

## Primary Angioplasty in the ACCEPT Registry: Why has it Been Difficult to Accept and Implement the Radial Artery Access as Preferential?

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Obtaining arterial access is the initial and fundamental step of coronary intervention procedures. Since its first application for coronary angiography<sup>1</sup> and percutaneous coronary intervention<sup>2</sup>, the radial approach has been known to have important clinical benefits, associated with a reduction in vascular and bleeding complications at the puncture site, and with early ambulation and greater patients' satisfaction as compared with the femoral approach. Recently, evidence from large randomized studies and meta-analyses<sup>3,4</sup> has suggested that, for patients diagnosed with ST-segment elevation myocardial infarction (STEMI), the primary intervention via radial access is associated with a significant reduction in mortality rates and lower incidence of adverse cardiac events. Because of the consistency of those findings, international guidelines<sup>5</sup> have recommended the radial approach for STEMI (class IIa, level of evidence B).

Incorporation of the radial access, however, has not been widespread, differing worldwide. More than 80% of the coronary interventions in France are performed via the radial artery approach. Data from the British Cardiovascular Intervention Society - National Institute for Clinical Outcomes Research (BCIS-NICOR)<sup>6</sup> have indicated a rapid increase in the use of that approach in recent years, from 12.5% in 2006 to 49.5% in 2010. In the United States, however, only 16% of the interventions from 2007 to 2012 have used the radial artery access<sup>7</sup>. Until recently, Brazilian data were scarce. According to the Brazilian Cardiovascular Intervention Center (Cenic), from 2005 to 2008, the radial access was used in 12.6% of the cases, and no significant increase has been observed in those years<sup>8</sup>. In a welcome and recently published article, Andrade et al.<sup>9</sup> have reported an updated overview on the subject. They used data from a large Brazilian prospective and multicenter registry designed by the Brazilian Society of Cardiology, comprising 47 public and private hospital centers, representative of all the Brazilian regions. Those authors have assessed the occurrence of ischemic and hemorrhagic adverse events in 588 patients submitted to primary angioplasty via the femoral and radial accesses

in 2010 and 2011. The radial technique was used in 30.3% of the cases, but was not associated with a reduction in the occurrence of death, reinfarction or stroke. Severe bleedings were reported in only 1.1% of the patients and did not statistically differ according to the arterial access used. Although the low incidence of cardiac and hemorrhagic complications can reflect the quality of the centers selected and the experience of the interventional cardiologists with both vascular access, as suggested by the researchers, the results of that registry indicate a dissociation between the available scientific evidence, which points to the significant benefits of the radial access in STEMI, and the actual use of that technique and its results in daily practice.

### Radial access and the reduction in mortality and adverse cardiac events

Although the causal relationship remains controversial, several studies have reported that the radial access for primary angioplasty is associated with a reduction in mortality and in adverse cardiac events (Table 1). The largest clinical trial comparing the arterial accesses for percutaneous coronary intervention, the randomized and multicenter Radial Versus Femoral Access for Coronary Intervention (RIVAL) trial<sup>10</sup>, has selected individuals with acute coronary syndromes (ACS) with or without ST-segment elevation, to whom the invasive strategy had been indicated. Individuals with the following characteristics were excluded: cardiogenic shock or previous coronary artery bypass grafting (CABG) - which could make coronary angiography and the study of bypass grafts via the radial access difficult -, and peripheral arterial disease that could make the femoral approach unfeasible. Of the 7,021 patients randomized for femoral (n = 3,514) or radial (n = 3,507) access, 1,958 individuals (28%) were diagnosed with STEMI. In that specific subgroup, patients undergoing coronary angiography and angioplasty via radial access had lower rates of mortality (1.3% versus 3.2%, p = 0.006) and of the combined outcome of death, infarction and stroke (2.7 versus 4.6%, p = 0.031) at 30 days, as compared with individuals undergoing the procedure via femoral access. The beneficial results of the RIVAL trial in the subgroup of STEMI patients have been replicated in the Radial Versus Femoral Randomization Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS)<sup>11</sup>, a randomized clinical trial with 1,001 patients. Mortality at 30 days was significantly lower in patients undergoing angioplasty via radial access (5.2% versus 9.2%, p = 0.020). In addition, the subanalysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial<sup>12</sup> has revealed a significantly lower incidence of death and reinfarction at 30 days in individuals treated via the radial access (1.0% versus 4.3%; p = 0.02).

### Keywords

Angioplasty; Radial Artery; Harm Reduction; Fibrinolytic Agents; Femoral Artery / complications.

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Although those trials have been designed to neither specifically assess the occurrence of death as primary outcome nor to unravel the potential mechanisms associated with its reduction, the favorable impact on the incidence of bleedings has been assumed to be the major determinant of the lower mortality of patients treated via the radial access.

### Radial access and the reduction in bleeding

The implementation of more diversified and potent antithrombotic and antiplatelet regimens has determined a significant decrease in the rates of death, infarction and recurring ischemia of patients with ACS. The reduction in ischemic events is, however, opposed to the risk of hemorrhagic complications, whose presence and severity are currently recognized as important short- and long-term prognostic factors<sup>13,14</sup>. Several observational studies have shown the association between bleedings and the appearance of thrombotic cardiac events<sup>15,16</sup>. That evidence supports the adoption of a new paradigm in the ACS treatment: therapies or strategies that preserve the anti-ischemic efficacy and reduce the occurrence of bleeding cause an even greater reduction in the incidence of adverse cardiac events.

The complications related to femoral artery puncture account for a significant amount of hemorrhagic events occurring in patients with ACS. Because of its superficial location, hemorrhages in the radial access site are rare, rapidly noted and easily controlled. Thus, that access is one of the major tools of the interventional cardiologist to reduce bleedings (Table 2). Data from approximately 330 thousand patients with STEMI included in the North American National Cardiovascular Data Registry (NCDR)<sup>17</sup> have shown a significant decrease in the bleeding rate with the radial access as compared with the femoral access (odds ratio, 0.62; 95% CI: 0.53-0.72;  $p < 0.0001$ ). In the RIFLE-STEACS trial, major bleedings after angioplasty were defined based on the Bleeding Academic Research Consortium (BARC)<sup>18</sup> criterion greater than or equal to 2: patients randomized to the radial access have experienced a significant reduction

in bleedings (7.8% versus 12.2%,  $p = 0.026$ ), mainly at the puncture site<sup>11</sup>. In the HORIZONS-AMI trial, the incidence of major bleeding not related to CABG was 3.5% in patients undergoing primary angioplasty via radial access and 7.6% in those treated via the femoral access ( $p = 0.03$ )<sup>12</sup>. According to that study, even when drugs with a greater safety profile are used (bivalirudin), the radial access is beneficial. In addition and even consequent to the reduction in hemorrhagic complications, the radial access provides a lower rate of blood product transfusion: in the Mortality benefit Of Reduced Transfusion after PCI via the Arm or Leg (M.O.R.T.A.L) study<sup>19</sup>, patients with ACS undergoing transfusions had higher mortality at 30 days (odds ratio, 4.01; 95% CI: 3.08-5.22). The intervention via the radial access related to a 50% decrease in the need for blood products, and associated with lower mortality at 30 days (odds ratio, 0.71; 95% CI: 0.61-0.82;  $p < 0.001$ ) and at 12 months (odds ratio, 0.83; 95% CI: 0.71-0.98;  $p < 0.001$ ).

In those clinical trials, the magnitude of the association between arterial approach and hemorrhagic complications has varied according to the proposed definition of bleeding. Thus, by using a criterion that elevates the qualification threshold of what is understood as major bleeding, the association can be masked. In the RIVAL trial, the major bleeding outcome was defined according to criteria specifically elaborated for that clinical trial, and did not differ between the radial and femoral accesses (0.8% versus 0.9%,  $p = 0.87$ ). However, if ACUITY (Acute Catheterization and Urgent Intervention Triage strategy trial) bleeding definitions were used<sup>20</sup>, the bleeding rate was significantly higher in the femoral access group (4.5% versus 1.9%,  $p < 0.0001$ ). In addition to the lack of event adjudication, the definition used by Andrade et al.<sup>9</sup> can be one of the reasons for the low rate of severe bleeding observed in the ACCEPT registry; by considering severe hemorrhages only bleedings classified as BARC 3 or 5, events with potential clinical impact, such as the occurrence

**Table 1 – Mortality in different randomized trials of the radial and femoral arterial accesses**

Trial	RADIAL, n (%)	FEMORAL, n (%)	p
RIVAL <sup>10</sup> (n = 1,958)	12/955 (1.3)	32/1.003 (3.2)	0.006
RIFLE-STEACS <sup>11</sup> (n = 1,001)	26/500 (5.2)	46/501 (9.2)	0.020
HORIZONS-AMI <sup>12</sup> (n = 3,334)	7/200 (3.5)	126/3.134 (4)	0.69
STEMI-RADIAL <sup>21</sup> (n = 707)	8/348 (2.3)	11/359 (3.1)	0.64

**Table 2 – Major bleeding in different randomized trials of the radial and femoral arterial accesses**

Trial	RADIAL, n (%)	FEMORAL, n (%)	p
RIVAL <sup>10</sup> (n = 1,958)*	19/995 (2.0)	41/1.003 (4.1)	0.009
RIFLE-STEACS <sup>11</sup> (n = 1,001)	39/500 (7.8)	61/501 (12.2)	0.399
HORIZONS-AMI <sup>12</sup> (n = 3,334)	7/200 (3.5)	237/3.134 (7.6)	0.03
STEMI-RADIAL <sup>21</sup> (n = 707)	5/348 (1.4)	26/359 (7.2)	0.0001

of a large hematoma at the femoral puncture site that required the interruption of antithrombotic and antiplatelet drugs, were excluded from the analysis.

### Myths and challenges of the radial access in STEMI

As shown in the ACCEPT registry, most Brazilian centers still use the femoral access in STEMI. Because of several reasons, many cardiologists can hesitate to indicate or incorporate the radial access in that scenario. Most limitations of that approach are not supported by scientific evidence. For patients with STEMI, vascular access for primary angioplasty should be obtained rapidly to minimize the duration of ischemia and to prevent myocardial necrosis from extending. In the NCDR registry, the use of the radial access was associated with a mild increase in the door to balloon time (78 versus 74 minutes), with no influence on in-hospital outcomes<sup>17</sup>. The ST-Elevation Myocardial Infarction treated by RADIAL or femoral approach (STEMI-RADIAL) multicenter randomized clinical trial<sup>21</sup> has reported the low need for crossover of the femoral access (3.7%) and the use of a smaller volume of contrast medium for primary angioplasty with the radial approach (170 ± 71 versus 182 ± 60 mL;  $p = 0.01$ ).

In addition, the option for one or the other approach has been shown to be related to changes in some technical aspects

of primary angioplasty; although uncertain, such variations are likely to have a clinical impact. The BCIS-NICOR registry<sup>6</sup> has shown that the use of manual thromboaspiration was frequent in patients treated via the radial access, and stenting was most frequently performed with no need for predilation (direct implantation): such strategies relate to lower rates of distal embolization and no-reflow. According to the Brazilian experience<sup>8</sup>, glycoprotein IIb-IIIa inhibitors have been more commonly used for the radial access. Those drugs begin to act rapidly and have a potent antiplatelet effect, being thus very useful under circumstances of large thrombotic load and slow-flow during the coronary intervention, in which the radial access provides greater safety for the use of glycoprotein IIb-IIIa inhibitors. In the European EUROTRANSFER registry<sup>22</sup>, patients treated with abciximab had a lower bleeding rate with the radial access (1.2% versus 9.4% as compared with the femoral access,  $p < 0.001$ ).

Of all the challenges identified, the need for a higher learning curve to achieve proficiency with the radial procedures is the most important. In recent years, a significant increase has been reported in teaching and incorporation of that technique in training centers of interventional cardiologists<sup>23,24</sup>. The radial access requires greater dedication and commitment, which should never be a drawback when additional clinical benefits are aimed at for our patients.

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