Clinical Research

Influence of Bleeding Risk on Outcomes of Radial and Femoral Access for Percutaneous Coronary Intervention: An Analysis From the GLOBAL LEADERS Trial

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ABSTRACT

Background: Radial artery access has been shown to reduce mortality and bleeding events, especially in patients with acute coronary syndromes. Despite this, interventional cardiologists experienced in femoral artery access still prefer that route for percutaneous coronary intervention. Little is known regarding the merits of each vascular access in patients stratified by their risk of bleeding.

RÉSUMÉ

Contexte : Il a été démontré que l’acès par l’artère radiale réduit la mortalité et les hémorragies, en particulier chez les patients présentant un syndrome coronarien aigu. Malgré cela, les cardiologues interventiionnels qui ont acquis de l’expérience en matière d’acès par l’artère fémorale préfèrent encore utiliser cette voie lorsqu’ils doivent pratiquer une intervention coronarienne percutanée. On connaît mal

Bleeding is one of the strongest periprocedural predictors of mortality in patients receiving percutaneous coronary intervention (PCI). In patients with acute coronary syndromes (ACS), radial access reduces bleeding, vascular complications, and all-cause mortality compared with femoral access. These findings have been replicated in large cohorts of randomized controlled trials, such that the radial approach continues to gain momentum as the default access site for PCI. Guidelines and consensus statements recommended it as the preferred vascular access site in ACS patients.

However, many operators continue to perform PCI via the femoral approach regardless of ischemic syndrome for personal reasons, such as a lack of experience with radial access, or for procedural reasons, such as to acquire better guiding catheter support in scenarios such as left main bifurcations, severe calcifications, tortuous coronary arteries, rotational atherectomy, and chronic total occlusions. Because the shortcoming...
of femoral access is largely due to increased bleeding, the question remains whether femoral access is still associated with worse clinical outcomes when the patient has a low risk of bleeding.

The PRECISE-DAPT (Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual-Antiplatelet Therapy) score was initially designed to evaluate the risk of bleeding in PCI patients receiving dual-antiplatelet therapy (DAPT). It stratified the risk of bleeding according to age, hemoglobin, leukocytes, creatinine clearance, and history of bleeding. Patients with a high PRECISE-DAPT score were shown to have a higher risk of bleeding and mortality. In the present study, we aimed to compare clinical outcomes between radial and femoral artery access according to the risk of bleeding stratified by the PRECISE-DAPT score, to understand the interaction between bleeding risk and vascular access site in the outcomes of contemporary PCI procedures.

Methods

Design

The present study is a prespecified subgroup analysis of the GLOBAL LEADERS trial, which is a prospective, multicentre, open-label, randomized controlled trial (ClinicalTrials.gov Identifier: NCT01813435). In brief, GLOBAL LEADERS trials enrolled a total of 15,991 patients at 130 hospitals in 18 countries (Europe, Asia, Brazil, Australia, and Canada) from July 1, 2013, to November 9, 2015. The study population consisted of patients scheduled to undergo PCI for stable coronary artery disease (CAD) or ACS. The full inclusion and exclusion criteria and details can be found in previous reports. Notably, patients prescribed oral anticoagulation therapy were excluded from the trial.

In the GLOBAL LEADERS trial, patients were randomized 1:1 to receive either 12-month DAPT or 1-month DAPT followed by 23-month ticagrelor monotherapy. The present study examined outcomes from index PCI to 30 days, as in previous studies of vascular access site. During this period, all patients received DAPT therapy.

The trial was approved by the institutional review board at each centre and followed the ethical principles of the Declaration of Helsinki. Every patient provided written informed consent before participation in the trial.

Patients

The patient flow diagram is shown in Figure 1. There were 14,629 participants from the GLOBAL LEADERS trial included in this study. All of the analyses were performed according to the access site: femoral or radial.

The patient’s risk of bleeding was calculated with the PRECISE-DAPT online calculator. The distribution of the PRECISE-DAPT score is shown in Supplemental Figure S2.
We dichotomized the overall population according to the median PRECISE-DAPT score of 16, with 7447 patients in the low (PRECISE-DAPT score < 16) and 7182 patients in the high (PRECISE-DAPT score ≥ 16) bleeding score groups, respectively.

**Outcomes**

The event definitions have been reported previously. All clinical events were compared at 30 days. The primary end point was a composite of all-cause mortality or new Q-wave myocardial infarction (MI). The key secondary safety end point was site-reported bleeding assessed according to the Bleeding Academic Research Consortium (BARC) criteria (grade 3 or 5).

Other secondary end points included a composite end point of all-cause mortality, stroke, or nonfatal new Q-wave MI and its individual components. Other additional end points include BARC 2 and a composite of BARC 2, 3, or 5 bleeding events. In the GLOBAL LEADERS trial, 20% of reported events were checked against source documents. Composite end points were analyzed hierarchically. Individual components of the composite end points were reported nonhierarchically.

**Statistics**

Propensity scores (PSs) were calculated by including the variables of demographic characteristics (age, sex, body mass index), ACS/stable CAD, coexisting medical conditions (diabetes, insulin-dependent diabetes, hypertension, hypercholesterolemia, current smoker, previous bleeding, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, renal failure, myocardial infarction, PCI, or coronary artery bypass graft), antiplatelet therapy, PRECISE-DAPT score, and each component of complex PCI. PSs were distributed in a range of 0.1 to 0.75. Therefore, no case was considered to have an extreme PS and none were trimmed. The distribution of PSs are shown in Supplemental Figure S1.

The data were analyzed with the use of R-Project (R Foundation, Vienna, Austria). Continuous variables are presented as mean ± SD. The differences in baseline characteristics (Table 1) between the radial and femoral cohorts in each bleeding risk stratum are presented as mean difference in continuous variables and absolute risk difference in categoric variables.

Details of missing data are presented in Supplemental Table S1. All missing data were considered as missing completely at random and were filled in the database by multiple imputations for PS computations. Means of 2 continuous variables were compared by means of independent-sample Student t test or Mann-Whitney U test as appropriate. The frequencies of categoric variables were compared by means of Fisher exact test. Survival was estimated with the Kaplan-Meier method, and differences in survival were evaluated with a log-rank test. Cox proportionality assumptions were checked by the Schoenfeld residuals against the transformed time, and the assumptions were met in all models. Cox proportional hazard models adjusted to PS were then used to compare the end points in different vascular approaches in the low and high bleeding score population, respectively. A value of \( P < 0.05 \) was considered to be significant.

**Results**

From July 1, 2013, to November 9, 2015, there were 15,991 patients randomized in the GLOBAL LEADERS trial. Among them 14,629 (91.5%) participants were included and analyzed in the present study. There were 7447 patients categorized in the low bleeding score group (PRECISE-DAPT score < 16; mean score 9.8 ± 3.7) and 7182 patients...
Table 1. Characteristics of the patients at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low bleeding score</th>
<th>High bleeding score</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>58.34 ± 8.31</td>
<td>59.40 ± 7.93</td>
<td>0.80 (0.43-1.18)</td>
</tr>
<tr>
<td>Male</td>
<td>4763/5676 (83.9%)</td>
<td>1476/1771 (83.3%)</td>
<td>-0.57 (-2.55 to 1.41)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²</td>
<td>28.48 ± 4.76</td>
<td>28.13 ± 4.49</td>
<td>-0.35 (-0.60 to -0.10)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1216/5675 (21.4%)</td>
<td>385/1769 (21.8%)</td>
<td>0.34 (-1.86 to 2.54)</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>318/5663 (5.6%)</td>
<td>100/1762 (5.7%)</td>
<td>0.06 (-1.18 to 1.30)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3794/5652 (67.1%)</td>
<td>1280/1761 (72.7%)</td>
<td>5.56 (3.14-7.97)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3799/5699 (69.1%)</td>
<td>1225/1692 (72.4%)</td>
<td>3.31 (0.86-5.77)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1970/5676 (34.7%)</td>
<td>577/1771 (32.6%)</td>
<td>-2.13 (-4.64 to 0.38)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>106/5671 (1.9%)</td>
<td>17/1771 (1.0%)</td>
<td>-0.91 (-1.48 to -0.33)</td>
</tr>
<tr>
<td>Previous peripheral vascular disease</td>
<td>236/5628 (4.2%)</td>
<td>90/1755 (5.1%)</td>
<td>0.93 (-0.22 to 2.09)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>212/5651 (3.8%)</td>
<td>69/1764 (3.9%)</td>
<td>0.16 (-0.87 to 1.19)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1277/5667 (22.5%)</td>
<td>461/1764 (26.1%)</td>
<td>3.60 (1.28-5.92)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1713/5653 (30.2%)</td>
<td>640/1769 (36.2%)</td>
<td>5.99 (3.46-8.53)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>140/5674 (2.5%)</td>
<td>159/1769 (9.0%)</td>
<td>6.52 (5.13-7.91)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>23/5676 (0.4%)</td>
<td>9/1771 (0.5%)</td>
<td>0.10 (-0.27 to 0.47)</td>
</tr>
<tr>
<td>Previous bleeding</td>
<td>0.56/5661 (0.0%)</td>
<td>0/17171 (0.0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable coronary artery disease</td>
<td>2828/5676 (49.8%)</td>
<td>1050/1771 (59.3%)</td>
<td>9.46 (6.83-12.1)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2848/5676 (50.2%)</td>
<td>721/1771 (40.7%)</td>
<td>2494/5109 (48.8%)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
<td>1224/2073 (59.0%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>2546/5676 (44.9%)</td>
<td>924/1771 (52.2%)</td>
<td>7.32 (4.66-9.98)</td>
</tr>
<tr>
<td>Ticagrelan</td>
<td>3130/5676 (55.1%)</td>
<td>847/1771 (47.8%)</td>
<td>2282/5109 (44.6%)</td>
</tr>
<tr>
<td>PRECISE-DAPT score</td>
<td>9.74 (3.68)</td>
<td>9.98 (3.70)</td>
<td>0.23 (0.37-0.43)</td>
</tr>
<tr>
<td>Complex PCI</td>
<td>1515/5544 (27.3%)</td>
<td>518/1718 (30.2%)</td>
<td>2.82 (0.36-5.29)</td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>1106/5544 (20.0%)</td>
<td>364/1718 (21.2%)</td>
<td>1.24 (-0.96 to 3.44)</td>
</tr>
<tr>
<td>Lesions treated ≥ 3</td>
<td>427/5574 (7.7%)</td>
<td>152/1718 (8.9%)</td>
<td>1.15 (-0.37 to 2.60)</td>
</tr>
<tr>
<td>Stents implanted ≥ 3</td>
<td>926/5544 (16.7%)</td>
<td>330/1718 (19.2%)</td>
<td>2.51 (0.40-4.61)</td>
</tr>
<tr>
<td>Bifurcation PCI with ≥ 2 stents</td>
<td>1635544 (3.0%)</td>
<td>73/1718 (4.3%)</td>
<td>1.31 (0.26-2.36)</td>
</tr>
<tr>
<td>Total stent length &gt; 60 mm</td>
<td>722/5544 (13.0%)</td>
<td>213/1718 (12.4%)</td>
<td>-0.62 (-2.42 to 1.17)</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>34.91 (24.59)</td>
<td>34.67 (25.79)</td>
<td>-0.21 (-1.56 to 1.13)</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; CI, confidence interval; PCI, percutaneous coronary intervention.

* Patients with PRECISE-DAPT score < 16 were categorized into the low bleeding score stratum and those with PRECISE-DAPT score ≥ 16 were categorized into the high bleeding score stratum.
categorized in the high bleeding score group (PRECISE-DAPT score ≥ 16; mean score 23.4 ± 7.0). Table 1 shows the baseline characteristics according to bleeding risk and site of vascular access in each bleeding risk stratum.

Outcomes for the overall population compared by vascular access and bleeding risks

In the overall population, there was no statistical difference between access sites in the rate of the primary end point of all-cause mortality or new Q-wave MI (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.42-1.15; P = 0.159; Fig. 2A). However, radial access was associated with a significantly lower rate of the key secondary safety end point of BARC 3 or 5 bleeding (HR 0.55, 95% CI 0.36-0.84; P = 0.005; Fig. 2B).

Compared with the high bleeding score group, patients in the low bleeding score group had significantly lower rates of the primary (HR 0.46, 95% CI 0.28-0.77; P = 0.003; Fig. 2C) and key secondary safety (HR 0.38, 95% CI 0.24-0.60; P < 0.001; Fig. 2D) end points.

Interaction between vascular access and bleeding risk

Among patients with a high bleeding score, the rates of all-cause mortality or new Q-wave MI (HR 0.48, 95% CI 0.27-0.86; P = 0.014) and BARC 3 or 5 (HR 0.55, 95% CI 0.34-0.89; P = 0.015) were significantly lower in the radial
compared with the femoral group (Fig. 3, A and B). In contrast, in the low bleeding score cohort, no statistical differences in the primary (HR 3.12, 95% CI 0.73-13.36; P = 0.125) or secondary safety (HR 0.70, 95% CI 0.30-1.61; P = 0.402) end points were observed between radial and femoral access (Fig. 3, C and D).

Outcomes of propensity score–adjusted Cox regression in the low and high bleeding score population

Propensity scores were calculated with the use of the variables described earlier. The outcomes of PS-adjusted Cox regression models are presented in Table 2. In the high bleeding score cohort, compared with femoral access, the rates of all-cause mortality or new Q-wave MI (HR 0.47, 95% CI 0.26-0.85; P = 0.012; Pinteraction = 0.019), all-cause mortality (HR 0.48, 95% CI 0.26-0.89; P = 0.020; Pinteraction = 0.045), the composite end point of all-cause mortality, stroke, or new Q-wave myocardial infarction (HR 0.51, 95% CI 0.31-0.83; P = 0.007; Pinteraction = 0.033), BARC 3 or 5 bleeding (HR 0.57, 95% CI 0.35-0.95; P = 0.030; Pinteraction = 0.631), and BARC 2, 3, or 5 bleeding (HR 0.67, 95% CI 0.51-0.89; P = 0.005; Pinteraction = 0.707) were all significantly lower in the radial access group. The rates of stroke (HR 0.59, 95% CI 0.31-1.32; P = 0.199; Pinteraction = 0.826) did not differ significantly between the access groups.
However, in the low bleeding score cohort, no significant difference was observed in any of the aforementioned clinical outcomes. Interestingly, radial access was associated with a nonstatistically significant higher rate of all-cause mortality or new Q-wave MI compared with femoral access.

In addition, we calculated the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) scores in our studied population. The distributions of the 3 bleeding scores are shown in Supplemental Figure S2. Using the same methods mentioned above (cutoff points at the median of the score), the cutoff points for low or high bleeding according to the CRUSADE and ACUITY score were 19 and 9, respectively. Propensity scores were generated for the same variables, but the PRECISE-DAPT score was replaced in the model by the CRUSADE or ACUITY score. In high bleeding score patients, all-cause mortality or new Q-wave MI was significantly higher in the femoral access group when the risk of bleeding was defined using the ACUITY, but not the CRUSADE score. BARC 3 or 5 event rates were all significantly higher in the femoral access group using both scores. In the low bleeding score patients, in line with the results observed with the PRECISE-DAPT score, all-cause mortality or new Q-wave MI and BARC 3 or 5 events rates were not statistically different between radial and femoral access, as presented in Supplemental Table S2. The outcomes using a PRECISE-DAPT score of 25 as the cutoff point comparing low vs high bleeding risk (because the PRECISE-DAPT study defined patients with a PRECISE-DAPT score ≥ 25 as high bleeding risk) are presented in Supplemental Table S3.

### Discussion

In an “all-comers” population, we showed that rates of all-cause mortality or new Q-wave MI and BARC 3 or 5 bleeding after PCI were not significantly different between radial and femoral access when the patient was at low bleeding risk (PRECISE-DAPT score < 16), but favoured radial access in patients with high bleeding risk (PRECISE-DAPT score ≥ 16).

Previous randomized controlled trials that enrolled patients with ACS or ST-segment-elevation MI showed that radial access was associated with a reduction in mortality and major bleeding events. However, in trials that included patients with ACS and stable CAD, radial access only lowered the hazards of bleeding, not mortality. The reason for this discrepancy between coronary syndromes could be because patients with ACS receive more potent antithrombotic drugs, which invariably increases their bleeding propensity. These patients therefore have most to gain from radial access, which is associated with fewer vascular complications and less bleeding, ultimately leading to lower mortality. In line with trials that enrolled patients with both ischemic syndromes, we observed that, compared with femoral access, radial access was not associated with lower mortality, but did consistently lower the rate of BARC 3 or 5 bleeding events.

To date, guidelines and consensus statement only recommended the radial approach as the preferred vascular access in...
ACS patients. However, in daily practice, PCI operators may consider the femoral artery as the primary vascular access site for a complex PCI procedure or for other reasons regardless of coronary syndrome. Under those circumstances, operators may evaluate bleeding risk before choosing the site of vascular access. A report using data from the British Cardiovascular Intervention Society database indicated that radial access was independently associated with reduced 30-day mortality and that the magnitude of this effect was related to baseline bleeding risk. In line with that finding, in an all-comers population in which patients were treated with contemporary PCI techniques and antiplatelet therapy, we showed that in patients at low risk of bleeding, using femoral access did not lead to significantly increased bleeding events. Nevertheless, in patients at high risk of bleeding, for better clinical outcomes radial access should always be used whenever considered feasible.

The consensus of the Academic Research Consortium for high bleeding risk concluded that the increased risk of bleeding in patients with ACS is more likely to be attributable to more aggressive antiplatelet therapy, rather than the ACS. Therefore, the consensus did not consider ACS as a high bleeding risk criterion. In agreement with this, we found that after adjusting for bleeding risk and concomitant antiplatelet therapy, there was no interaction between ischemic syndromes (ACS vs stable CAD) and vascular approaches for mortality or BARC 3 or 5 events (all-cause mortality or new Q-wave MI: $P_{interaction} = 0.740$; all-cause mortality: $P_{interaction} = 0.711$; BARC 3 or 5: $P_{interaction} = 0.296$). In contrast, after adjustment for ischemic syndromes and antiplatelet therapy, an interaction between vascular approaches and bleeding risk remains (Table 2; all-cause mortality or new Q-wave MI: $P_{interaction} = 0.019$; all-cause mortality: $P_{interaction} = 0.045$; BARC 3 or 5: $P_{interaction} = 0.631$). Speculatively, these findings suggest that the superior outcomes of radial access might be driven not only by the type of coronary syndrome, but also by the propensity for bleeding of enrolled patients. These unresolved questions need exploring in adequately powered clinical studies.

To rank the risk of bleeding in the GLOBAL LEADERS trial, we used the PRECISE-DAPT score, which was developed to ascertain the balance between ischemic and bleeding risk/benefit when using short- or long-term DAPT. The PRECISE-DAPT study included both ACS and stable CAD patients and censored bleeding events occurring from the index PCI to day 7 in an effort to eliminate those bleeding events related directly to the procedure. Besides using the PRECISE-DAPT score, we also evaluated bleeding risk with the CRUSADE and ACUITY scores. The CRUSADE score was derived in a non–ST-segment-elevation MI population and attempted to quantify the risk of major in-hospital bleeding. The ACUITY score included ACS patients and aimed to stratify major bleeding risk within 30 days after the index PCI.

None of these aforementioned scores can ideally evaluate the risk of bleeding in the present analysis. However, compared with the CRUSADE and ACUITY studies, the PRECISE-DAPT study included patients with stable CAD or ACS, as in the GLOBAL LEADERS trial. Although historically the PRECISE-DAPT study did not include events until 7 days after the index PCI, in our analysis it still satisfactorily estimated the intrinsic 30-day bleeding risk of each patient after PCI and therefore suitably differentiated the bleeding events of each patient as a function of the site of vascular access (Table 2). Therefore, we feel justified in using the PRECISE-DAPT score to rank the risk of bleeding in our study.

Instead of using the 4 strata assessed by the PRECISE-DAPT study, we dichotomized the overall population into 2 strata by the median PRECISE-DAPT score. The reason behind this is that for a binary decision such as the choice of radial or femoral access, dichotomizing the choices into 2 categories might be simpler and more practical for the practitioner.

Besides using the PRECISE-DAPT score, we also analyzed the results of the trial according to the CRUSADE and ACUITY scores. The results of these scores were in line with the results using the PRECISE-DAPT score, confirming the robustness of our study conclusions.

Limitations

First, although the PS method was performed to try to estimate the true effect for the different vascular approaches, the usual deficiencies of observational studies exist, such as the inability to include all relevant confounders, especially those not measured, causing bias that cannot be adjusted.

Second, 8.8% of the overall population from the GLOBAL LEADERS database were not included in the present study owing to missing data, brachial access, or dual radial-femoral access.

Third, given the inherent limitations of subanalyses, our findings can be be interpreted only as hypothesis generating and cannot make strong inferences or necessitate changes in practice by professionals.

Conclusion

The present findings suggest that the outcomes of mortality or new Q-wave MI and BARC 3 or 5 bleeding were not significantly different between radial and femoral access in patients at low risk of bleeding (PRECISE-DAPT score < 16). However, it strongly favoured radial access in patients at high bleeding risk (PRECISE-DAPT score ≥ 16).

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References


Supplementary Material

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