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Original article

Bivalirudin Versus Unfractionated Heparin in Acute Coronary Syndromes: An Updated Meta-analysis of Randomized Trials

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ABSTRACT

Introduction and objectives: Contrasting data have been reported on bivalirudin as an anticoagulation strategy during percutaneous coronary interventions, offering theoretical benefits on bleeding complications but raising concerns on a potential increase in the risk of stent thrombosis. We performed an updated meta-analysis to evaluate the efficacy and safety of bivalirudin compared with unfractionated heparin in patients undergoing percutaneous interventions for acute coronary syndromes.
Methods: Literature archives and main scientific sessions were scanned. The primary efficacy endpoint was 30-day overall mortality. Secondary endpoints were stent thrombosis and major bleeding. A prespecified analysis was conducted according to clinical presentation.
Results: Twelve randomized trials were included, involving 32 746 patients (52.5% randomized to bivalirudin). Death occurred in 1.8% of the patients, with no differences between bivalirudin and heparin (odds ratio = 0.91; 95% confidence interval, 0.77-1.08; *P* = .28; *P* for heterogeneity = .41). Similar results were obtained for patients with non–ST-segment elevation and in ST-segment elevation myocardial infarction. A significantly higher rate of stent thrombosis was observed with bivalirudin (odds ratio = 1.42; 95% confidence interval, 1.09-1.83; *P* = .008; *P* for heterogeneity = .09). Bivalirudin was associated with a significant reduction in the rate of major bleeding (odds ratio = 0.60; 95% confidence interval, 0.54-0.75; $P < .00001$; *P* for heterogeneity $< .0001$), which, however, was related to the differential use of glycoprotein IIb/IIIa inhibitors ($r = -0.02$ [−0.033 to −0.0032]; *P* = .02) and did not translate into survival benefits.
Conclusions: In patients undergoing percutaneous coronary interventions, bivalirudin is not associated with a reduction in mortality compared with heparin but does increase stent thrombosis. The reduction in bleeding complications observed with bivalirudin does not translate into survival benefits but is rather influenced by a differential use of glycoprotein IIb/IIIa inhibitors.

Bivalirudina frente a heparina no fraccionada en síndromes coronarios agudos: un metanálisis actualizado de ensayos aleatorizados

Palabras clave:
Bivalirudina
Heparina
Intervención coronaria percutánea
Metanálisis

RESUMEN

Introducción y objetivos: Se han presentado datos contradictorios respecto al uso de bivalirudina como estrategia de anticoagulación durante las intervenciones coronarias percutáneas, puesto que aporta beneficios teóricos en cuanto a las complicaciones hemorrágicas, pero preocupa el posible aumento del riesgo de trombosis del *stent*. Se realizó un metanálisis actualizado para evaluar la eficacia y la seguridad de la bivalirudina comparada con la heparina no fraccionada en pacientes sometidos a intervenciones percutáneas por síndromes coronarios agudos.
Métodos: Se realizó una búsqueda de artículos en la literatura médica y en actas de reuniones científicas importantes. El objetivo principal de eficacia fue la mortalidad total a 30 días. Los objetivos secundarios fueron evaluar trombosis del *stent* y hemorragias mayores. Se llevó a cabo un análisis preespecificado según la forma de presentación clínica.
Resultados: Se incluyeron 12 ensayos aleatorizados con un total de 32.746 pacientes (el 52,5% asignados aleatoriamente a bivalirudina). La mortalidad fue del 1,8%, sin que se apreciaran diferencias entre la bivalirudina y la heparina (*odds ratio* = 0,91; intervalo de confianza del 95%, 0,77-1,08; p = 0,28; p para la heterogeneidad = 0,41). Se obtuvieron resultados similares en los pacientes con infarto de miocardio sin y con elevación del segmento ST. Se observó una tasa de trombosis del *stent* significativamente superior con bivalirudina (*odds ratio* = 1,42; intervalo de confianza del 95%, 1,09-1,83; p = 0,008; p para la heterogeneidad = 0,09). La bivalirudina se asoció a una reducción significativa de la tasa de hemorragias

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mayores (*odds ratio* = 0,60; intervalo de confianza del 95%, 0,54-0,75; p < 0,00001; p para la heterogeneidad < 0,0001) que, sin embargo, estaba relacionada con la diferencia existente en el uso de inhibidores de la glucoproteína IIb/IIIa (r = –0,02 [–0,033 a –0,0032]; p = 0,02) y no se tradujo en un efecto favorable en supervivencia.

Conclusiones: En pacientes sometidos a intervenciones coronarias percutáneas, la bivalirudina, comparada con la heparina, no se asoció a una reducción de la mortalidad, pero sí a un aumento de trombosis del *stent*. La reducción de las complicaciones hemorrágicas observada con el uso de bivalirudina no se tradujo en un efecto beneficioso en la supervivencia, en cambio estuvo influida por una diferencia en el uso de inhibidores de la glucoproteína IIb/IIIa.

Abbreviations

ACS: acute coronary syndrome
NSTEMI: non—ST-segment elevation myocardial infarction
PCI: percutaneous coronary intervention
STEMI: ST-segment elevation myocardial infarction
UFH: unfractionated heparin

INTRODUCTION

Increasing complexity in patients admitted for acute coronary syndrome (ACS) is rendering more and more challenging the management of antithrombotic therapies, requiring continuous balancing between the risks of bleeding and thrombotic complications.[1–3]

Bivalirudin has been proposed as an alternative strategy to unfractionated heparin (UFH) for anticoagulation during percutaneous coronary interventions (PCI), offering several theoretical advantages including activity against clot-bound thrombin, inhibition of thrombin-induced platelet activation, short plasma half-life, and a lower dependence on renal clearance.[4]

Moreover, the first studies suggested that bivalirudin could provide similar effectiveness to UFH, but with a significant reduction in bleeding complications.[5,6] However, these trials did not consider patients with ACS, in whom the balance between bleeding and ischemic events is more complex.

In these settings, more recent clinical trials and pooled analyses[7–9] have suggested that bivalirudin could be associated with an even higher risk of stent thrombosis and myocardial infarction, while offering no advantage in the reduction of hemorrhagic complications, besides raising the hypothesis that the differences in bleedings observed with bivalirudin could be affected by access-site bleedings or by greater use of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, in association with UFH.

Therefore, the MATRIX trial[10] has been conducted, comparing bivalirudin with UFH in ACS patients, randomly assigned to undergo PCI by either the radial or femoral route, showing no advantage from the use of bivalirudin in terms of ischemic, bleeding or combined endpoints. Therefore, the aim of the current study was to perform the most comprehensive meta-analysis to evaluate the safety and efficacy of bivalirudin compared with UFH during PCI, including the data from most recent randomized trials in the setting of ACS.

METHODS

Eligibility and Search Strategy

The literature was scanned by formal searches of electronic databases (MEDLINE, Cochrane and EMBASE) for clinical studies and scientific session abstracts, searched on the TCT,[11] EuroPCR,[12] ACC,[13] AHA,[14] and ESC,[15] websites for oral presentations and/or expert slide presentations from January 1990 to September 2015. The following keywords were used: "bivalirudin and acute coronary syndrome" or "bivalirudin versus heparin" or "bivalirudin and trial". No language restrictions were enforced.

Data Extraction and Validity Assessment

Data were independently abstracted by 2 investigators. If the data were incomplete or unclear, authors were contacted, when possible. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle.

Outcome Measures

The primary efficacy endpoint was overall mortality at 30 days of follow-up. The secondary endpoint was the occurrence of stent thrombosis at 30 days. The primary safety endpoint was the occurrence of major bleedings (according to per protocol definition) within the first 30 days from randomization. A prespecified meta-analysis was conducted according to patients' presentation (non—ST-segment elevation ACS or ST-segment elevation myocardial infarction [STEMI]).

Data Analysis

The statistical analysis was performed using the Review Manager 5.23 freeware package, SPSS 17.0 statistical package. Odds ratios (OR) and 95% confidence intervals (95%CI) were used as summary statistics. The pooled OR was calculated by using a fixed effect model. The Breslow-Day test was used to examine the statistical evidence of heterogeneity across the studies ($P < .1$). A random-effect model was also applied to confirm our results (DerSimonian and Laird random-effects model). The study quality was evaluated by the same 2 investigators according to a score, which, as previously described,[16] was expressed on an ordinal scale, allocating 1 point for the presence of each of the following: *a)* statement of objectives; *b)* explicit inclusion and exclusion criteria; *c)* description of the intervention; *d)* objective means of follow-up; *e)* availability of data on endpoint events; *f)* power analysis; *g)* description of statistical methods; *h)* multicenter design; *i)* discussion of withdrawals, and *j)* details on medical therapy. A meta-regression analysis was carried out to evaluate the following: the relationship between the benefits in mortality from bivalirudin vs UFH and patients' risk profile (as log of the OR for mortality in the control group); the impact on mortality of the reduction in bleeding complications with bivalirudin (as log of the OR for bleeding events in the bivalirudin vs control groups); the bleeding reduction with bivalirudin and patients' risk profile (as log of the OR for bleeding events in the control group). The study