is consistent with the utility of this approach. In addition, it seems prudent to administer heparin less aggressively than in TIMI-9A, ie, in doses sufficient to induce effective anticoagulation without undue prolongation of the aPTT or ACT. A reasonable approach is the one used in GUSTO-Pa (5000-U bolus; 1000 U/h; titration to a heparin level of 0.2 to 0.4 U/mL plasma, as assayed by protamine titration, which is generally [and loosely] equivalent to an aPTT of 60 to 85 seconds).

Perhaps the most important lesson to be learned from the TIMI-9A, GUSTO-IIA, and HIT-III trials is that one key consequence of clinical trials is the generation of new hypotheses. The lack of apparently favorable results with clot-selective fibrinolytic agents in GISSI-2 and ISIS-3 stimulated the performance of subsequent studies that ultimately demonstrated their value when coupled with conjunctive anticoagulation and showed that the benefit conferred by coronary thrombolysis is contingent on the rapidity and persistence of recanalization of thrombotically occluded infarct-related arteries as documented in GUSTO-I. The present reports will undoubtedly generate needed hypotheses and stimulate the performance of mechanistic studies that will clarify the causes of the adverse effects encountered in TIMI-9A and GUSTO-IIA, thereby leading to further refinements in monitoring dosage, duration of administration, and titration of conjunctive anticoagulants. Thus, the benefits for victims of acute myocardial infarction of an already effective therapeutic modality, coronary thrombolysis, will be enhanced further.

References


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