Both percutaneous coronary interventions (PCIs) and acute coronary syndromes disrupt the integrity of the arterial wall. Whether spontaneous or man-made, these intimal defects and subsequent thrombosis lead to myocardial ischemia. Since the 1960s, antithrombotic agents have been the mainstay of both medical and interventional approaches to patient management. All current treatment strategies incorporate underly ing thrombin inhibition with either unfractionated or fractionated heparin. The addition of aspirin, fibrinolytics, and platelet glycoprotein (GP) IIb/IIIa integrin inhibitors to modern regimens has not displaced the use of antithrombotic agents in clinical practice.

Bivalirudin, a 20-amino-acid peptide, is a bivalent, direct thrombin inhibitor with several advantages over heparin; these advantages include (1) high specificity and potency for thrombin inhibition, (2) a lack of dependence on antithrombin III for anticoagulant activity, (3) the ability to inactivate both clot-bound and free thrombin, and (4) a lack of aggregatory effects on platelets. The efficacy and safety of bivalirudin have been evaluated in several clinical trials for unstable angina, acute myocardial infarction (MI), and PCI indications. This report provides a meta-analysis of all available studies to evaluate the impact of bivalirudin on clinical outcomes.

Methods

Randomized, controlled trials of bivalirudin were identified through a review of all studies performed in the course of compound development and through a MEDLINE search. Peer-reviewed reports published between 1966 and 1998 were searched for the words “bivalirudin,” “Hirulog,” and “random,$,” where $ is a wild card. We excluded studies of normal volunteers. Publicly presented data from the drug-development database were used to evaluate patients at similar time points.

Because no placebo-controlled trials were available, an alternative approach was used to establish bivalirudin as an active anticoagulant. Two dose-ranging studies (Table 1) compared subtherapeutic bivalirudin doses (those producing an activated partial thromboplastin time less than twice the control time) with therapeutic bivalirudin anticoagulation (activated partial thromboplastin time less than twice the control time).

Conclusions—Bivalirudin is at least as effective as heparin, with clearly superior safety. Thus, it provides an unprecedented net clinical benefit over heparin in patients with ischemic heart disease. (Circulation. 1999;100:2049-2053.)

Key Words: bivalirudin meta-analysis mortality myocardial infarction hemorrhage
TABLE 1. Subtherapeutic Bivalirudin-Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Year</th>
<th>Load, mg/kg</th>
<th>Infusion, mg · kg⁻¹ · h⁻¹</th>
<th>Duration, h</th>
<th>Bivalirudin Control Regimen</th>
<th>Primary End Point (In-Hospital)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topol et al</td>
<td>291</td>
<td>1990</td>
<td>0.45</td>
<td>1.8</td>
<td>4</td>
<td>Three dose groups:</td>
<td>Death, MI, bypass, abrupt closure</td>
<td>Angioplasty for unstable angina</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.55</td>
<td>2.2</td>
<td></td>
<td>0.15 mg/kg B, then 0.6 mg · kg⁻¹ · h⁻¹</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>2.5</td>
<td></td>
<td>0.25 mg/kg B, then 1.0 mg · kg⁻¹ · h⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.35 mg/kg B, then 1.4 mg · kg⁻¹ · h⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 7</td>
<td>410</td>
<td>1992</td>
<td>None</td>
<td>0.25</td>
<td>72</td>
<td>0.02 mg · kg⁻¹ · h⁻¹</td>
<td>Death, MI, ischemia, revasc</td>
<td>Unstable angina or non-Q wave MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
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</tr>
</tbody>
</table>

B indicates bolus; I, infusion; Load, loading dose; and revasc, rapid clinical deterioration requiring revascularization.

inactive to active. Prospectively, a dose level was considered inactive if thrombotic, abrupt vessel closure occurred at a frequency of ≥2 per 25 patients or ≥3 per 50 patients. The 3 active-dose arms were compared with the 3 inactive-dose arms in a manner similar to the published results. Bleeding events and MIs were adjudicated by the investigators. The Thrombin Inhibition in Myocardial Ischemia (TIMI) 7 trial compared 3 bivalirudin doses (0.25, 0.5, and 1 mg · kg⁻¹ · h⁻¹) with a much lower bivalirudin dose (0.02 mg · kg⁻¹ · h⁻¹), which had been shown to be subtherapeutic in a short-term pilot study. An MI was defined as a creatine kinase (CK)-MB fraction exceeding normal or, when CK-MB was not available, a total CK bundle-branch block with chest discomfort of ≥30 minutes or abnormal enzymes. The definition for major hemorrhage was identical to the definition used in HERO-1. The unpublished TIMI 8 study (data on file, The Medicines Company) was terminated after the enrollment of 133 (of a planned 5320) patients because development of the drug was temporarily abandoned by the sponsor (Biogen, Inc). Clinical end points were determined by the local investigators. The available data from TIMI 8 were included in the overview to reflect the totality of evidence.

Clinical End Points

Clinical outcomes that were studied included death, MI, the composite of death or MI, and major hemorrhage. The definitions for each end point were those specified in the individual study protocols. Each outcome was evaluated at an early end point (7 days or in-hospital). Three of the heparin-controlled trials had extended follow-up, permitting analysis at a late time point (30 to 50 days).

Statistical Analysis

ORs summarizing the effectiveness of bivalirudin were calculated with the use of Fast*Pro software. These ORs were combined with the assumption of an empirical Bayes model with the formulas of Hedges and Olkin. Risk differences between control and treatment arms were computed for the vents of each trial and were combined with the use of the same model. The empirical Bayes method is a random-effects model that reduces to a fixed-effects model when the studies are homogeneous. (A homogeneous collection of studies attempts to estimate the same underlying value.) The random-effects model accommodates heterogeneity by assuming that the true effect differs among studies and therefore must be represented by a distribution of values instead of a single value. The result is a wider range of uncertainty about the variable of interest than is calculated.

TABLE 2. Heparin-Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Year</th>
<th>Load, mg/kg</th>
<th>Infusion, mg · kg⁻¹ · h⁻¹ × duration</th>
<th>Heparin Regimen</th>
<th>Primary End Point (In-Hospital)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 8</td>
<td>133</td>
<td>1993</td>
<td>0.1</td>
<td>0.25 × 72 h</td>
<td>70 U/kg B, then 15 U · kg⁻¹ · h⁻¹</td>
<td>In-hospital/14-day death or MI</td>
<td>Unstable angina or non-Q wave MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2 × 14−20 h</td>
<td>175 U/kg B, then 15 U · kg⁻¹ · h⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bittl et al</td>
<td>4312</td>
<td>1992</td>
<td>1.0</td>
<td>2.5 × 4 h, then 0.2 × 14−20 h</td>
<td>5000 U B, then 1000 U/h I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Théroux et al</td>
<td>116</td>
<td>1991</td>
<td>None</td>
<td>0.5 × 12 h, then 0.1 × 84 h</td>
<td>5000 U B, then 1000 U/h I alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HERO-1</td>
<td>412</td>
<td>1992</td>
<td>0.125</td>
<td>0.25 × 12 h, then 0.125 × 36−48 h</td>
<td>5000 U B, then 1000−1200 U/h I</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 × 12 h, then 0.25 × 36−48 h</td>
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</tr>
</tbody>
</table>

B indicates bolus; I, infusion; Load, loading dose; and revasc, rapid clinical deterioration requiring revascularization.
with equal- or fixed-effects models. The number of events prevented per patient treated is the reciprocal of the risk difference. Significance was determined with the extent of the 95% CI; the 2-sided probability value can be determined by measuring twice the area of the probability distribution beyond unity.

Although the empirical Bayes model accommodates the variability among studies, the extent of heterogeneity in the collected trials was examined with the use of the \( Q \) statistic of DerSimonian and Laird. This method approximates a \( \chi^2 \) statistic to test the null hypothesis that all of the studies estimate the same true value. The test reflects the probability that differences at least as extreme as the observed results of the individual studies could have occurred through chance (eg, due only to sampling). If the probability is sufficiently low, the null hypothesis is rejected and the studies are said to be heterogeneous.

**Results**

**Inactive-Dose, Bivalirudin-Controlled Trials**

The 2 trials with bivalirudin-control arms, Topol et al\(^6\) and TIMI 7,\(^7\) enrolled 701 patients. At the early time point, the combined OR for death was 0.42 (95% CI 0.10 to 1.81; \( P = 0.24 \)) in favor of therapeutic anticoagulation. There was a highly significant (\( P = 0.009 \)) reduction in MI associated with therapeutic bivalirudin doses, with a combined OR of 0.30 (95% CI 0.12 to 0.73). The absolute risk difference was equivalent to 33 fewer MIs per 1000 patients treated with therapeutic doses (\( -0.033; 95\% \text{ CI } -0.063 \) to \( -0.0040 \)). Similarly, the risk of the composite of death or nonfatal MI was significant lower (OR 0.31, 95% CI 0.14 to 0.68; \( P = 0.003 \)), corresponding to an absolute difference of 41 fewer events per 1000 patients treated with therapeutic bivalirudin doses (\( -0.041; 95\% \text{ CI } -0.073 \) to \( -0.0086 \); Figure 1A). There was no significant difference in major in-hospital hemorrhage (OR 1.04, 95% CI 0.42 to 2.54; \( P = 0.94 \); Figure 1B).

**Heparin-Controlled Trials**

The 4 heparin-controlled trials enrolled 4973 patients. At the early time point, there was no significant reduction in mortality rates with bivalirudin (OR versus heparin 0.94, 95% CI 0.47 to 1.87; \( P = 0.86 \)). For nonfatal MI, the combined OR was 0.71 (95% CI 0.49 to 1.03; \( P = 0.07 \)), equivalent to 8 fewer MIs per 1000 patients treated with bivalirudin (\( -0.0075; 95\% \text{ CI } -0.018 \) to 0.0028). The combined OR for the composite of death or nonfatal MI was 0.75 (95% CI 0.54 to 1.05; \( P = 0.09 \)), or 7 fewer events per 1000 patients treated with bivalirudin (\( -0.0065; 95\% \text{ CI } -0.017 \) to 0.0035; Figure 2A).
Three trials (4857 patients) had late (30- to 50-day) follow-up. There was no significant difference in mortality rates between the 2 arms (OR for bivalirudin versus heparin 0.92, 95% CI 0.50 to 1.70; \( P = 0.80 \)). Bivalirudin was associated with a significant reduction in MI (OR 0.73, 95% CI 0.55 to 0.97; \( P = 0.035 \)). The combined absolute risk difference was about 15 fewer MIs per 1000 patients treated with bivalirudin (−0.015; 95% CI, −0.030 to 0.0001). For death or nonfatal MI, the combined OR was 0.73 (95% CI, 0.57 to 0.95; \( P = 0.020 \)) in favor of bivalirudin. The absolute risk difference was equal to 14 fewer events per 1000 patients treated with bivalirudin (−0.014; 95% CI −0.027 to −0.0003; Figure 2B).

Data for in-hospital major hemorrhage were available for 4964 patients. There was a highly significant (\( P < 0.001 \)) reduction in hemorrhagic events in patients receiving bivalirudin, with a combined OR of 0.41 (95% CI 0.32 to 0.52). The absolute risk difference was equal to 58 fewer events per 1000 patients treated with bivalirudin (−0.072 to −0.043; Figure 2C).

Heterogeneity Analysis

The DerSimonian and Laird statistic revealed no significant heterogeneity for any end point, with the exception of late MI (\( P = 0.05 \)). The prematurely terminated TIMI 8 trial was responsible for this effect, which was not seen for the composite end point (death or nonfatal MI).

Discussion

Although heparin is the mainstay of anticoagulation, it has several limitations, including a narrow therapeutic window, variable pharmacokinetics, immune-mediated thrombocytopenia, and the inability to inactivate platelet-bound factor Xa and clot-bound thrombin. The risk of major hemorrhage, including intracranial and retroperitoneal bleeding, ranges from 1% to 5% for regimens of aspirin and heparin in low-risk patients \(16–18\) and is as high as 19% for patients with concomitant thrombolytic therapy. \(19\) Direct thrombin inhibitors have sought to improve the risk/benefit ratio of anticoagulation for acute coronary syndromes. Clinical trials of hirudin, a natural protein anticoagulant from the European leech (\textit{Hirudo medicinalis}), have shown promising reductions in death and nonfatal MI but at least some increase in the rate of hemorrhage. \(20-22\)

The present systematic overview shows that bivalirudin reduces death and nonfatal MI rates for patients with ischemic heart disease. This benefit is consistent for both PCI and acute coronary syndrome groups. This reduction is also statistically significant when therapeutic bivalirudin doses are compared with subtherapeutic doses. No truly placebo-controlled anticoagulant trial has ever been conducted for patients undergoing PCI, and any such trial would now likely be considered ethically unacceptable. In direct comparisons of bivalirudin with heparin, bivalirudin consistently reduces the incidence of death or MI at least to the same degree as does unfractionated heparin. The principal benefit of bivalirudin appears to be in a reduction in major hemorrhage, with a consistent, highly significant (\( P < 0.001 \)) advantage over heparin.

The binding kinetics of bivalirudin with thrombin suggest a mechanism for potential advantages over heparin and natural hirudin. \(23\) The binding of bivalirudin to thrombin is reversible—thrombin slowly cleaves the bivalirudin Arg3-Pro4 bond, resulting in recovery of thrombin active-site functions. Thus, bivalirudin acts as a complete, noncompetitive thrombin inhibitor, enabling initially inhibited thrombin molecules to interact with other clotting substrates and to contribute to coagulation if required.

For this analysis, we chose to use the hard end points of death and MI because these end points are least confounded by subjective observations, although none of the individual trials were designed to have adequate statistical power to detect a difference in the composite end point. The benefit observed in the composite end point stems largely from reductions in MI. Definitions of nonfatal MI varied among trials, with different enzyme, electrocardiographic, and clinical criteria. Despite this limitation, any MI, however defined, constitutes an undesirable event for patients, and we have reported results consistent with the primary end point definitions adopted for each study, separately.

Differences in treatment doses, treatment duration, and concomitant therapies can produce disparity among trials included in meta-analyses. \(24\) Efforts to accumulate all available information inevitably increase the potential for heterogeneity in pooled data. Formal tests for heterogeneity have low power. Thus, statistical failure to reject the null hypothesis of homogeneity does not imply equality \(25\) but rather a lack of unacceptable heterogeneity. The TIMI 8 trial contributed to the statistical heterogeneity observed for the late-MI end point. Trials that stop early because of unexpected positive or negative results may exaggerate the difference between the treatment arms for the individual trial \(26\) but do not appear to substantially affect overviews that include such studies. \(27\) The TIMI 8 trial, which had only a small randomized cohort, was terminated for reasons unrelated to the data, which reduces the likelihood of bias. In this overview, the methods used to calculate the combined ORs accommodate heterogeneity in their assumptions. \(13,28\) Even so, identification of sources of clinical and statistical heterogeneity remains important when placing the overview results into a clinical context.

Approximately 87% of patients participating in heparin-controlled studies of bivalirudin were enrolled in the trial by Bittl et al. \(9\) The large size of this study strongly influences the overall estimates of bivalirudin effect. Notably, the clinical benefit of bivalirudin appears to be reproducible and consistent among the trials. The reductions in the composite end point are in large part attributable to reductions in MIs. This is not surprising, because the overall mortality rates were low in the populations studied.

The hemorrhagic risk associated with heparin limits its value as a single agent administered in high doses and in combination with antiplatelet and thrombolytic agents in lower doses. There is a clear need to identify safer, more effective anticoagulants. Previous agents have been unable to overcome the Scylla and Charybdis of thrombotic complications and hemorrhagic risk. Increased bleeding complications have heretofore been a consistent liability for incremental
improvements in antithrombotic potential. Taken together, the existing trials of bivalirudin show effectiveness at least equal to that of heparin, with markedly improved safety. The totality of evidence defines bivalirudin as a unique compound with unparalleled net benefit, establishing a new precedent for the development of novel anticoagulants.

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David F. Kong, Eric J. Topol, John A. Bittl, Harvey D. White, Pierre Théroux, Vic Hasselblad
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