

## **Anticoagulation after Stroke in Patients with Atrial Fibrillation: To Bridge or Not with Low-Molecular-Weight Heparin?**

This is a pre print version of the following article:

*Original:*

Altavilla, R., Caso, V., Bandini, F., Agnelli, G., Tsivgoulis, G., Yaghi, S., et al. (2019). Anticoagulation after Stroke in Patients with Atrial Fibrillation: To Bridge or Not with Low-Molecular-Weight Heparin?. *STROKE*, 50(8), 2093-2100 [10.1161/STROKEAHA.118.022856].

*Availability:*

This version is available <http://hdl.handle.net/11365/1131366> since 2021-03-03T12:17:20Z

*Published:*

DOI: <http://doi.org/10.1161/STROKEAHA.118.022856>

*Terms of use:*

**Open Access**

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. Works made available under a Creative Commons license can be used according to the terms and conditions of said license.

For all terms of use and more information see the publisher's website.

(Article begins on next page)

**Anticoagulation after stroke in patients with atrial fibrillation: to bridge or not with low-molecular-weight heparin?**

Riccardo Altavilla MD, PhD<sup>1\*</sup>, Valeria Caso MD, PhD<sup>1\*</sup>, Fabio Bandini MD<sup>2</sup>, Giancarlo Agnelli MD<sup>1</sup>, Georgios Tsivgoulis MD<sup>3,4</sup>, Shadi Yaghi MD<sup>5</sup>, Karen L. Furie MD<sup>5</sup>, Prasanna Tadi MD<sup>5</sup>, Cecilia Becattini MD<sup>1</sup>, Marialuisa Zedde MD<sup>6</sup>, Azmil H Abdul-Rahim MD<sup>7</sup>, Kennedy R Lees MD<sup>7</sup>, Andrea Alberti MD<sup>1</sup>, Michele Venti MD, PhD<sup>1</sup>, Monica Acciarresi MD<sup>1</sup>, Cataldo D'Amore MD<sup>1</sup>, Maria Giulia Mosconi MD<sup>1</sup>, Ludovica Anna Cimini MD<sup>1</sup>, Jessica Fusaro MD<sup>1</sup>, Paolo Bovi MD<sup>8</sup>, Monica Carletti MD<sup>8</sup>, Alberto Rigatelli MD<sup>8</sup>, Manuel Cappellari MD<sup>8</sup>, Jukka Putaala MD<sup>9</sup>, Liisa Tomppo MD<sup>9</sup>, Turgut Tatlisumak MD<sup>9,10</sup>, Simona Marcheselli MD<sup>11</sup>, Alessandro Pezzini MD<sup>12</sup>, Loris Poli MD<sup>12</sup>, Alessandro Padovani MD, PhD<sup>12</sup>, Luca Masotti MD<sup>13</sup>, Vieri Vannucchi MD<sup>13</sup>, Sung-Il Sohn MD, PhD<sup>14</sup>, Gianni Lorenzini MD<sup>15</sup>, Rossana Tassi MD<sup>16</sup>, Francesca Guideri MD<sup>16</sup>, Maurizio Acampa MD<sup>16</sup>, Giuseppe Martini MD<sup>16</sup>, George Ntaios MD<sup>17</sup>, George Athanasakis MD<sup>17</sup>, Konstantinos Makaritsis MD<sup>17</sup>, Efstathia Karagkiozi MD<sup>17</sup>, Konstantinos Vadikolias MD<sup>18</sup>, Chrysoula Liantinioti MD<sup>4</sup>, Maria Chondrogianni MD<sup>4</sup>, Nicola Mumoli MD<sup>19</sup>, Domenico Consoli MD<sup>20</sup>, Franco Galati MD<sup>20</sup>, Simona Sacco MD<sup>21</sup>, Antonio Carolei MD<sup>21</sup>, Cindy Tiseo MD<sup>21</sup>, Francesco Corea MD, PhD<sup>22</sup>, Walter Ageno MD<sup>23</sup>, Marta Bellesini MD<sup>23</sup>, Giorgio Silvestrelli MD, PhD<sup>24</sup>, Alfonso Ciccone MD<sup>24</sup>, Alessia Lanari MD<sup>24</sup>, Umberto Scoditti MD<sup>25</sup>, Licia Denti MD<sup>26</sup>, Michelangelo Mancuso MD<sup>27</sup>, Miriam Maccarrone MD<sup>27</sup>, Leonardo Ulivi MD<sup>27</sup>, Giovanni Orlandi MD<sup>27,28</sup>, Nicola Giannini MD<sup>27</sup>, Gino Gialdini MD<sup>27</sup>, Tiziana Tassinari MD<sup>29</sup>, Maria Luisa De Lodovici MD<sup>30</sup>, Giorgio Bono MD<sup>30</sup>, Christina Rueckert MD<sup>31</sup>, Antonio Baldi MD<sup>32</sup>, Sebastiano D'Anna MD<sup>32</sup>, Danilo Toni MD, PhD<sup>33</sup>, Federica Letteri MD<sup>33</sup>, Martina Giuntini MD<sup>28</sup>, Enrico Maria Lotti MD<sup>34</sup>, Yuriy Flomin MD<sup>35</sup>, Alessio Pieroni MD<sup>33</sup>, Odysseas Kargiotis MD<sup>36</sup>, Theodore Karapanayiotides MD, PhD<sup>37</sup>, Serena Monaco MD<sup>38</sup>, Mario Maimone Baronello MD<sup>38</sup>, Laszló Csiba MD<sup>39</sup>, Lilla Szabó MD<sup>39</sup>, Alberto Chiti MD<sup>40,27</sup>, Elisa Giorli MD<sup>40</sup>, Massimo Del Sette MD<sup>40,41</sup>, Davide Imberti MD<sup>42</sup>, Dorjan Zabzuni MD<sup>42</sup>, Boris Doronin MD<sup>43</sup>, Vera Volodina MD<sup>43</sup>,

Patrik Michel, PD-MER<sup>44</sup>, Peter Vanacker MD<sup>45</sup>, Kristian Barlinn MD<sup>46</sup>, Lars-Peder Pallesen MD<sup>46</sup>, Jessica Barlinn MD<sup>46</sup>, Dirk Deleu, MD, PhD<sup>47</sup>, Gayane Melikyan MD<sup>47</sup>, Faisal Ibrahim MD<sup>47</sup>, Naveed Akhtar MD<sup>47</sup>, Vanessa Gourbali MD<sup>48</sup>, and Maurizio Paciaroni MD<sup>1</sup>.

\*contributed equally

<sup>1</sup>Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Italy

<sup>2</sup>Department of Neurology, Ospedale San Paolo, Savona, Italy

<sup>3</sup>Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA

<sup>4</sup>Second Department of Neurology, “Attikon” University Hospital, National & Kapodistrian University of Athens, School of Medicine, Athens, Greece

<sup>5</sup>Division of Stroke and Cerebrovascular Diseases, Department of Neurology, The Warren Alpert Medical School of Brown University, Providence, RI, USA

<sup>6</sup>Neurology Unit, Stroke Unit, Arcispedale Santa Maria Nuova, Azienda Unità Sanitaria Locale – IRCCS, Reggio Emilia, Italy.

<sup>7</sup>Medical School and Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom.

<sup>8</sup>SSO Stroke Unit, UO Neurologia, DAI di Neuroscienze, AOUI Verona, Italy

<sup>9</sup>Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland

<sup>10</sup>Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden

<sup>11</sup>Neurologia d'urgenza e Stroke Unit, Istituto Clinico Humanitas, Rozzano, Milano, Italy

<sup>12</sup>Department of Clinical and Experimental Sciences, Neurology Unit, University of Brescia, Italy

<sup>13</sup>Internal Medicine, Santa Maria Nuova Hospital, Firenze, Italy

<sup>14</sup>Department of Neurology, Keimyung University School of Medicine, Daegu, South Korea

- <sup>15</sup>SC Medicina e Chirurgia d'Accettazione e d'Urgenza, Ospedale Lotti Pontedera, Azienda USL Toscana Nordovest
- <sup>16</sup>Stroke Unit, AOU Senese, Siena, Italy
- <sup>17</sup>Department of Medicine, University of Thessaly, Larissa, Greece
- <sup>18</sup>Department of Neurology, Democritus University of Thrace, University Hospital of Alexandroupolis, Greece
- <sup>19</sup>Department of Internal Medicine, Ospedale Civile di Livorno, Italy
- <sup>20</sup>Stroke Unit, Jazzolino Hospital, Vibo Valentia, Italy
- <sup>21</sup>Department of Neurology, University of L'Aquila, Avezzano Hospital, Italy
- <sup>22</sup>UO Gravi Cerebrolesioni, San Giovanni Battista Hospital, Foligno
- <sup>23</sup>Department of Internal Medicine, Insubria University, Varese, Italy
- <sup>24</sup>S.C. di Neurologia e S.S. di Stroke Unit, ASST di Mantova, Mantova, Italy
- <sup>25</sup>Stroke Unit, Neuroscience Department, University of Parma, Italy
- <sup>26</sup>Stroke Unit - Dipartimento Geriatrico Riabilitativo – University of Parma, Italy
- <sup>27</sup>Clinica Neurologica – Azienda Ospedaliero-Universitaria, Pisa, Italy
- <sup>28</sup>Neurologia, Ospedale Apuano, Massa Carrara, Italy
- <sup>29</sup>Stroke Unit-Department of Neurology, Santa Corona Hospital, Pietra Ligure (Savona), Italy
- <sup>30</sup>Stroke Unit, Neurology, Insubria University, Varese, Italy
- <sup>31</sup>Abteilung für Neurologie, Oberschwabenklinik gGmbH, Ravensburg, Germany
- <sup>32</sup>Stroke Unit, Ospedale di Portogruaro, Portogruaro (Venice), Italy
- <sup>33</sup>Department of Neurology and Psychiatry, Sapienza University of Rome, Italy
- <sup>34</sup>U.O. Neurologia Presidio Ospedaliero di Ravenna Azienda USL della Romagna, Italy
- <sup>35</sup>Stroke and Neurorehabilitation Unit MC 'Universal Clinic 'Oberig' Kyiv, Ukraine
- <sup>36</sup>Stroke Unit, Metropolitan Hospital, Piraeus, Greece
- <sup>37</sup>2nd Department of Neurology, AHEPA University Hospital, Thessaloniki, Greece
- <sup>38</sup>Stroke Unit, Ospedale Civico, Palermo, Italy

<sup>39</sup>Stroke Unit, University of Debrecen, Hungary

<sup>40</sup>Stroke Unit, Department of Neurology, Sant'Andrea Hospital, La Spezia, Italy

<sup>41</sup>Divisione di Neurologia, Ospedale Galliera, Genoa, Italy.

<sup>42</sup>Department of Internal Medicine, Ospedale Civile di Piacenza, Italy

<sup>43</sup>Municipal Budgetary Healthcare Institution of Novosibirsk. City Clinical Hospital # 1.

Novosibirsk (Russia) at the Novosibirsk State Medical University (Russia)

<sup>44</sup>Centre Cérébrovasculaire, Service de Neurologie, Département des Neurosciences Cliniques

Centre Hospitalier Universitaire Vaudois, Lausanne (Switzerland)

<sup>45</sup>Department of Neurology, Born Bunge Institute, Antwerp University Hospital, Antwerp, Belgium

<sup>46</sup>Department of Neurology, Dresden University Stroke Center, Dresden, Germany

<sup>47</sup>Neurology, Hamad Medical Corporation, Doha, Qatar

<sup>48</sup>Department of Neurology, Evangelismos Hospital, Athens

### **Corresponding Author**

Riccardo Altavilla MD, PhD

Stroke Unit and Division of Cardiovascular Medicine

Santa Maria della Misericordia Hospital

Piazzale Menghini 1

06129 Perugia, Italy

riccardoaltavilla@yahoo.it

**Keywords:** cardioembolic stroke, atrial fibrillation, anticoagulant therapy, secondary prevention

## **Abstract**

**Background and purpose** – Bridging therapy with low molecular weight heparin (LMWH) reportedly leads to a worse outcome for acute cardioembolic stroke patients due to a higher incidence of intracerebral bleeding. However, this practice is common in clinical settings.

This observational study aimed to compare 1) the clinical profiles of patients receiving and not receiving bridging therapy; 2) overall group outcomes; 3) outcomes according to the type of anticoagulant prescribed.

**Methods** – We analyzed data of patients from the prospective RAF and RAF NOACs studies. The primary outcome was defined as the composite of ischemic stroke, TIA, systemic embolism, symptomatic cerebral bleeding and major extra-cerebral bleeding observed at 90 days after the acute stroke.

**Results** - Of 1,810 patients who initiated oral anticoagulant therapy, 371 (20%) underwent bridging therapy with full-dose LMWH. Older age and presence of leukoaraiosis were inversely correlated with the use of bridging therapy. Forty-two bridged patients (11.3%) reached the combined outcome vs 72 (5.0%) of the non-bridged patients ( $p = 0.0001$ ). At multivariable analysis, bridging therapy was associated with the composite endpoint (OR 2.3; 95% CI 1.4-3.7,  $p < 0.0001$ ), as well as ischemic (OR 2.2; 95% CI 1.3-3.9,  $p = 0.005$ ) and hemorrhagic (OR=2.4; 95% CI 1.2-4.9,  $p = 0.01$ ) endpoints separately.

**Conclusions** – Our findings suggest that patients receiving LMWH have a higher risk of early ischemic recurrence and hemorrhagic transformation compared to non-bridged patients.

## **Introduction**

Oral anticoagulant therapy (OAC) is the treatment of choice for secondary prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF). For this indication, the currently approved OACs are vitamin K antagonists (VKAs) and non-vitamin K antagonists oral anticoagulants (NOACs). VKAs are slower than NOACs in reaching the therapeutic anticoagulant effect, as their mechanism of action is the inhibition of vitamin-K dependent coagulation factors, which requires few days. The effect of VKAs is measured through the international normalized ratio (INR) that, as reflects the activity of VKA, requires few days to reach the therapeutic target. In some cases, a temporary therapy with full-dose low molecular weight heparin (LMWH) can be given alongside warfarin until the therapeutic INR level is achieved. Moreover, bridging therapy is used to counteract the transient prothrombotic effect in the initial phase of OAC treatment (1).

The advantages of NOACs are their rapidity of action (2-3 hours for dabigatran, 2-4 hours for rivaroxaban, 3-4 hours for apixaban, 1-2 hours for edoxaban) and fast reversal, similar to heparin in that respect. Moreover, their standard dosages do not require titration, whereas VKAs do.

Despite evidence that full-dose LMWH can be harmful in acute stroke care (2) in particular in the presence of atrial fibrillation (3), there are anecdotal reports of its use in selected patients (4, 5). Mostly, acute heparin treatment is used as bridging therapy until the therapeutic range of OACs is achieved, the so-called bridging therapy (1).

By using data from the prospective RAF (6) and RAF-NOACs (7) studies, we aimed to evaluate 1) clinical profiles of patients who received or not bridging therapy; 2) differences in outcomes between these two groups and 3) differences in outcomes according to the type of OAC prescribed.

## **Patients and methods**

We analyzed the data of patients from the prospective RAF and RAF NOACs studies that enrolled consecutive patients with acute ischemic stroke and NVAF. The methods and results of the RAF studies have been previously described in detail described in detail (6,7), and the data are available

from the corresponding author upon reasonable request. Both studies were approved by the local Institutional Review Board (IRB) if required. Patient exclusion criteria for both studies were: high risk of bleeding, defined as clinically significant liver disease (acute or chronic hepatitis, cirrhosis, or alanine aminotransferase level greater than three times the upper limit of normality), creatinine clearance (CrCl) <30 mL/min (for apixaban the threshold was 25 mL/min), life expectancy of <3–6 months, the presence of uncontrolled hypertension (8), and the ongoing prescription of medications having known metabolic interactions with any type of OACs.

A non-contrast cerebral computed tomography (CT) or cerebral magnetic resonance (MR) scan was performed on admission for each patient, to exclude for the presence of intracranial hemorrhage. Thrombolysis treatment was administered according to standard protocol, when appropriate. All of the participating centers provided Stroke Unit Care according to current international recommendations for acute ischemic stroke treatment (9-10). Stroke physicians were free to make decisions on the type of anticoagulant to be used for secondary prevention, as well as its starting time.

NVAF was classified as paroxysmal (episodes terminating spontaneously within 7 days), persistent (episodes lasting more than 7 days requiring pharmacologic and/or electrical stimulation), or permanent (persisting for more than 1 year, either because cardioversion failed or had not been attempted) (11).

A second brain CT scan or MR was performed 24-72h from stroke onset for all patients. Hemorrhagic transformation (HT) was defined on CT scan as any degree of hyperdensity within the area of low attenuation and was classified as either hemorrhagic infarction (HI) or parenchymal hematoma (PH) (12, 13). On MRI, HT was defined as hypointensity on axial T1-weighted (T1W) or T2-weighted (T2W) images. HT was considered to be symptomatic if it was associated with an increase of 4 points or more in the NIHSS score and there was no evidence of intracranial bleeding on the first CT (14). The sites and sizes of the qualifying infarcts were determined based on standard templates (15, 16) as: 1) small, when a lesion was  $\leq 1.5$  cm in the anterior or posterior

circulation; 2) medium, when a lesion was in a superficial cortical branch of middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery (PCA), in a cortical superficial branch of the anterior cerebral artery (ACA); 3) large anterior, when a lesion involved the complete territory of MCA, PCA, or ACA, in 2 superficial cortical branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in more than 1 artery territory (e.g. MCA associated to ACA territories); 4) large posterior, when a lesion was  $\geq 1.5$  cm in the brain stem or cerebellum (13).

For the purpose of this analysis, bridging therapy was defined as any temporary full-dose of LMWH (e.g. 100 UI/Kg of enoxaparin twice a day) started together before or with VKAs, in order to cover the time needed by the latter to reach the therapeutic effect (1) or as any full-dose (given for at least 24 hours) of LMWH prior to the use of a NOAC.

### **Risk factors**

Data on stroke risk factors were collected as previously described (6,7): age, sex, history of hypertension (blood pressure of  $\geq 140/90$  mm Hg at least twice before stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting serum glucose level  $\geq 126$  mg/dL preprandial on 2 examinations, glucose level  $\geq 200$  mg/dL postprandial, or  $HbA1c \geq 6.5\%$ , or under antidiabetic treatment), current cigarette smoking, past smoking (cessation less than 5 years ago), hyperlipidemia (total cholesterol  $\geq 200$  mg/dL or triglyceride  $\geq 140$  mg/dL or already under lipid lowering therapy), history of symptomatic ischemic heart disease (myocardial infarction, history of angina or existence of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent claudication of presumed atherosclerotic origin; or ankle/arm systolic blood pressure ratio  $< 0.85$  in either leg at rest; or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), alcohol abuse ( $\geq 300$  g per week), obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), or previous stroke/TIA). White matter changes (leukoaraiosis) defined on

the first CT (or MRI) examination as ill-defined and moderately hypodense (or hyperintensity on T2-weighted on MRI) areas of  $\geq 5$  mm according to published criteria were investigated (17). Leukoaraiosis in the deep white matter was dichotomized into absent versus mild, moderate, or severe. Other baseline variables obtained at admission for all patients included: fasting serum glucose, fasting serum cholesterol (total, HDL, and LDL), platelet count, international normalized ratios (INR), activated partial thromboplastin time (aPTT), systolic blood pressure, and diastolic blood pressure.

Data on the use of any antiplatelet, anticoagulants or thrombolytic agent, before admission, at baseline and during the follow-up period, were recorded.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was calculated before and after the index event (18).

### **Evaluation of Outcomes**

Patients were followed-up prospectively through face-to-face or telephone interviews. Study outcomes at 90 days were: 1) recurrent ischemic cerebrovascular events (stroke or TIA) and/or symptomatic systemic embolisms; 2) symptomatic cerebral bleedings and/or major extra-cerebral bleedings.

The primary study outcome was the composite of stroke, TIA, systemic embolism, symptomatic cerebral bleeding and major extra-cerebral bleeding (6,7). HTs found on neuroimaging 24-72 hours after onset were not considered outcome events unless classified as symptomatic.

Stroke was defined as the sudden onset of a new focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and categorized as ischemic or hemorrhagic. TIA was defined as a transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging, surgery, or autopsy. Cerebral bleeding was considered symptomatic if associated with a decline in neurological status (an increase of 4 points or more in the NIHSS score or leading to death). Major extra-cerebral bleeding was defined

as a reduction in the hemoglobin level of at least 2 g per deciliter, requiring blood transfusion of at least 2 units, or symptomatic bleeding in a critical area or organ (19).

Disability and mortality at 90 days were also assessed using the modified Rankin Scale (mRS).

Non-disabling functional outcome was defined as an mRS score of 0-2.

### **Statistical analysis**

Differences in patient characteristics between the two groups (bridging vs non-bridging therapy) were assessed utilizing the Chi-square test. Univariable analysis was performed to compare clinical features at admission and their risk factors. The two continuous variables, NIHSS score and age, are reported as mean values and standard deviations (SD). Whereas, categorical variables are reported as percentages.

Multivariable logistic regression was performed to investigate independent variables and their possible correlations with the bridging therapy. The variables included in the model were: NIHSS score, the presence of diabetes mellitus, arterial hypertension, dyslipidemia, paroxysmal AF, pacemaker; lesion size, leukoaraiosis, CHA<sub>2</sub>DS<sub>2</sub>VASc score after the event, as well as the histories of previous stroke or TIA, current smoking habit, congestive heart failure and/or myocardial infarction.

Univariable analysis was used to compare the combined outcomes of the two groups, for recurrence of ischemic stroke and occurrence of bleeding. The same analysis was performed to compare the combined outcomes of the two OAC regimens.

Given the difference of numbers of patients in the two groups, and the possible presence of confounding factors influencing outcomes, a propensity score (PS) matching was also performed, and outcomes were evaluated in the two groups, each of 323 patients, obtained after matching (20); the PS is the probability that a patient would have been treated with bridging therapy with LMWH given his pretreatment variables. Equal PS values guarantee equal distribution of measured pretreatment variables at baseline on the sample level; thus, PS is an attempt to create homogeneous

groups for comparison when data from a randomization procedure are not available. The individual propensity scores for analyzing bridging and non-bridging therapy groups were estimated with a logit model including the following variables: age, sex, NIHSS at admission, vascular risk factors, lesion size, use of NOACs and CHA<sub>2</sub>DS<sub>2</sub>Vasc. To estimate treatment effects, Cox proportional hazards models were performed on the entire cohort to derive crude and PS-adjusted Hazard Ratios (HRs).

The observed correlation between the combined outcome (survival) and the set of variables was analyzed using the proportional Cox model; here all the variables included in our multivariable analysis were used. Patients were censored at the time of an outcome event, death or lost during follow-up.

## Results

A total of 2,164 patients were enrolled in the RAF (n = 1,037) and RAF NOACs (n = 1,127) studies. Patients who did not start any anticoagulation were excluded, as well as those who were treated only with LMWH. This resulted in 1,821 patients, of whom another 11 were excluded due to incomplete data related to the administration of OAC therapy. A further 30 patients were lost during follow-up.

After index acute ischemic stroke, 371/1,810 patients (20.49%) underwent bridging therapy with LMWH (Figure I of Supplemental Material).

OAC was initiated with warfarin in 561/1,780 patients (31.52%) and NOACs were started in 1,219/1,780 (68.48%). The median for initiating bridging therapy was 7 days (Inter Quartile Range - IQR 11), while for the non-bridging group this number was a median of 8 days (IQR 14). Mean NIHSS at admission was  $7.2 \pm 6.3$  in the bridging group and  $7.7 \pm 6.2$  in the non-bridging group (p = ns).

### *Clinical characteristics of the bridging and non-bridging groups*

The bridging and non-bridging groups differed for age, sex, the percentage of medium-sized lesions, of large anterior circulation lesions, and for the presence of leukoaraiosis (Table 1). The mean ages were  $73.0 \pm 9.7$  years vs  $76.1 \pm 9.4$  years, respectively (p<0.001). Of the 371 bridging patients, 197 (53.1%) were male, while 663 (46.1%) in the non-bridging group (p=0.017). In the bridging group, 153 patients (41.2%) had medium-sized lesions vs 469 (32.6%) in the non-bridging group (p=0.010); large anterior lesions were present in 41 (11.1%) of bridging patients and 232 (16.1%) non-bridging patients (p=0.006). Leukoaraiosis was diagnosed in 143 (38.5%) and 786 (54.6%) patients, respectively (p=0.001).

41/371 (11.0%) in the bridging group were simultaneously taking an antiplatelet agent (either aspirin 100 mg per day or clopidogrel 75 mg per day), while in the non-bridging group patients under antiplatelet therapy were 200/1,439 (13.9%), being statistically similar ( $p = 0.2$ ).

At multivariable analysis, age (OR 0.97; 95% CI 0.95-0.98,  $p = 0.001$ ) and leukoaraiosis (OR 0.60, 95% CI 0.47-0.78,  $p = 0.001$ ) were inversely correlated with the use of bridging therapy (Table I of Supplemental Material).

### *Outcomes in the bridging and non-bridging groups*

Overall, 42/371 bridging patients (11.3%) experienced the combined outcome, compared to 72/1,409 in the non-bridged group (5.1%) ( $p = 0.0001$ ). Within the bridging group, 29/42 (69%, 7.8% of all outcomes) versus 44/72 (61.11%, 3.1% of all outcomes) in the non-bridging group had an ischemic stroke, respectively. Major bleedings occurred in 19/42 patients (45.23%, 5.1% of all outcomes) in the bridging group and 32/72 (44.44%, 2.3% of all outcomes) in the non-bridging group ( $p=0.08$ ) (Table 2).

In the multivariable analysis, bridging therapy was associated with combined outcome (OR 2.3; 95% CI 1.4-3.7,  $p < 0.0001$ ), ischemic event (OR 2.2; 95% CI 1.3-3.9,  $p = 0.005$ ) and hemorrhagic event (OR 2.4; 95% CI 1.2-4.9,  $p = 0.01$ ) (Table 3).

Propensity score matching was performed on 323 patients in each group. The two groups were comparable for age ( $74.3 \pm 8.7$  years in the non-bridging group vs.  $74.0 \pm 8.5$  years in the bridging group,  $p = 0.7$ ), sex (170 males, 52.6% of the total, in the non-bridging group vs. 161 males, 49.8% of the total, in the bridging group,  $p = 0.5$ ), NIHSS at admission ( $7.5 \pm 6.3$  vs.  $7.6 \pm 6.3$ ); also, they were comparable for clinical characteristics; NOACs were used as anticoagulants in 114 patients (35.3%) in the non-bridging group vs 115 patients (35.6%) in the bridging group ( $p = 1.0$ ) (Table II of Supplemental Material).

The Propensity score analysis confirmed the results of the multivariable analysis; bridging therapy was associated with combined outcome (HR 3.08; 95% CI 1.68-5.64,  $p < 0.001$ ), ischemic event

(HR 4.50; 95% CI 1.88-10.75,  $p < 0.003$ ) and hemorrhagic event (HR 2.71; 95% CI 1.16-6.37,  $p = 0.017$ ) (Table 4); the same results were confirmed after the PS was adjusted for age, sex, NIHSS at admission, vascular risk factors, lesion size and CHA2DS2Vasc: combined outcome had a HR 2.23 (95% CI 1.41-3.52,  $p < 0.001$ ), ischemic event a HR 2.23 (95% CI 1.29-3.88,  $p < 0.003$ ) and hemorrhagic event a HR 2.24 (95% CI 1.15-4.36,  $p = 0.017$ ) (Table 4).

In Figure II of the Supplemental Material the cumulative hazard rates for the combined outcome, in respect to treatment group, according to the Cox regression model (HR 0.95; 95% CI 0.60-1.49;  $p = 0.8$ ) are reported.

#### *Outcomes according to the type of OAC used in the bridging and non-bridging groups*

Out of the 1,780 included patients, 1,219 were treated with NOACs and 561 with VKAs. The combined outcome was observed in 62 (5.1%) and 52 (9.3%) patients, respectively ( $p = 0.01$ ). An ischemic outcome was observed in 35 (2.9%) and 38 (6.8%) of the patients treated with NOACs of VKA, respectively ( $p = 0.0001$ ). The NOACs and VKAs groups did not differ concerning the hemorrhagic events that were 29 (2.4%) and 22 (3.9%), respectively.

In the bridging group, 120 patients were treated with NOACs and 251 with VKAs; in the non-bridging group, 1,099 patients were treated with NOACs and 310 with VKAs. Within each group, no statistically significant differences were observed in either the combined outcome or the hemorrhagic event rate according to the type of OAC used. However, a statistically significant difference was observed for the rate of ischemic events in the non-bridging group: 27 events (2.5%) in patients treated with NOACs vs 17 events (5.5%) in patients treated with VKAs ( $p = 0.015$ ).

When stratifying each group according to the type of OAC, no statistically significant differences were observed between and within each group in outcome rates.

## Discussion

This combined analysis of the RAF and RAF NOACs data suggested that bridging therapy was associated with overall higher risks of early ischemic recurrence and symptomatic intracranial bleeding; independently of the type of OACs administered. The latter finding is in line with that reported by IST, where an increase in hemorrhagic stroke was reported (1.2% for heparin vs 0.4% for aspirin). Data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry on bridging reported a higher incidence of myocardial infarction, stroke or systemic embolism, major bleeding, hospitalization, or death within 30 days was also significantly higher in patients receiving bridging (13% versus 6.3%; adjusted odds ratio, 1.94;  $P=0.0001$ ) (21).

Bridging therapy with heparin is sometimes started in subacute ischemic stroke, as it is thought to reduce the risk of ischemic recurrence due to a possible prothrombotic activity of warfarin at treatment initiation (22). However, reliable data on warfarin's role in blocking endogenous anticoagulants has yet to be proven. It is plausible that warfarin alone might be more effective than bridging therapy with warfarin in the sub-acute phase of AF-associated stroke.

Another possible explanation of the increased ischemic stroke risk of heparin may be its under-dosing as patient body weights are generally based on estimation. Moreover, our study did not allow to distinguish between ischemic recurrence in a different vascular territory from the index stroke, and recurrence in the same vascular territory, that may have been a progression of the first ischemia. (23).

In our study, bridging therapy with NOACs was also associated with a higher rate of ischemic events compared to those receiving NOACs alone. Besides RAF-NOAC, there are only a few prospective data available from observational studies on the safety and efficacy of early secondary prevention using NOACs after cardioembolic stroke. Of these, the SAMURAI-NVAF study reported that no ICH was recorded after a NOAC-initiation within a median of four days post stroke (24). Whereas, another observational study reported no significant difference in the rate of recurrent

ischemic events when comparing early NOAC treatment within 7 days and after 7 days (25). Ongoing studies such as the “TIMING of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation” (26) and The “Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients with Atrial fibrillation study (ELAN; 27) are designed to estimate the benefit of early versus late initiation of NOACs in patients with acute ischemic stroke related to AF without bridging therapy. Regarding the use of antiplatelets prior to initiating oral anticoagulation, 11.0% of bridging and 13.9% of non-bridging patients had been prescribed aspirin or clopidogrel. Therefore, it does not seem plausible that the associations would significantly increase bleeding risks in patients treated with LMWH.

When comparing bridging versus non-bridging outcomes associated with OAC type, the risk profile associated with bridging appeared similar between NOACs and VKAs, therein suggesting that bridging therapy should be avoided particularly in patients who will be treated with NOACs in secondary prevention (see Cox regression survival curve, Figure II of Supplemental Material).

An analysis of the patient profiles indicated that older patients (mean age 76.1 vs 73.0 years), those with leukoaraiosis and/or with large anterior circulation lesions were less likely to receive bridging therapy. This might reflect a routine use of LMWH in only selected cases, since leukoaraiosis and large infarct volume are clinical predictors of both symptomatic and asymptomatic HT (28-30), both spontaneous (28) and after thrombolytic therapy (31).

However based on our study results, there seems to be still overuse of LMWH due to a non-adherence to current guidelines. This overuse may also be due to the slower reversal of VKA and to the absence, at the time of enrollment of the RAF and RAF NOACs, of an antidote for NOACs in case of bleeding (32). Regarding the choice of patients to be treated with bridging therapy, there could have been a selection bias. Moreover, unrecorded factor that can sway clinician decisions on the use of bridging therapy may include dysphagia in acute stroke phase, preferring subcutaneous to oral administrations.

A limitation of this analysis was that it was non-randomized, so it is possible that some confounding factors might have influenced the outcome results. We did not have information on the exact time when INR reached the target level in warfarin-treated patients. Moreover, the sizes of the two groups were not equally represented, since only 20.5% of patients underwent bridging therapy with LMWH. Moreover, we are unable to specify the types of bleedings, as the RAF and RAF NOACs studies were not designed to collect such data.

In conclusion, our study suggests that the use of full-dose LMWH preceding oral anticoagulation in atrial fibrillation patients hospitalized for a recent ischemic stroke was associated with a higher risk of early ischemic recurrence and hemorrhagic events.

#### **Acknowledgements:**

The Authors thank ARS Umbria for its unrestricted support.

#### **Disclosures:**

V. Caso: honoraria as a member of the speaker bureau and as consultant or advisory board of Boehringer Ingelheim, Bayer, Daichii-Sankyo, Pfizer, Ever Pharma. All honoraria were paid to ARS UMBRIA.

G. Agnelli: honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer.

C. Becattini: honoraria as a member of the speaker bureau of Bristol Meyer Squibb and Bayer.

J. Putaala: honoraria for lectures related to atrial fibrillation and anticoagulants for Orion Pharma, Bristol Meyer Squibb, Pfizer, Bayer, and Boehringer Ingelheim.

T. Tatlisumak: Member of the Steering Committee of the NAVIGATE ESUS trial. Advisory board membership: Bayer, Sanofi Aventis, Lumosa, Boehringer Ingelheim, Pfizer. Research contracts with Boehringer Ingelheim, Bayer, Portola, Pfizer, Sanofi Aventis, BrainsGate.

G. Ntaios: member of the Steering Committee of the NAVIGATE ESUS trial. Speaker fees/Advisory Boards/Research support from Amgen; Bayer; BMS/Pfizer; Boehringer Ingelheim; Elpen; European Union; Galenica; Sanofi; Winmedica. No fees are directly received personally.

W. Ageno: speaker's honoraria from, and participated in scientific advisory boards for Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo; research support from Bayer and Boehringer Ingelheim.

D. Toni: honoraria as a member of speaker bureau and as advisory board of Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb and Bayer.

P. Michel: Research Grant by Swiss National Science Foundation and Swiss Heart Foundation; speaker fees by Bayer, Boehringer Ingelheim, Covidien, St. Jude Medical; honoraria as advisory relationship by Pierre-Fabre, Bayer, Bristol Meyer Squibb, Amgen, and Boehringer Ingelheim.

P. Vanacker: honoraria as a member of speaker bureau of Daiichi-Sankyo and as advisory board of Boehringer Ingelheim.

M. Paciaroni: honoraria as a member of the speaker bureau of Aspen, Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol Meyer Squibb, Daiichi Sankyo, Medtronic and Pfizer.

The other authors have nothing to disclose.

## References

1. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e326S-e350S.
2. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke*. 2007;38:423-30.
3. Whiteley WN, Adams HP Jr, Bath PM, Berge E, Sandset PM, et al. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet Neurol*. 2013;12:539-45.
4. Al-Sadat A, Sunbuli M, Chaturvedi S. Use of intravenous heparin by North American neurologists. *Stroke* 2002;33:1574–77.
5. Caplan LR. Resolved: heparin may be useful in selected patients with brain ischemia. *Stroke* 2003;34:230–31.
6. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, et al. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. *Stroke*. 2015;46:2175-82.
7. Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, et al. Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) Study. *J Am Heart Assoc*. 2017;6:e0007034.

8. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-20.
9. European Stroke Organisation (ESO) Executive Committee. Guidelines for management of ischemic stroke and transient ischemic attack. *Cerebrovasc Dis*. 2008;25:457–507.
10. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46-e110.
11. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-354. Erratum in: *Circulation*. 2007;116:e138.
12. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, Del Zoppo GJ; for the rtPA Acute Stroke Study Group. Neuroradiologic evaluation of patients with acute stroke treated with rtPA. *AJNR Am J Neuroradiol*. 1993;14:3–13.

13. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. *Stroke*. 2008;39:2249–2256.
14. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.
15. Tatu L, Moulin T, Bogousslavsky J, Duvemoy H. Arterial territories of the human brain: cerebral hemispheres. *Neurology*. 1998;50:1699–1708.
16. Tatu L, Moulin T, Bogousslavsky J, Duvemoy H. Arterial territories of the human brain: brainstem and cerebellum. *Neurology*. 1996;47:1125–1135.
17. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin A, Sjogren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322.
18. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–272.
19. Schulman S, Kearon C. Definition of major bleeding in clinical investigations and anti-hemostatic medical products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.
20. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
21. Steinberg BA, Peterson ED, Kim S, Thomas L, Gersh BJ, Fonarow GC, et al. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation Investigators and Patients. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation*. 2015;131:488-94.

22. Freedman MD. Oral anticoagulants: pharmacodynamics, clinical indications and adverse effects. *J Clin Pharmacol.* 1992;32:196-209.
23. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet.* 2000;355:1205-10.
24. Toyoda K, Arihiro S, Todo K, Yamagami H, Kimura K, Furui E, et al. SAMURAI Study Investigators. Trends in oral anticoagulant choice for acute stroke patients with nonvalvular atrial fibrillation in Japan: the SAMURAI-NVAF study. *Int J Stroke.* 2015;10:836-42.
25. Seiffge DJ, Traenka C, Polymeris A, Hert L, Peters N, Lyrer P, et al. Early start of DOAC after ischemic stroke: Risk of intracranial hemorrhage and recurrent events. *Neurology.* 2016;87:1856-1862.
26. Oldgren J, Åsberg S. Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial. <https://clinicaltrials.gov/ct2/show/NCT02961348>. Last accessed January 30, 2019.
27. Fischer U. Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation (ELAN): an International, Multicentre, Randomised - controlled, Two-arm, Assessor-blinded Trial. <https://clinicaltrials.gov/ct2/show/NCT03148457>. Last accessed January 30, 2019.
28. Tan S, Wang D, Liu M, Zhang S, Wu B, Liu B. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. *J Neurol.* 2014;261:905–12.
29. Kalinin MN, Khasanova DR, Ibatullin MM. The hemorrhagic transformation index score: a prediction tool in middle cerebral artery ischemic stroke. *BMC Neurol. BioMed Central;* 2017;17:177.

30. Fierini F, Poggesi A, Pantoni L. Leukoaraiosis as an outcome predictor in the acute and subacute phases of stroke. *Expert Rev Neurother.* 2017;17:963-975.
31. Liu Y, Zhang M, Chen Y, Gao P, Yun W, Zhou X. The degree of leukoaraiosis predicts clinical outcomes and prognosis in patients with middle cerebral artery occlusion after intravenous thrombolysis. *Brain Res.* 2018;1681:28-33.
32. Husted S, Verheugt FW, Comuth WJ. Reversal Strategies for NOACs: State of Development, Possible Clinical Applications and Future Perspectives. *Drug Saf.* 2016;39:5-13.

## Tables:

Clinical characteristics of patients (n = 1810)			
	Bridging therapy	Non-bridging therapy	p value
	(n = 371)	(n = 1439)	
Age (years)	73.0±9.7	76.1±9.4	0.0001
Male sex	197 (53.1%)	663 (46.1%)	0.017
NIHSS at admission	7.2±6.3	7.7±6.2	n.s.
Diabetes mellitus	80 (21.6%)	297 (20.6%)	n.s.
Hypertension	275 (74.1%)	1124(78.1%)	n.s.
Dyslipidemia	118 (31.8%)	510 (35.4%)	n.s.
Paroxysmal AF	153 (41.2%)	656 (45.6%)	n.s.
Smoking habit	46 (12.4%)	140 (9.7%)	n.s.
History of Stroke/TIA	84 (22.6%)	382 (26.5%)	n.s.
History of CHF	74 (19.9%)	232(16.0%)	n.s.
History of MI	48 (12.9%)	183 (12.7%)	n.s.
History of PAD	40 (10.8%)	116 (8.1%)	n.s.
PMK	21 (5.7%)	93 (6.5%)	n.s.
HT 24-72 hrs	40 (10.8%)	135 (9.4%)	n.s.
CHA <sub>2</sub> DS <sub>2</sub> -VASc after >4	255 (68.7%)	1094 (76.0%)	p = 0.03
Antiplatelet therapy	41 (11.0%)	200 (13.9%)	n.s.
<b>Cerebral Infarct Pattern</b>			
Small	153 (41.2%)	582 (40.4%)	n.s.
Medium	153 (41.2%)	469 (32.6%)	0.010
Large anterior circulation	41 (11.1%)	232 (16.1%)	0.006
Large posterior circulation	15 (4.0%)	92 (6.4%)	n.s.
Leukoaraiosis	143 (38.5%)	786 (54.6%)	0.0001

**Table 1:** Clinical characteristics of study patients (n=1810). NIHSS = National Institute of Health Stroke Scale; AF = Atrial fibrillation; CHF = Congestive Heart Failure; MI = Myocardial Infarction; PAD = peripheral artery disease; PMK = pacemaker; HT = hemorrhagic transformation.

Univariable analysis (n = 1780)			
	Bridging therapy (n = 371)	Non-bridging therapy (n = 1409)	p value
Combined outcome	42 (11.3%)	72 (5.1%)	0.0001
Ischemic outcome	29 (7.8%)	44 (3.1%)	0.0001
Hemorrhagic outcome	19 (5.1%)	32 (2.3%)	0.008

**Table 2:** univariable analysis; differences in outcomes at 90 days between patients treated with bridging with LMWH and those without bridging therapy.

Logistic Regression Analysis		
	OR (95% CI)	p
Bridging therapy (combined outcome)	2.3 (1.4 - 3.7)	<0.0001
Bridging therapy (ischemic outcome)	2.2 (1.3 - 3.9)	0.005
Bridging therapy (hemorrhagic outcome)	2.4 (1.2 – 4.9)	0.01

**Table 3:** Multivariable analysis adjusted for NIHSS score, diabetes mellitus, arterial hypertension, dyslipidemia, paroxysmal AF, pacemaker; lesion size, leukoaraiosis, CHA<sub>2</sub>DS<sub>2</sub>VASc score after the event, history of previous stroke or TIA, type of oral anticoagulant (VKA vs. NOAC), current smoking, congestive heart failure and/or myocardial infarction; differences in outcomes at 90 days between patients treated with bridging with LMWH and those without bridging therapy.

Propensity score matching: outcomes				
	<i>no bridging therapy (n = 323)</i>	<i>bridging therapy (n = 323)</i>	<i>HR (95% CI)</i>	<i>P value</i>
combined outcome	13 (4.0%)	40 (12.3%)	Unadjusted 3.08 (95% CI 1.68-5.64) Adjusted 2.23 (95% CI 1.41-3.52)	0.0001
ischemic outcome	6 (1.9%)	27 (8.3%)	Unadjusted 4.50 (95% CI 1.88-10.75) Adjusted 2.23 (95% CI 1.29-3.88)	0.003
hemorrhagic outcome	7 (2.2%)	19 (5.9%)	Unadjusted 2.71 (95% CI 1.16-6.37) Adjusted 2.24 (95% CI 1.15-4.36)	0.017

**Table 4:** Propensity score matching: outcomes

## **SUPPLEMENTAL MATERIAL**

**Supplemental Table I:** Clinical features of patients associated to the use of bridging therapy with LMWH at multivariable analysis.

Logistic regression		
	OR (95% CI)	P value
Age	0.97 (0.95 - 0.98)	0.0001
Male sex	1.30 (0.98 - 1.74)	n.s.
NIHSS at admission	0.99 (0.98 - 1.02)	n.s.
diabetes mellitus	0.92 (0.65 - 1.30)	n.s.
Hypertension	0.87 (0.62 - 1.22)	n.s.
Dyslipidemia	0.87 (0.66 - 1.13)	n.s.
Paroxysmal AF	0.78 (0.61 - 1.00)	n.s.
smoking habit	0.87 (0.59 - 1.30)	n.s.
History of Stroke/TIA	0.84 (0.63 - 1.12)	n.s.
History of CHF	1.15 (0.81 - 1.63)	n.s.
History of MI	0.90 (0.60 - 1.33)	n.s.
PMK	0.81 (0.48 - 1.37)	n.s.
Large anterior circulation lesion	0.68 (0.46 - 1.01)	n.s.
Leukoaraiosis	0.60 (0.47 - 0.78)	0.0001
CHA <sub>2</sub> DS <sub>2</sub> -VASc after stroke	1.18 (1.00 - 1.40)	n.s.

---

NIHSS = National Institute of Health Stroke Scale

AF = atrial fibrillation

CHF = congestive heart failure

MI = myocardial Infarction

PMK = pacemaker

**Supplemental Table II:** Propensity score matching for characteristic of patients (n = 323).

Propensity score matching: characteristics of the patients			
	No Bridging therapy	Bridging therapy	p value
	(n = 323)	(n = 323)	
Age (years, mean and median)	74.3±8.7	74.0±8.5	0.7
	75.0	75.0	
NIHSS at admission (mean and median)	7.5±6.3	7.6±6.3	0.8
	6.0	6.0	
Sex M	170 (52.6%)	161 (49.8%)	0.5
Hypertension	253 (78.3%)	247 (76.5%)	0.6
Diabetes Mellitus	73 (22.6%)	71 (22.0%)	0.9
Hyperlipidemia	117 (36.2%)	105 (32.5%)	0.4
Paroxysmal AF	126 (39.0%)	142 (43.9%)	0.2
History of stroke/TIA	92 (28.4%)	77 (23.8%)	0.2
Current smoker	29 (9.0%)	33 (10.2%)	0.7
CHF	56 (17.3%)	57 (17.6%)	1.0
History of MI	44 (13.6%)	44 (13.6%)	1.0
Pacemaker	23 (7.1%)	18 (5.7%)	0.5
Small lesion	140 (43.3%)	135 (41.8%)	0.8
NOACs	114 (35.3%)	115 (35.6%)	1.0
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	237 (73.4%)	242 (72.7%)	0.6

---

NIHSS = National Institute of Health Stroke Scale

AF = atrial fibrillation

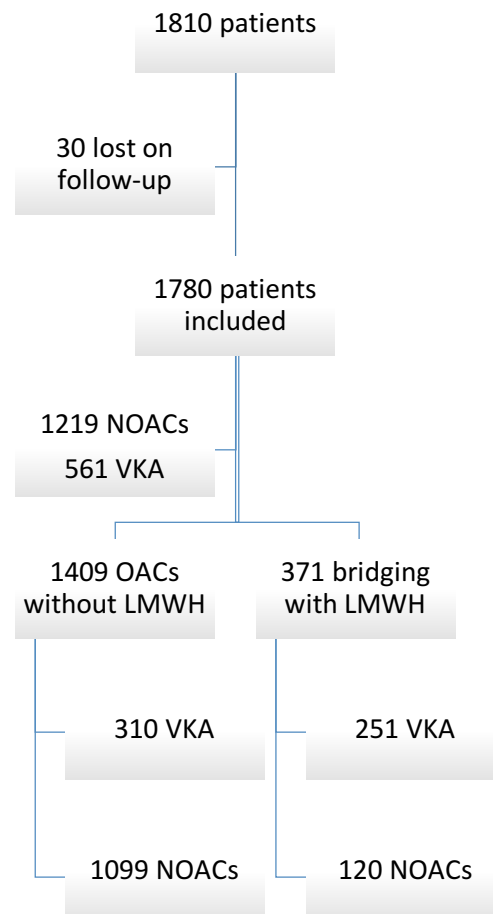
CHF = congestive heart failure

MI = myocardial Infarction

PMK = pacemaker

NOACs = non-vitamin k antagonists oral anticoagulants

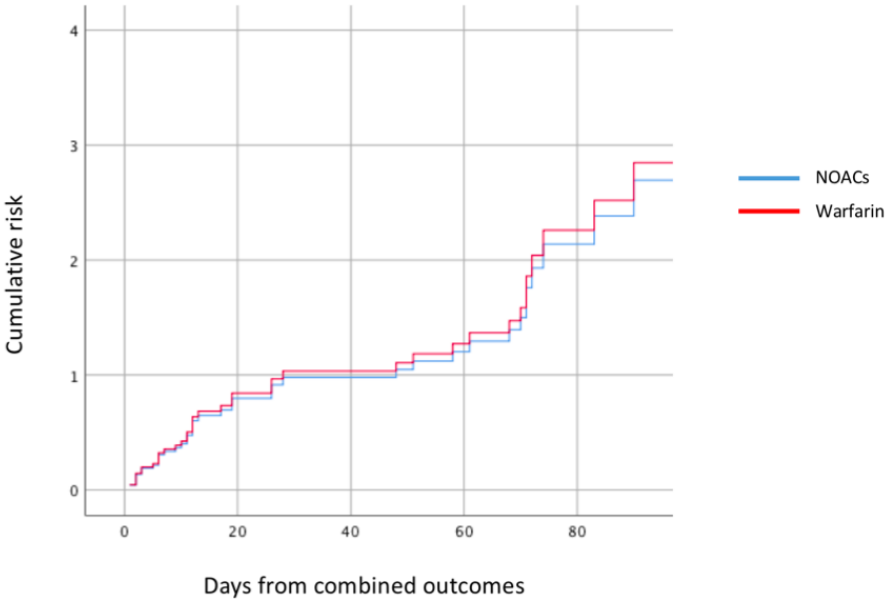
**Supplemental Figure I:** patients selection.



---

VKA = vitamin k antagonists oral anticoagulants  
NOACs = non-vitamin k antagonists oral anticoagulants  
LMWH = low molecular weight heparin

**Supplemental Figure II:** Cumulative risk of combined outcome according to Cox regression model in patients who underwent bridging therapy with LMWH.



Blue line: patients treated with NOACs.  
Red line: patients treated with warfarin.  
HR 0.95 (95% CI 0.60-1.49), p=0.8.