Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention

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Aims
To evaluate the effectiveness and safety of bivalirudin as used in routine care. Bivalirudin has been studied as an alternative to heparin plus glycoprotein IIb/IIIa inhibitor (GPI) during percutaneous coronary intervention (PCI). Trials have indicated that bivalirudin is non-inferior to heparin with respect to death and repeat revascularization and may decrease the risk of major bleeds. The use of bivalirudin in routine care has not been evaluated.

Methods and results
Using a representative database, we identified 127,185 individuals who underwent inpatient PCI between June 2003 and December 2006 and were administered either bivalirudin plus provisional GPI or the comparator, heparin plus GPI. We estimated relative risks of blood transfusion, repeated PCI, and in-hospital death. The adjusted hazard ratio (HR) for blood transfusion was 0.67 (0.61–0.73); instrumental variable analysis showed an HR of 0.72 (0.12–4.47). We observed a risk of in-hospital death of 0.80% in the bivalirudin group and 2.1% in the heparin group; the adjusted HR was 0.51 (0.44–0.60).

Conclusion
In our non-randomized study of routine care, we observed a reduction in blood transfusions and in short-term mortality for patients treated with bivalirudin compared with heparin plus GPI. The mortality benefit was more pronounced in our study than in randomized trials.

Keywords
Anti-thrombotic treatments • Pharmacoepidemiology • Instrumental variable analysis • Confounding factor (epidemiology) • Percutaneous coronary intervention

Introduction
Bivalirudin (Angiomax, The Medicines Company), a direct thrombin inhibitor, was approved in December 2000 for use in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty.1 In June 2005, an additional indication was added for the use of bivalirudin alongside provisional glycoprotein IIb/IIIa inhibitor (GPI) for patients undergoing percutaneous coronary intervention (PCI). The added indication was largely based on the REPLACE-2 trial,2–4 which showed that compared with heparin plus GPI, bivalirudin with provisional GPI was non-inferior with respect to outcomes including bleeds, repeat revascularization, and death, and additionally lowered the risk of major bleeds. As such, bivalirudin has become a common treatment for patients undergoing PCI.5,6 More recently, trials have confirmed the non-inferiority result from REPLACE-2,7–9 and that bivalirudin monotherapy may significantly reduce the risk of major bleeds7–9 and, in one case, the short-term risk of death.8

None of these trials was conducted within the context of routine care. Notably, each had exclusion criteria that may have removed the highest risk patients from the population under study and thereby may have masked certain risks or benefits of the drug. As such, we sought to study the routine care safety and effectiveness of bivalirudin plus provisional GPI compared
with heparin plus GPI. We analysed data from the Premier administrative in-hospital database using multivariate regression adjustment and instrumental variable analysis (IVA).

Methods

Data source

We conducted a cohort analysis using data drawn from the Premier Perspective Database, an inpatient administrative database covering approximately one-sixth of all hospitalizations in the USA.10 Premier provides a variety of services to the hospitals that submit their data, including tabulation, benchmarking, and normative information. Detailed service-level information available for each hospital includes medications dispensed, procedures carried out, and laboratory tests ordered, as well as physician and hospital characteristics.11 Further available from the UB-92 form12 submitted for each hospitalization are patient demographics, primary and secondary diagnoses, discharge status, and source of admission (including emergency room, urgent care facility, and elective).13 Premier data routinely undergo quality and completeness checks—data verification, reconciliation, and validation—as well as checks on clinical resource consumption, manual data audit, and a warehouse audit (C. Craver, personal communication). For this study, Premier provided a de-identified data set containing observations from June 2003 through December 2006. Patient admission was recorded as month and year, and subsequent admissions were recorded as number of days from this first admission date. All charges are recorded at the day level; time of day was not recorded.

Patients and cohort definition

Patients were eligible to enter the cohort as of their first study-period inpatient admission in which they underwent PCI.14,15 Occurrence of PCI was defined as the charge of at least one necessary supply (coronary stent, balloon) and/or one necessary professional service (coronary stent placement, coronary angiography). On the day of PCI, exposure status was determined, and those who did not meet the definition of exposed or comparison groups (see what follows) were excluded from the analysis. We further excluded outpatient procedures, as well as patients from rural hospitals and those from hospitals performing fewer than an average of two PCIs per day. On the basis of secondary discharge codes, we excluded patients with a history of haemostatic disorders (idiopathic thrombocytopenia, haemophilia, protein S deficiency, protein C deficiency, or leukaemia). Excluded patients were not eligible even if they met the inclusion criteria at a future time.

Exposure and outcome definition

The primary exposure was defined as a recorded charge for bivalirudin with or without GPI on the day of the index PCI, and no administration of heparin on that day. The comparison group was defined as those administered at least 1000 units of heparin plus GPI on the day of the index PCI. Patients receiving any other drug regimens were excluded. Follow-up for all outcomes started on the day the index PCI was performed, and we required all outcomes to occur within the index hospitalization. The primary outcome of blood transfusion was defined as a charge code for order of any blood product (whole blood, red blood cells, fresh frozen plasma, platelets, or cryoprecipitate) and was intended to be a proxy for major bleeds. Secondary outcomes were defined as (i) death occurring in hospital,16 determined from the UB-92 form, and (ii) repeat PCI within the same hospital admission.

Patient characteristics

We adjusted for patients’ socio-demographic factors: age, sex, white vs. non-white race, low vs. non-low income, and married or living with partner vs. living alone. Low income was defined as Medicaid patient or indigent payer. These factors were determined from the patients’ UB-92 discharge forms. We further adjusted for year of admission. We adjusted for whether patients were admitted on an urgent basis with a primary discharge ICD-9 code of 410 (myocardial infarction, MI), 411 (other acute or subacute forms of ischaemic heart disease), or 414.01 (coronary atherosclerosis of native coronary artery), as well as whether the PCI was performed within 1 day of the patient’s hospital admission.

On the basis of the up to 100 secondary discharge codes filed for the index admission, we measured certain patient co-morbidities: diabetes, hypertension, liver disease, COPD/asthma, cancer, smoking, old MI, old stroke, endocarditis, ischaemic heart disease, peripheral artery disease, and chronic kidney disease. Finally, we noted a number of factors about the hospital in which the index PCI occurred: teaching vs. non-teaching status, location (midwest, northeast, south, or west of the USA, and urban/rural), hospital size (number of beds), and high-volume hospitals (an average of 10 or more PCIs performed per day).

Statistical analyses

In our primary analysis, we estimated unadjusted and adjusted hazard ratios (HRs). Patients were censored at the earliest of hospital discharge, death, occurrence of the outcome in question, or 120 days; each outcome was studied separately. Hazard ratios were estimated using Cox proportional hazards models,17 and standard errors were estimated robustly with the ‘sandwich’ estimate of variance18 to account for clustering within hospitals. Estimates were adjusted for all factors noted earlier and described in Table 1. No variable selection techniques were used.

In a secondary analysis, we examined cumulative incidence on the risk difference and odds ratio scales. Risk differences were estimated using least squares regression,19,20 and odds ratios were estimated with logistic regression.21 To inform whether these cumulative incidence models would capture differential lengths of follow-up time in the exposed and comparison groups, we compared the median overall length of follow-up in each group, as well as the median time to each outcome. P-values for difference were derived from the Wilcoxon rank sum test.

To determine whether bivalirudin may perform differentially in a subgroup of patients who may have received their PCI on an acute basis, we repeated the analyses among patients who (i) were admitted to the hospital via urgent care, who (ii) had a primary discharge diagnosis code of 410 (MI), 411 (other acute or subacute forms of ischemic heart disease), or 414.01 (coronary atherosclerosis of native coronary artery) and who (iii) had his or her PCI performed within 1 day of admission. To examine the effect within less acute patients, we further assessed those who met these criteria, but who were not admitted via urgent care. These may have been patients scheduled for elective PCIs. We did a further sensitivity analysis in which we considered three treatment groups: bivalirudin with provisional GPI, heparin plus GPI, and heparin alone, under the theory that those given heparin alone may be sicker than those given heparin plus GPI.

Instrumental variable analysis

The Premier database lacks patient-level details used in clinical decision-making and may thus under-report pre-existing conditions. With respect to our study outcomes, incompletely recorded covariates include history of prior procedures, overall health status,
Table 1  Characteristics of patients diagnosed with myocardial infarction or acute coronary syndrome and treated with bivalirudin or heparin plus glycoprotein IIb/IIIa inhibitor, June 2003–December 2006

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Stratified by actual treatment</th>
<th>Stratified by the instrumental variable used, hospital preference</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients treated with bivalirudin (n = 32,541)</td>
<td>Patients treated with heparin plus GPI (n = 94,644)</td>
<td>Difference</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>66.2 (± 12.1)</td>
<td>62.4 (± 12.6)</td>
<td>3.9</td>
</tr>
<tr>
<td>Male (%)</td>
<td>62.1</td>
<td>67.7</td>
<td>−5.6</td>
</tr>
<tr>
<td>White race (%)</td>
<td>74.1</td>
<td>71.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Low income (%)</td>
<td>4.6</td>
<td>5.3</td>
<td>−0.7</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td>Married or partner</td>
<td>57.9</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Unmarried</td>
<td>37.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>4.6</td>
<td>−0.8</td>
</tr>
<tr>
<td>History of</td>
<td>Tobacco use (%)</td>
<td>21.4</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>PCI (%)</td>
<td>42.4</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Venous thrombo-embolism (%)</td>
<td>2.7</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Stroke (%)</td>
<td>9.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Diagnosis of</td>
<td>COPD/asthma (%)</td>
<td>2.7</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Cancer (%)</td>
<td>6.4</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus (%)</td>
<td>27.7</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Hypertension (%)</td>
<td>62.3</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Liver disease (%)</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Peripheral artery disease (%)</td>
<td>11.9</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Endocarditis (%)</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease (%)</td>
<td>6.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Overall difference in patient characteristics</td>
<td></td>
<td></td>
<td>0.141</td>
</tr>
<tr>
<td>Procedure characteristics (%)</td>
<td>Urgent care CV admission</td>
<td>67.6</td>
<td>−11.6</td>
</tr>
<tr>
<td></td>
<td>PCI within 1 day of admission</td>
<td>74.8</td>
<td>−8.5</td>
</tr>
</tbody>
</table>

| Number of stents charged (%) | None (angioplasty alone) | 2.6 | 3.8 | −1.2 | 1.7 | 4.0 | −2.3 |
|                             | 1–2                        | 91.7 | 92.1 | −0.3 | 92.7 | 91.7 | 1.1 |
|                             | 3+                         | 5.7 | 4.2 | 1.5 | 5.6 | 4.4 | 1.2 |

Continued
Table 1  Continued

<table>
<thead>
<tr>
<th>Hospital characteristics (%)</th>
<th>Stratified by actual treatment</th>
<th>Stratified by the instrumental variable used, hospital preference*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients treated with bivalirudin (n = 32 541)</td>
<td>Patients treated with heparin plus GPI (n = 94 644)</td>
</tr>
<tr>
<td></td>
<td><strong>65.7</strong></td>
<td><strong>50.1</strong></td>
</tr>
<tr>
<td>Teaching hospital</td>
<td><strong>58.8</strong></td>
<td><strong>45.1</strong></td>
</tr>
<tr>
<td>Average volume more than 10 stents/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–399</td>
<td><strong>28.2</strong></td>
<td><strong>37.8</strong></td>
</tr>
<tr>
<td>400–649</td>
<td><strong>40.4</strong></td>
<td><strong>39.1</strong></td>
</tr>
<tr>
<td>650+</td>
<td><strong>31.3</strong></td>
<td><strong>23.2</strong></td>
</tr>
<tr>
<td>Region of the USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West</td>
<td><strong>13.5</strong></td>
<td><strong>12.6</strong></td>
</tr>
<tr>
<td>Midwest</td>
<td><strong>6.4</strong></td>
<td><strong>25.6</strong></td>
</tr>
<tr>
<td>South</td>
<td><strong>57.0</strong></td>
<td><strong>49.5</strong></td>
</tr>
<tr>
<td>Northeast</td>
<td><strong>23.2</strong></td>
<td><strong>12.3</strong></td>
</tr>
</tbody>
</table>

*Hospital preference is defined by whether <5% or >80% of prescribing is bivalirudin in the calendar quarter in which the patient was seen; <5% yields a prediction of the heparin+GPI; >80% yields a prediction of bivalirudin.

Overall difference in patient characteristics is measured using the Mahalanobis distance, a statistic which accounts for correlation among covariates. Stratification by an instrumental variable should lead to greater similarity between the groups and thus a lower Mahalanobis distance.
and preventive steps taken. Other important covariates not measured include high serum creatinine, coronary artery disease, and ejection fraction. Pre-admission use of drugs such as aspirin, warfarin, nitrates, and clopidogrel is also not recorded in the Premier database, and since times of day were not recorded, drugs used directly before PCI are indistinguishable from those used just after.

To mitigate bias due to unmeasured confounders, we used IVA, a post hoc analytic technique based on statistical principles similar to those used in the analysis of randomized trials. To use IVA, one must identify a naturally varying phenomenon in the observed data, which like the coin in a randomized trial, predicts the treatment a patient will receive but is neither directly nor indirectly associated with the outcome, except through the effect of the treatment itself. This observed phenomenon is encoded as an instrumental variable (IV), or instrument. As an example, studies have used the distance an ambulance driver must travel to reach an advanced cardiac care facility to predict whether a patient will receive basic or advanced cardiac treatment. With a valid instrument and IVA, it is not necessary to adjust for patient-level factors; this is parallel to trials not requiring patient-level adjustment after stratifying by the randomizing variable.

In our study, we defined an instrument that sought to identify hospitals that were likelier than not to administer bivalirudin to a particular patient, based on information known about the hospital’s treatment practices during the calendar quarter during which the patient underwent PCI (Figure 1A). The instrument was based on the hospital’s ‘preference’ for bivalirudin over heparin plus GPI. The preferences were hypothesized to be the result of local practices, formulary decisions, or medical guidelines. Since the instrument was hospital-based, we believed that it may retain an association with the study outcomes, as quality of care and outcomes are known to vary with hospital. To mitigate any such association, we controlled for measured hospital characteristics including size, PCI volume, and teaching vs. non-teaching facility.

The instrument was designed to take advantage of hospitals that were very consistent in their choice of whether to administer bivalirudin. Study patients who were seen in a hospital that prescribed bivalirudin over heparin to 5% of their study patients during the calendar quarter in which the patient was treated were predicted to receive heparin plus GPI, whereas patients seen in facilities prescribing bivalirudin over 80% of their study patients were predicted to receive bivalirudin. Patients seen at hospitals with prescribing fractions >5% and <80% were excluded from the IVA since treatment choice may have been decided less by hospital preference and therefore be subject to confounding by unmeasured patient-level covariates. The 5% figure was chosen to identify those hospitals with minimal levels of bivalirudin prescribing, possibly because bivalirudin was not on the formulary or part of practice guidelines. The 80% figure was chosen to identify hospitals that used bivalirudin extensively, though they may not have given it to all patients.

For the IVA-based estimate of the risk difference, we performed two-stage least squares (2SLS) regression. For the IVA-based estimate of the hazard ratio, we performed a two-stage regression in which the treatment was predicted as a function of the IV and the confounders using a logistic model, and the outcome was predicted using Cox proportional hazards regression as a function of the predicted treatment and the confounders. Standard errors were estimated with non-parametric bootstrapping with 500 replications. Strength of the instruments was characterized by partial $r^2$ values and partial F-statistics. Reduction in imbalance of patient characteristics in the treated and untreated cohorts was measured by the Mahalanobis distance. All models were run in Stata version 9 (Stata Corp., College Station, TX, USA) using built-in procedures and the ivreg2 extension.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written. See Appendix 1 for a more technical description of our IVA methods.

**Results**

We analysed 326 556 patients who underwent PCI, of whom 283 660 met our inclusion criteria (Figure 2). 127 185 of these patients were treated according to the definition of the exposure or comparator groups (26% exposed to bivalirudin). Characteristics of this cohort are displayed in the left columns of Table 1. Significant imbalances existed between the bivalirudin and heparin groups, including history of hypertension and diabetes; those exposed to bivalirudin were generally sicker than those not. Stratifying the cohort by the instrument—conceptually similar to stratifying by the randomizing variable in a trial—yielded a smaller patient population (hereafter, the ‘IVA subpopulation’) and a reduction in imbalance between the groups (right columns of Table 1), as evidenced by the shrinking of the Mahalanobis distance from 0.141 to 0.104.

With respect to the primary outcome of blood transfusions, as represented in the database by order of any blood product, the multivariate analysis indicated a 33% risk reduction [HR = 0.67; 95% confidence interval (CI) = 0.61–0.73] when patients were treated with bivalirudin compared with heparin plus GPI (Table 2 and Figure 3). The IVA showed a weaker protective effect (HR = 0.72; 95% CI = 0.12–4.47). As expected with the relatively inefficient two-stage models and smaller IVA subpopulation, the IVA CI was much wider than its non-IVA counterpart.

We also observed bivalirudin to be protective against in-hospital death, with a 49% risk reduction in the multivariate analysis (HR = 0.51, 95% CI = 0.44–0.60). The results for death did not include the null value in the 95% CI. In the fully adjusted analysis, we observed a null result for reduction for within-admission repeat PCI (HR = 0.96, 95% CI = 0.90–1.03).

For our secondary cumulative risk analysis, we had a concern that the length of follow-up may be differential by exposure status, which could then give one of the exposure groups more opportunity to accrue outcomes. To assess this possibility, we compared lengths of follow-up and median times-to-event, each stratified by exposure (Table 3). Overall follow-up time, and time to in-hospital death showed significant differences, while time to receiving a blood product and within-admission repeat PCI did not. Using values between the observed 25th percentiles and medians of times-to-event, we chose 1 day of follow-up for blood products, 2 days for repeat PCI, and 3 days for death. In the analyses using these restricted follow-up times (Table 4), we observed equal or greater protective effects of each of the outcomes compared with the primary analysis with unrestricted follow-up. In the sensitivity analysis in which we employed three treatment groups, we observed no increased risk of in-hospital death (HR = 1.01; 95% CI = 0.95–1.08) or administration of a blood product (HR = 1.00; 95% CI = 0.91–1.09) among the heparin monotherapy group compared with the heparin plus GPI...
group, and a slightly decreased risk of within-admission repeat PCI (HR = 0.90; 95% CI = 0.85–0.95).

In the IVA, the instrument we used applied the hospital’s frequency of treatment with bivalirudin or heparin plus GPI in the quarter in which the patient was treated. As a motivation for the time-based aspects of the instrument, we examined the uptake of bivalirudin over the time period under study. Figure 1A shows a general upward trend in the usage of the drug, and in Figure 1B, a trend towards increasing numbers of hospitals using bivalirudin even minimally (>1% line). The 5% and 80% lines indicate that the instrument is reasonably discriminatory, especially for hospitals using bivalirudin at least 80% of the time, where the

Figure 1 (A) By quarter of calendar time, percentage of percutaneous coronary intervention (PCI) patients exposed to bivalirudin in hospitals represented in the Premier Perspective Database. (B) By quarter of calendar time (2003–2006), percentage of hospitals reaching thresholds of administering bivalirudin to <5% and >80% of patients receiving percutaneous coronary intervention, and hospitals administering bivalirudin to >1% of those patients.
instrument would predict heparin as the treatment to patients seen at $<10\%$ of the hospitals over the study period.

Instrument strength is an important aspect of IVA.\textsuperscript{35} We observed a partial $r^2$ value of 0.22 and a first-stage partial $F$-statistic of 68.3 ($P < 0.0001$), meeting the commonly cited definition of a non-weak instrument of $F > 10$.\textsuperscript{35}

For the outcomes of within-admission repeat PCI and death, we observed little difference in the unadjusted risks for the entire study population and the IVA subpopulation (Table 2). In addition, we saw little substantial difference in adjusted hazard ratios among the patients admitted via urgent care vs. those admitted through other means (Figure 3 and Table 5). The outcome of need for blood transfusion differed in the subgroups more substantially than did the other two outcomes (Figure 3). The IVA results between the two subgroups diverged more than did the fully adjusted results.

**Discussion**

We performed a non-randomized study in administrative data to examine the effectiveness of bivalirudin in routine care. Our multivariate-adjusted results suggested that bivalirudin use in routine care has a short-term protective effect against several negative outcomes, including haemorrhage requiring transfusion, death, and possibly repeat PCI, when compared to heparin plus GPI. Findings from our instrumental variable analysis, which attempted to take both measured and unmeasured confounders into account, support the conclusions of the REPLACE-2...
randomized trial\textsuperscript{3} with respect to non-inferiority of bivalirudin vs.
heparin plus GPI for these negative outcomes. The protection
against blood transfusions described in several trials\textsuperscript{4,7,9} was simi-
larly observed in our study. We also observed a statistically signifi-
cant protective effect against in-hospital death that was observed in
only one of the trials.\textsuperscript{8} Despite the possibility of residual confound-
ing or an inappropriate IV, we believe that our findings suggest that
bivalirudin is as effective and safe in routine care as it was shown to
be in trials, and may have additional previously unrecognized
benefits.

Like REPLACE-2, but unlike HORIZONS-AMI and ACUITY, our
patients were a mix of those undergoing primary and elective PCs.
HORIZONS-AMI considered STEMI patients only, whereas
ACUITY looked at the broader category of acute coronary syn-
drome (ACS) patients. The design of our study also differed from
that of the trials. Most importantly, the trials continued to
follow patients after their discharge; we considered only endpoints
that occurred in-hospital. Given that, our follow-up time was
shorter than that of the trials, and we therefore expected that
event rates in our routine care population would differ from
those in trials. With respect to blood transfusions, we observed
an event rate in the heparin group comparable with that of
REPLACE-2; the relative risk from our fully adjusted analysis
(HR = 0.67; 0.61–0.73) was similar to that observed in the
heparin group of REPLACE-2 (OR = 0.67; 0.45–1.01). Compared
with patients enrolled in HORIZONS-AMI, our patients were some-
what older and had higher prevalence of several risk factors, but we
saw lower event rates in the comparison group of our study than
that of HORIZONS-AMI, likely because of HORIZONS’ MI
population. That said, the relative risk estimate for blood transfusion
in HORIZONS (OR = 0.58; 0.38–0.87) was qualitatively similar to
our result of HR = 0.67. Relative risks are generally closer to the
null in populations with higher baseline risks.\textsuperscript{41}

Mortality was substantially higher in our study of routine care
(2.1% in the heparin group) than in REPLACE-2 (0.4%), likely
because our routine care population was at higher baseline risk
for death than the trial’s subjects. Relative risk of death was
HR = 0.51 (0.44–0.60) vs. OR = 0.58 (0.23–1.48) in
REPLACE-2, and was significant in our study. HORIZONS-AMI
reported a frequency of death of 3.1% in their comparison
group, higher than that we observed. Their reported relative risk
of death, OR = 0.66 (0.44–1.00), was numerically but not qualitati-
vely different from our findings.

We approached the Premier database with an eye towards
possible residual confounding due to limited information on clinical
details recorded in the administrative data. If, for example, sicker
patients were more likely to receive bivalirudin during PCI
because it was perceived equally effective but safer than its alterna-
tives, this would result in a bias towards less protective effect of
bivalirudin. The overall similarity of the crude and adjusted
results suggested that either there may have been little unmea-
sured confounding in our analysis, or the measured covariates
did not account for a substantial portion of the unmeasured con-
ounding that existed. We therefore employed IVA, which is a
method that, under the strong assumptions noted in Appendix 1,
can provide consistent effect estimates even in the presence of
unmeasured confounders. The Durbin–Wu–Hausman test con-
firmed that the treatment was correlated with other variables in
the model (P < 0.0001), and suggests that the treatment was con-
founded and that IV estimation was required.\textsuperscript{42}

Table 2 Results for in-hospital outcomes among 127 185 myocardial infarction or acute coronary syndrome patients
admitted to US hospitals and treated with either bivalirudin or heparin plus glycoprotein IIb/IIIa inhibitor

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events in bivalirudin group</th>
<th>Events in heparin group</th>
<th>IR in bivalirudin group</th>
<th>IR in heparin group</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 unit of blood product</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>988</td>
<td>4349</td>
<td>1.08</td>
<td>1.18</td>
<td>0.93 (0.85–1.00)</td>
</tr>
<tr>
<td>Unadjusted (IV subpopulation)</td>
<td>544</td>
<td>3626</td>
<td>0.89</td>
<td>1.16</td>
<td>0.77 (0.69–0.86)</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67 (0.61–0.73)</td>
</tr>
<tr>
<td>Instrumental variable analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.72 (0.62–0.83)</td>
</tr>
<tr>
<td>Within-admission repeat PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1118</td>
<td>5423</td>
<td>1.61</td>
<td>1.95</td>
<td>0.83 (0.78–0.89)</td>
</tr>
<tr>
<td>Unadjusted (IV subpopulation)</td>
<td>717</td>
<td>4719</td>
<td>1.64</td>
<td>1.99</td>
<td>0.82 (0.76–0.89)</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.96 (0.90–1.03)</td>
</tr>
<tr>
<td>Instrumental variable analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.83 (0.49–1.40)</td>
</tr>
<tr>
<td>In-hospital death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>261</td>
<td>1959</td>
<td>0.30</td>
<td>0.56</td>
<td>0.57 (0.49–0.65)</td>
</tr>
<tr>
<td>Unadjusted (IV subpopulation)</td>
<td>162</td>
<td>1665</td>
<td>0.29</td>
<td>0.56</td>
<td>0.56 (0.46–0.66)</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51 (0.44–0.60)</td>
</tr>
<tr>
<td>Instrumental variable analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51 (0.34–0.78)</td>
</tr>
</tbody>
</table>

Fully adjusted models are adjusted for all variables noted in Table 1, as well as year of service.
IR, incidence rate; HR, hazard ratio; CI, 95% confidence interval; IV, instrumental variable; Death, in-hospital death within index stay; Repeat PCI, performance of second PCI
procedure. Blood products include whole blood, platelets, fresh frozen plasma, cryoprecipitate, and red blood cells.
There is an extensive literature on the correlation between hospital facility and quality of care; which hospital patients choose to go to may well have a bearing on their outcomes. This correlation may introduce a violation of the assumption that the instrument should not be related to outcome, as hospital preference for bivalirudin may be related to quality of care. The literature suggested several important factors that may contribute to this relationship, including hospital size, teaching or non-teaching status, and frequency of performing the procedure in question. Though we controlled for each of these factors in our IVA, we cannot rule out the possibility that residual confounding may persist. Further, as an inexpensive and widely available drug, heparin use may have been under-reported in the administrative data, especially in those patients who received GPI.
but had no recorded heparin use. In a study of bivalirudin vs. heparin plus GPI, unrecorded use of heparin in the bivalirudin group could introduce bias that would not necessarily move point estimates towards the null.

In one of our subgroup analyses, we attempted to isolate those patients undergoing early emergency PCI in order to broadly approximate a primary PCI population. Because of potential misclassification, we do not assert that this was wholly a primary PCI population. Misclassification may come from several sources: (i) both elective and primary PCIs will generally happen soon after admission; (ii) some hospitals may, by protocol, examine elective PCI patients in the emergency room before admission; and (iii) the 414.01 diagnosis code may capture many patients with unstable angina, who may in turn be more likely to be scheduled for elective PCI. To address these concerns, we performed a sensitivity analysis in which we excluded the patients with 414.01 diagnoses, and separately ER admission based on professional charges in the ER rather than recorded admission source. These sensitivity analyses led to no meaningful differences in the observed results.

We examined bivalirudin in the context of routine care of PCI patients treated across the USA. Our non-randomized study showed that bivalirudin is protective compared to heparin plus GPI with regard to the risk of blood transfusions, and may even exceed trial estimates for protection against death. Because of conventional analyses’ potential for bias as a result of residual confounding, IVA-based methods, with their known limitations, may help in studying the safety and effectiveness of medications outside the constrained setting of clinical trials.

Acknowledgements
We wish to acknowledge Todd Conlyn, Todd Gorsuch, and Chris Craver of Premier, Inc. for their help in the creation of our study database.

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Conflict of interest: none declared.

Appendix 1. Instrumental variable analysis methods and discussion

Instrumental variable analysis
Instrumental variable analysis is one of several techniques that attempt to mitigate the bias introduced by unmeasured confounding present in observational data. Instrumental variables are of particular interest in pharmacoepidemiology studies, as such studies grapple with potential for bias from confounding by indication and other unmeasured effects, particularly in administrative databases.

A valid instrument is a variable that is unconfounded with respect to outcome and as such can be plausibly substituted for treatment in an outcome model. To serve this function, the IV must meet three main criteria: (i) it must be related to treatment, (ii) it must have no direct relation to outcome, and (iii) it must have no indirect relation to outcome, except via the effect of the treatment under study. Additionally, many IVs make further assumption of no-treatment-effect heterogeneity.

The usual estimation technique used in IVA is 2SLS. 2SLS can be conceptualized as two sequential least squares estimation procedures: the first stage predicts treatment as a function of the instrument and any covariates, and the second stage predicts outcome as a function of the predicted treatment. This two-stage approach serves to substitute the unconfounded prediction of treatment for treatment itself. 2SLS produces an estimate of risk difference rather than risk or HR; in this paper, for the HR, we employed a modified technique in which the treatment was predicted as a function of the IV and the covariates using a logistic model, and outcome was predicted as a function of predicted

Table 5  Risk of in-hospital outcomes among subpopulations of patients differing in markers of acuteness of condition

<table>
<thead>
<tr>
<th>Population and outcome</th>
<th>Unadjusted HR (CI)</th>
<th>Fully adjusted HR (CI)</th>
<th>IVA HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population limited to patients receiving PCI on the first day of care and via an urgent care admission (n = 78,731)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 unit of blood product</td>
<td>0.66 (0.59–0.73)</td>
<td>0.52 (0.46–0.58)</td>
<td>0.87 (0.16–4.68)</td>
</tr>
<tr>
<td>Within-admission repeat PCI</td>
<td>0.96 (0.88–1.05)</td>
<td>1.08 (0.99–1.18)</td>
<td>1.06 (0.54–2.07)</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>0.48 (0.40–0.59)</td>
<td>0.43 (0.35–0.52)</td>
<td>0.51 (0.30–0.89)</td>
</tr>
<tr>
<td>Population limited to patients receiving PCI on the first day of care but not via an urgent care admission (n = 24,471)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 unit of blood product</td>
<td>0.55 (0.46–0.67)</td>
<td>0.46 (0.38–0.57)</td>
<td>0.25 (0.04–1.66)</td>
</tr>
<tr>
<td>Within-admission repeat PCI</td>
<td>0.76 (0.65–0.88)</td>
<td>0.85 (0.72–0.99)</td>
<td>0.46 (0.24–0.87)</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>0.57 (0.41–0.80)</td>
<td>0.49 (0.35–0.68)</td>
<td>0.54 (0.21–1.40)</td>
</tr>
</tbody>
</table>

Fully adjusted models are adjusted for all variables noted in Table 1, as well as year of service. HR, hazard ratio; CI, 95% confidence interval.
treatment and covariates using Cox proportional hazards regression.33

Application of preference instrument

Our study used an instrument intended to identify hospitals’ preference for using bivalirudin as opposed to heparin plus GPI in the course of PCI treatment. Like its ‘cousin’ physician prescribing preference,29,38 hospital-based preference is founded on the notion that in certain instances, prescribing may vary more among hospitals than it does within a particular facility.52,53 It is posited that this diminished within-hospital variation is a result of facilities’ preference for one treatment regimen over another, whether because of cost, current research, practice guidelines, or formulary decisions. Under the assumption that on average, patient outcomes do not vary systematically from one hospital to another in a manner that is related to hospitals’ prescribing patterns, this preference should be independent of a patient’s outcome, since the preference is broadly applied throughout the hospital and, within reason, is applied non-differentially to patients who could benefit equally from either drug regimen. Given that preference may change over time, we estimated all preferences within the calendar quarter in which the patient was treated.

Violations of the IV assumptions are possible. One can imagine a situation in which, for example, teaching hospitals might be on the ‘leading edge’ of new treatments and therefore prefer bivalirudin when other hospitals do not, and might also have overall better results because of volume and skill. In this scenario, there would be a relationship between the IV and outcome. It is possible to relax the IV assumptions to say that the IV must be independent of outcome conditional on measured factors related to outcome such as teaching vs. non-teaching hospital, volume of procedures, and number of beds. But, even with these variables accounted for, IV-to-outcome associations could still occur if there is a relationship via unmeasured factors that cannot be controlled for.

We applied the IV diagnostics described by Brookhart and Schneeveis.24 These tests examined whether the presence of the instrument introduced confounding by measured factors and looked for evidence of treatment effect heterogeneity.

References


38. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables 2: in 25 variations, the physician prescribing preference generally was strong and reduced imbalance. *J Clin Epidemiol* 2009; published online ahead of print.


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