Università Campus Bio-Medico di Roma

Corso di Dottorato di Ricerca in Scienze Biomediche Integrate e Bioetica - Scienze dell'Invecchiamento e della Rigenerazione Tissutale
XXX ciclo a.a. 2014-2015

Anticoagulation after stroke in patients with atrial fibrillation:

to bridge or not with low-molecular weight heparin?

Riccardo Altavilla

Coordinatore
Prof. Paolo Pozzilli

Tutore
Prof. Fabrizio Vernieri

19 Luglio 2018

Summary

Chapter 1. Ischemic stroke

1.1 *Definition of acute ischemic stroke*

1.2 *Etiological classification of ischemic stroke*

1.3 *Diagnosis of ischemic stroke*

1.4 *Risk factors for ischemic stroke*

1.4.1 Hypertension

1.4.2 Smoking

1.4.3 Diabetes mellitus

1.4.4 Dyslipidemia

1.4.5 Carotid stenosis

1.4.6 Atrial Fibrillation

1.5 *Acute reperfusion therapy*

1.5.1 Alteplase

1.5.2 Mechanical thrombectomy

1.6 *Antiaggregation in the acute phase of stroke*

Chapter 2. Atrial fibrillation and cardioembolic stroke

2.1 *Prognosis of cardioembolic ischemic stroke*

2.2 *Risk of hemorrhagic transformation in cardioembolic stroke*

2.2.1 Classification of hemorrhagic transformation

2.2.2 Risk factors for hemorrhagic transformation

2.3 *Effect of hemorrhagic transformation on outcomes*

Chapter 3. **Anticoagulation in secondary stroke prevention**

3.1 *Anticoagulation*

3.1.1 Warfarin

3.1.2 Dabigatran

3.1.3 Rivaroxaban

3.1.4 Apixaban

3.1.5 Edoxaban

3.2 *Differences between vitamin k-based and direct oral anticoagulants*

3.3 *Heparin in acute ischemic stroke*

3.4 *When to start anticoagulation after ischemic stroke*

3.4.1 The RAF study

3.4.2 The RAF NOACs study

Chapter 4. Anticoagulation after stroke in patients with atrial fibrillation: to bridge or not with low-molecular weight heparin?

4.1 *Introduction*

4.2 *Patients and methods*

4.2.1 Risk factors

4.2.2 Evaluation of Outcomes

4.3 *Statistical analysis*

4.4 *Results*

4.4.1 Clinical characteristics of the bridging and non-bridging groups

4.4.2 Outcomes in the bridging and non-bridging groups

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

4.5 *Discussion*

Aknowledgements

Bibliography

Chapter 1. Ischemic stroke

1.1 Definition of acute ischemic stroke

Ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction (Sacco RL. et al. 2013). According to the same definition, CNS infarction is a “brain, spinal cord, or retinal cell death attributable to ischemia, based on:

1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded”.

These definitions of ischemic stroke and brain ischemia have been adopted after the technical advances in neuroradiological techniques, which allow the immediate distinction among stroke, focal deficits with sudden onset due to causes other than ischemia and transient blood supply deficits without evidence of brain infarction (transient ischemic attack or TIA). All the previous definitions of stroke relied upon the assumption that the sudden deficit was of vascular origin; anyway, urgent brain computed tomography (CT) scan has a high specificity in excluding brain hemorrhages, but low sensitivity in the detection of an ischemic lesion, particularly in the acute phase and in case of small strokes. Thus, the new definition is the result of the new insights offered

by the introduction of magnetic resonance imaging (MRI) and in particular of diffusion-weighted images in the acute phase of stroke (Furlan M. et al 1996; Olivot JM. et al. 2010; Brazzelli M. et al. 2009).

1.2 Etiological classification of ischemic stroke

Ischemic stroke can be classified according to the presumed mechanism of the focal brain injury (etiological classification), on the type and on the anatomical localization of the vascular lesion.

The most used etiological classification is the TOAST (Adams HP. Jr. et al. 1993), which divides ischemic strokes into 5 major categories:

- Large-artery atherosclerosis, either extracranial or intracranial;
- Cardiac embolism;
- Small-vessel disease;
- Other determined causes, grouping a broad spectrum of disorders, for example dissection, hypercoagulable states, or sickle cell disease;
- Undetermined

This classification is based on the supposed mechanism of stroke, but the diagnostic workup is inadequate to establish the actual mechanism in as many as 30% of strokes, which thus remain of undetermined source. Moreover, stroke patients usually present more than one risk factor and more than one putative etiology.

1.3 Diagnosis of ischemic stroke

The clinical diagnosis of ischemic stroke should be confirmed by neuroradiological imaging, at least with CT scan or MRI. Brain CT scan can exclude hemorrhagic events; brain MRI can help excluding non-vascular causes of acute neurological dysfunction (stroke mimics), and in distinguishing real strokes from TIAs, and the critically injured brain tissue from the ischemic but not yet infarcted tissue (ischemic penumbra).

The diagnostic work-up for ischemic stroke should include tests to assess modifiable risk factors and causes of stroke.

1.4 Risk factors for ischemic stroke

After the acute management, aimed to restore reperfusion in the occluded artery territory if possible, the management of ischemic stroke in the stroke unit setting is based on the prevention of early and late complications and on the assessment and correction of treatable risk factors.

Different population studies identified the major modifiable risk factors for ischemic stroke (Harmsen P. et al. 2006; Hankey GJ. 2006; Grysiewicz RA. et al. 2008; O'Donnel MJ. et al. 2016):

- Hypertension
- Diabetes mellitus
- Smoking habit
- Dyslipidemia

Among non-modifiable risk factors there are (Grysiewicz RA. et al. 2008; Jerrard-Dunne P. et al. 2003; Jood K. et al. 2005; Meschia JF. et al. 2011; Howard VJ. 2013):

- Older age, particularly age >80 years (Grysiewicz RA. et al. 2008);
- Race and ethnicity, with risk higher for blacks than for whites (Howard VJ. 2013);
- Sex, with risk higher at most ages for men compared with women, except for ages 35 to 44 years and >85 years, where women have a similar or higher risk than men (Persky RW. et al. 2010; Bushnell C. et al. 2014; Arnao V. et al. 2016);
- Family history and genetic disorders, with a higher risk for monozygotic twins and those with genetic disorders predisposing to hypercoagulability or increased blood viscosity, such as sickle cell disease, or predisposing to small vessel diseases like cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy (Jerrard-Dunne P. et al. 2003; Jood K. et al. 2005; Meschia JF. et al. 2011).

Two important modifiable risk factors are also clinical conditions and individually represent mechanisms of disease for ischemic stroke, covering the majority of brain ischemias according to the TOAST classification:

- Atrial fibrillation

- Carotid artery stenosis

The risk of stroke is particularly increased in patients with two or more risk factors.

Different scales have been proposed to assess annual risk for stroke in the presence of one or more risk factors as suggested by calculators.

After the Framingham study, 2 separate scales have been proposed, respectively for men and women between 55 and 84 years of age, to assess the annual percentual risk for stroke (Wolf PA. et al.1991).

These tools always take into consideration atrial fibrillation, the most common cause of cardioembolic ischemic stroke, and the presence of coronary heart disease and other types of cardiovascular disease; when all of these risk factors and stroke mechanisms are considered together, they account for 60 to 80 percent of the population-attributable risk of ischemic stroke (Hankey GJ. 2006).

1.4.1 Hypertension

Arterial hypertension is the single most important treatable risk factor for stroke (O'Donnel MJ et al. 2016), and epidemiologic studies on patients with treated and untreated hypertension suggest a linear association between the rise in blood pressure above 110/75 mmHg and the increasing incidence of cardiovascular mortality (Lewington S. et al. 2002; Rapsomaniki

E. et al. 2014). It seems that non only systolic and diastolic blood pressure may be related to stroke risk, but also other variables connected to hypertension, including mean blood pressure, pulse pressure, blood pressure variability, blood pressure instability, and alterations of circadian physiologic rhythm, like nocturnal non-dipping pattern (Rothwell PM. et al. 2010).

Hypertension is associated with lacunar infarcts, an expression of small vessel disease, with an increased risk of subclinical or silent strokes and, in turn, of subsequent vascular dementia and recurrence of cerebrovascular events (Vermeer SE. et al. 2007; Prabhakaran S. et al. 2008; Das RR. et al. 2008).

Since arterial hypertension is usually associated to other cardiac and cerebral risk factors such as increasing body weight, dyslipidemia, glucose intolerance, and the metabolic syndrome, the association with stroke could not be causative; yet, some studies confirmed that a strict control of blood pressure with antihypertensive therapy is associated with a reduction in the risk of recurrent stroke (Rothwell PM. et al. 2011; PROGRESS Collaborative Group 2001; Yusuf S. et al. 2008; Liu L. et al. 2009; Arima H. et sl. 2011).

1.4.2 Smoking

Cigarette smoking is associated with an increased risk for all stroke subtypes and has a strong, dose-dependent relationship for both ischemic stroke and subarachnoid hemorrhage (Ockene IS. et al. 1997; Kawachi I. et al.

1993; Kurth T. et al. 2003; Wilson PW. et al. 1997; Li C. et al. 2005; Wolf PA. et al. 1988; Peters SA. et al. 2013), with a relative risk of stroke of 2.58 compared with people who never smoked (Kawachi I. et al. 1993); the excess risk for former smokers disappears within two to four years after the cessation of smoking.

Smoking habit is also associated with carotid stenosis, with an odds ratio for moderate carotid stenosis of 1.08 for each five pack-years of smoking, as demonstrated in the Framingham study (Wilson PW. et al. 1997).

There are no randomized controlled trials of smoking cessation for stroke prevention, but the risk of stroke declines after quitting and is eliminated after five years in observational studies (Kawachi I. et al. 1993; Wolf PA. et al. 1988; Wannamethee SG. et al.1995).

1.4.3 Diabetes mellitus

Diabetes mellitus is associated with a risk of ischemic stroke approximately double compared with non-diabetic population (Arvanitakis Z. et al. 2006; Janghorbani M. et al. 2007; Sarwar N. et al. 2010; Luitse MJ. et al. 2012; Peters SA. et al. 2014); this risk results higher in women than in men (Peters SA. et al 2014). Moreover, diabetic patients are more prone to the development of carotid stenosis in presence of dyslipidemia, endothelial dysfunction, and platelet and coagulation abnormalities, particularly in those

with uncontrolled diabetes and high levels of HbA1c (Vitelli LL. et al. 1997; Jørgensen L. et al. 2004.

1.4.4 Dyslipidemia

While high cholesterol level, in particular LDL, is a well-established risk factor for coronary heart disease and atherosclerosis, the association with stroke incidence appears to be more complex, in that the degree of risk varies for stroke subtypes (Yaghi S. et al. 2015).

It has been reported a weak but positive association of elevated cholesterol with ischemic stroke, particularly for large artery atherosclerotic and lacunar stroke subtypes (Yaghi S. et al. 2015; Leppälä JM. et al. 1999; Zhang X. et al. 2003; Kurth T. et al. 2007; Horenstein RB. et al. 2002; Tirschwell DL. et al. 2004) but some studies did not find this association (Shahar E. et al. 2003; Bots ML. et al. 2002).

Lipid-lowering therapy with statins decreases the risk of recurrent ischemic stroke in patients with hyperlipidemia, but a meta-analysis of lipid-lowering therapy found that diet or drug therapy other than statins did not significantly reduce the risk of stroke in subjects with elevated cholesterol levels (Corvol JC. et al. 2003).

1.4.5 Carotid stenosis

Prevalence of asymptomatic carotid stenosis ranges from 0.1 to 7.5% in the general population, with prevalence increasing with age (de Weerd M. et al. 2010).

The site most frequently affected by plaque formation is the carotid bifurcation, with extension into the proximal internal carotid artery.

Two mechanisms are involved in stroke or TIA from carotid stenosis (Petty GW. et al. 1999):

- luminal narrowing, causing a critical reduction of blood flow;
- plaque ulceration, causing artery-to-artery embolism, or thrombosis with occlusion of the vessel.

The risk of stroke due to carotid artery stenosis has been associated to percentage of stenosis, to plaque morphology and stability, but the estimate is questioned by recent advantage in primary prevention with aggressive medical treatment; a recent population-based study of patients with asymptomatic carotid artery stenosis of >50% who were treated with intensive medical therapy, showed an average annual rate of 0.34% for stroke and of 1.78% for TIA (Marquardt L. et al. 2010).

Carotid disease is considered symptomatic when focal neurologic symptoms with sudden onset are referable to the territory of distribution of the carotid ipsilateral to the significant atherosclerotic pathology. This definition

includes one or more TIAs with focal neurologic dysfunction or transient monocular blindness (amaurosis fugax), or one or more minor ischemic strokes (NASCET, 1991). Usually, the time span considered in this definition is 6 months, although a precise time limit is not supported by any evidence, but is rather a convention (Barnett HJM. et al. 1991; ECST 1991).

Carotid endarterectomy (CEA) is the treatment of choice for severe symptomatic carotid stenosis, and its efficacy was demonstrated in 3 trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET, 1991), the European Carotid Surgery Trial (ECST, 1998) and the Veterans Affairs Trials (Mayberg MR. et al. 1991). A pooled analysis of these three trials demonstrated an absolute risk reduction of 4.6% in moderate stenosis (50–69%) and of 16% in severe stenosis (≥ 70%) (Rothwell PM. et al. 2003).

Carotid artery stenting (CAS) is a comparable alternative treatment to CEA.

Other trials evaluated CEA versus medical therapy in asymptomatic carotid stenosis, and found more modest benefit (Halliday A. et al. 2004; Hobson RW. 2nd et al. 1993), in particular in an analysis conducted in recent years (Singh TD. et al. 2015) probably for the improvements in primary preventive medical treatment.

1.4.6 Atrial Fibrillation

Atrial fibrillation (AF) is the most common leading cardiac arrhythmia in the elderly (Go AS. et al. 2014), with higher prevalence in men and increasing with age (Go AS. et al. 2001). It has been estimated that AF is responsible for 10%–12% of all ischemic strokes (Goldstein LB. et al. 2011; Flint AC. et al. 2012).

AF has the following electrocardiographic characteristics:

- The RR intervals follow no repetitive pattern (“irregularly irregular”)
- There are no distinct P waves at ECG.

Hypertensive heart disease and coronary heart disease (CHD) are the most common disorders in patients with AF, as well as rheumatic heart disease, which is now uncommon in developed countries. It is thought that alterations in atrial structure and dimension, leading to subsequent alteration in the conduction of the electric stimuli, are the cause of AF.

The current classification of AF distinguishes 4 different forms (January CT. et al. 2014):

- Paroxysmal AF, which terminates spontaneously or with intervention within seven days of onset, and that may recur with variable frequency;
- Persistent AF, which fails to self-terminate within seven days and often requires pharmacologic or electrical cardioversion to restore sinus rhythm;

- Long-standing persistent AF, which has lasted for more than 12 months;
- Permanent AF, a persistent atrial fibrillation which is treated, as a medical decision, only with regard of rate control but not of rhythm control.

The proposed mechanism for stroke in AF patiens is a cardiac embolus, most commonly originating from the left atrium or left atrial appendage.

An ischemic stroke may occur in patients with AF either as its initial presenting manifestation or despite appropriate prophylaxis; it as been calculated that around 10% of patients with acute ischemic stroke or TIA have newly-detected AF (Rizos T. et al. 2012); however, in the case of paroxysmal AF, an additional 11% may be found within 30 days of discharge if searched with continuous electrocardiographic monitoring (Flint AC. et al. 2012), and longer monitoring protocols up to 6 months have comparable detection rates (Flint AC. et al. 2012; Tayal AH. and Callans DJ. 2010).

The risk of stroke in patients affected by AF has been extensively studied, and is predictable by use of specific scales, like $CHADS_2$ (Gage BF. et al. 2001) and CHA_2DS_2-VASc (Lip GY. et al. 2010).

CHA_2DS_2-VASc considers the following items: congestive heart failure (1 point), hypertension (1 point), age 65 to 74 years (1 point) or ≥75 years (2 points), Diabete Mellitus (1 point), prior stroke or TIA (2 points), female sex (1

point), and vascular disease other than cerebrovascular disease (1 point).

The annual risk of stroke increases with the score: 0.5% per year (0 points), 1.5% per year (1 point), 2.5% per year (2 points), 5% per year (3 points), 6% per year (4 points), and 7% per year (5–6 points).

Both $CHADS_2$ and CHA_2DS_2-VASc may underestimate stroke risk for patients with a recent TIA or ischemic stroke who have no other risk factors (Furie KL. et al. 2013; The STroke Risk in Atrial Fibrillation Working Group. 2007). Their risk for stroke may be closer to 7% to 10% per year (The STroke Risk in Atrial Fibrillation Working Group, 2007; EAFT, 1993).

1.5 Acute reperfusion therapy

The most important factor in acute stroke treatment is early treatment.

The immediate goal of reperfusion therapy for acute ischemic stroke is to restore blood flow to the regions of brain that are ischemic but not yet infarcted.

The two options for reperfusion therapy are:

- intravenous alteplase;
- mechanical thrombectomy.

1.5.1 *Alteplase*

Alteplase (recombinant tissue plasminogen activator, rtPA) is the only currently approved drug for the treatment of acute ischemic stroke.

Its benefit is time dependent, and the improvement in functional outcome at 3 to 6 months was demonstrated in different large randomized trials when rtPA is given within 4.5 hours of ischemic stroke onset (Lees KR. et al. 2013; Saver JL. et al. 2013; Wardlaw JM. Et al. 2012; Emberson J. et al. 2014; Prabhakaran S. et al. 2015; Whiteley WN. et al. 2016; Lees KR. Et al. 2016).

An analysis of a registry of over 58,000 patients treated with tPA within 4.5 hours of ischemic stroke symptom onset (Saver JL. et al. 2013) found that every progressive reduction of 15 minute in the time to start rtPA was associated with an increase in the odds of functional independence (4%), and with a decrease in the odds of death before discharge (4%) and of symptomatic hemorrhagic transformation of infarction (4%).

A meta-analysis on individual patient data from 6756 subjects, allocated to receive either iv rtPA or control within 3 to 6 hours from stroke onset in the NINDS, ATLANTIS, ECASS (1, 2, and 3), EPITHET, and IST-3 trials (Emberson J. et al. 2014), found that: within 3 hours of stroke onset, rtPA led to a good outcome for 33% versus 23% for controls; for treatment between 3 and 4.5 hours, rtPA led to good outcome in 35% of patients vs 30% of controls; beyond 4.5 hours, the proportion of patients with a good outcome was 33% in rtPA group vs 31% in control group.

Moreover, the results of the meta-analysis also showed that rtPA is effective regardless of patient age, stroke severity.

Treatment with intravenous alteplase within 4.5 hours of acute ischemic stroke onset is associated with a slightly increased early risk of intracerebral hemorrhage, which is anyway outweighted by its benefits (Whiteley WN. et al. 2012 and 2016).

For all these reasons, rtPA should be proposed as the first treatment in all eligible patients with acute ischemic stroke who present within 4.5 hour since onset.

Exclusion criteria for rtPA are all the situations leading to an increased risk of hemorrhage: recent (within 3 months) intracranial or intraspinal surgery or serious head trauma; presence of intracranial conditions that may increase the risk of bleeding; known bleeding diathesis; previous stroke within 3 months; arterial puncture at a non-compressible site in previous 7 days; uncontrolled hypertension at time of treatment (eg, >185 mm Hg systolic or >110 mm Hg diastolic); multilobar cerebral infarction (hypodensity $>^1/_3$ of the cerebral hemisphere); known bleeding diathesis including but not limited to current use of oral anticoagulants with an INR >1.7 (or PT >15 seconds), current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests; administration of heparin within 48 hours preceding the onset of stroke with an elevated aPTT greater than the upper limit of normal, platelet count <100,000/mm^3.

1.5.2 Mechanical thrombectomy

Mechanical thrombectomy (MT) is a recent approach fo acute ischemic stroke, and its use, through second-generation intra-arterial devices is safe and effective for reducing disability, and superior to standard treatment with intravenous rtPA alone for the treatment of acute ischemic stroke. This treatment is indicated for acute strokes with a documented large artery occlusion in a large intracranial vessel.

Five multicenter, randomized controlled trials were conducted on MT since 2015: MR CLEAN (Berkhemer OA. Et al. 2015), ESCAPE (Goyal M. et al. 2015), SWIFT PRIME (Saver JL. et al. 2015), EXTEND-IA (Campbell BC. et al. 2015), and REVASCAT (Jovin TG. et al. 2015). They all demonstrated the efficacy and safety of MT administered in acute ischemic strokes within 6 hours from symptoms onset, with regard of 90-days disability; moreover, the procedure does not increase the risk for symptomatic intracranial hemorrhage or 90-day mortality.

More recent trials focused on patients whose stroke onset was >6 hours or not known; these trials focused on patients selected with advanced neuroimaging to assess a mismatch between critically-injured brain tissue and salvageable ischemic penumbra. The DAWN trial (Nogueira RG. Et al. 2018) enrolled patients with acute stroke and occlusion of the intracranial internal carotid artery or the proximal middle cerebral artery who were last known to be normal 6 to 24 hours earlier; all the patients had a mismatch between the severity of the neurologic deficit measured by the NIHSS and the infarct volume

measured using diffusion-weighted MRI or perfusion CT. The trial resulted positive for higer rate of functional independence (defined as a modified Rankin scale score of 0 to 2) in the thrombectomy group compared with the control group. The DEFUSE 3 trial enrolled patients with ischemic stroke due to occlusion of the proximal middle cerebral artery or internal carotid artery who were last known to be well 6 to 16 hours earlier (Albers GW. et al. 2018), with an infarct size of <70 mL and a ratio of ischemic tissue volume to infarct volume of ≥1.8, measured at diffusion-weighted MRI or CT perfusion imaging. Functionally independence, defined as a modified Rankin scale score of 0 to 2, was higher in the endovascular therapy group compared with medical therapy alone.

1.6 Antiaggregation in the acute phase of stroke

After reperfusion therapy with rtPA and/or mechanical thrombectomy, the therapy for the acute phase of ischemic stroke is based on antiplatelet agents, which are effective for the prevention of recurrence. Aspirin (50 to 100 mg daily), clopidogrel (75 mg daily), and the combination of aspirin and extended release dipyridamole (25 mg/200 mg twice a day) are all feasible options for preventing recurrence of non-cardioembolic ischemic stroke, and recent evidences suggest that aggressive treatment with clopidogrel 600 mg + aspirin 100 mg at admission, followed by clopidogrel 75 mg + aspirin 100 mg for one

month can be more effective in preventing early recurrence in TIA and minor strokes (Johnston SC. et al. 2018).

In patients with stroke and atrial fibrillation, acute antithrombotic therapy may be warranted both to reduce disability and the risk of early recurrent stroke; at the same time, it seems to be reasonable to transiently stop anticoagulation in consideration of the high risk of hemorrhagic transformation of these patients.

Chapter 2. Atrial fibrillation and cardioembolic stroke

2.1 Prognosis of cardioembolic ischemic stroke

Cardiac embolism accounts for approximately 20% of ischemic strokes, and nonvalvular atrial fibrillation (NVAF) is the most common source of cardioembolic ischemic stroke, causing 10%–12% of all ischemic strokes (Goldstein LB. et al. 2011; Flint AC. et al. 2012) and 25% of strokes in patients older than 80 years.

A report comparing ischemic stroke in patients with AF and those with carotid disease from two major trials found that the ratio of hemispheric to retinal events was 25:1 with AF compared with 2:1 with carotid disease (Anderson DC. et al. 2002).

Moreover, AF is associated with longer transient ischemic attacks (TIAs) than carotid disease (Harrison MJ and Marshall J. 1984), and it has been recently observed that longer TIAs are more often associated with diffusivity restriction in acute MRI, thus suggesting that they should be classified as minor strokes according to the revised American Heart Association definition (Easton JD. et al. 2009).

All these data suggest that AF is associated with more severe ischemic strokes at presentation and with worse outcome both in terms of disability and mortality than those who have an ischemic stroke in the absence of AF, even

after adjustment for the advanced age of patients with AF-related stroke (Lin HJ. et al. 1996; Jørgensen HS. et al. 1996; Lamassa M. et al. 2001).

AF is also associated with silent cerebral infarctions and TIAs (Ezekowitz MD. et al. 1995; Kempster PA. et al. 1988; Cullinane M. et al. 1998), even in patients under oral anticoagulation.

On the other side, ischemic stroke in anticoagulated AF patients are typically smaller and carry a lower burden of mortality compared with not anticoagulated ones (Hylek EM. et al. 2003).

It is reasonable to assume that microembolization is common in AF patients, even despite oral anticoagulant therapy, but also that recurrence of ischemic stroke in treated AF patients may be due to small-size emboli and to a higher rate of strokes caused by other mechanisms, mainly by cerebral small artery disease (Hylek EM. et al. 2003).

Not only the long-term risk of ischemic stroke is higher in NVAF patients. In fact, the risk of an early recurrence of ischemic stroke, defined as a new stroke of presumed embolic origin, occurring within the first 2 weeks from an index event, is significantly higher in patients with NVAF than in strokes of other origins, with estimated rates ranging between 0.1% and 1.3% per day (Lin HJ. et al. 1996; Jørgensen HS. et al. 1996).

2.2 Risk of hemorrhagic transformation in cardioembolic stroke

Hemorrhagic transformation (HT), is a complication of acute ischemic stroke associated with poor long-term outcomes (Lei C. et al. 2014).

HT is the appearance of blood in the context of an ischemic lesion, and is usually defined as as any degree of hyperdensity within the area of low attenuation at brain CT scan, and which was not visible in the first acute CT scan (Wolpert SM. et al. 1993). On MRI, HT is defined as hypointensity on axial T1-weighted (T1W) or T2-weighted (T2W) images.

2.2.1 Classification of hemorrhagic transformation

The classification of HT distinguishes 4 degrees of HT (Wolpert SM. et al. 1993; Paciaroni M. et al. 2008):

- Hemorrhagic infarction type 1 (HI 1), characterized by small hyperdense petechiae;
- Hemorrhagic infarction type 2 (HI 2), characterized by confluent hyperdensity throughout the infarct zone without mass effect;
- Parenchymal hematoma type 1 (PH 1), a homogeneous hyperdensity with mass effect which occupy less than 30% of the infarct zone;
- Parenchimal hematoma type 2 (PH 2), a homogeneous hyperdensity occupying more than 30% of the infarct zone, with significant mass effect.

HT can be either spontaneous or associated with acute reperfusion therapies, and in major clinical trials on thrombolysis, it was considered to be symptomatic if associated with an increase of 4 points or more in the NIHSS score (Hacke W. et al. 2008).

Different determinants have been investigated for their association with HT; its incidence depends on many factors, such as age, blood glucose level, the use of thrombolytic therapy, and time window between stroke onset and start of the therapy (Jaillard A. et al. 1999; Kidwell CS. et al. 2002; The NINDS t-PA Stroke Study Group 1997).

The rate of spontaneous HT ranges from 13% to 43% for asymptomatic ones, and from 0.6% to 20% for symptomatic ones; therapy with rtPA increases the risk of HT, with rates ranging from 4.5 to 39.6% for asymptomatic HT and from 5.2 to 7.3% for symptomatic HT (Sussman ES. et al. 2013; Zhang J. et al. 2014); this data are from the major clinical trials on IV thrombolysis, which included only MCA strokes. A large cohort of consecutive patients with acute ischemic stroke found the incidence of HI to be about 9%, whereas that of PH was about 3% (Paciaroni M. et al. 2008).

HT in posterior circulation strokes are derived by observational studies on small cohorts of patients; one of these studies has reported posterior circulation strokes to have a lower risk of spontaneous HT in comparison to anterior circulation ones (Valentino F. et al. 2017). A second study has reported a lower degree of HT after any kind of reperfusion therapy in posterior

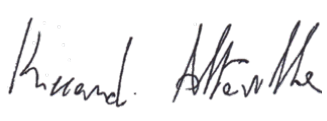
circulation strokes (Lee M. et al. 2012), and its authors suggested that the lower risk of HT can be attributable to the smaller size of posterior circulation strokes and to the different anatomy of collateral circulation, being the majority of posterior strokes caused by occlusion of terminal perforating arteries.

2.2.2 Risk factors for hemorrhagic transformation

The following risk factors for HT have been identified and studied (Zhang J. et al. 2014):

- Dimension of the ischemic stroke: there is a positive correlation between the stroke area and the incidence of HT (Tan S. et al. 2014; Terruso V. et al. 2009) with risk remarkably increasing in case of massive infarction (Wang BG. et al. 2014; Kerenyi L. et al. 2006). The phenomenon is due also to the presence of oedema, which causes compression of the peripheral vasculature, and thus increases the risk of HT after its resolution.
- Area of stroke: HT often occurs in the cerebral cortex and in grey matter, because these areas are full of collateral vessels which can cause a reperfusion injury.
- NIHSS score: higher NIHSS is a predictor of larger strokes, thus it is also a predictor of HT (Kidwell CS. et al. 2002).

- Hyperglycemia: elevated blood glucose in the setting of ischemic stroke can be an expression of either diabetes mellitus (already diagnosed or not), or a stress response to the acute clinical situation. Whatever the cause, hyperglycemia has been related to an increased risk of HT both in experimental animal models of stroke (Xing Y. et al. 2011) and in clinical trials (Paciaroni M. et al. 2008). Hyperglycemia during acute ischemic stroke predisposes to PH with a linear relationship (Paciaroni M. et al. 2009). The proposed mechanism of hyperglycemia is the hypoxia and malnutrition of the artery wall, and the inhibition of the autoregulation of cerebral vessels with increased stiffness, all factors promoting degeneration and necrosis.
- Lower total cholesterol levels and LDL-cholesterol levels are associated to HT (Nardi K. et al. 2011; Bang OY. Et al. 2007; D'Amelio M. et al. 2011), with a mechanism not yet established.
- Lower platelet count is a risk factor for early HT in patients with non-lacunar ischemic stroke (Prodan CI. et al. 2010).
- Collateral vessels: the presence of good collaterals favours the ischemic penumbra, and thus it limits the size of stroke. Once again, with poor collaterals stroke size are greater and the frequency of HT higher (Bang OY et al. 2011).
- IV rt-PA: thrombolytic treatment is independently associated with HT (Paciaroni M. et al. 2008).



- Atrial fibrillation: AF is associated with larger size of ischemic strokes and thus with an increased risk of HT (Tan S. et al. 2014, Nogueira RG. et al. 2014) and worse outcome (Lee JH. Et al. 2010). Some studies also found a correlation between the volume of oedema at baseline CT scan in cardioembolic stroke, with a risk of about 95% in case of >10 cm^3 (Tu HT. et al.2013).

2.3 Effect of hemorrhagic transformation on outcomes

Previous studies suggest that HT does not have a serious negative effect on the clinical outcome in the majority of stroke patients. Quite the opposite, mild to moderate HT can represent a sign of successful treatment and vascular recanalization (Kablau M. et al. 2011). However, some other data suggest that the prognosis is dependent on the type of HT, and that PH2 is a significant predictor of early neurological deterioration and higher mortality at 3 months (Sussmann ES. et al. 2013; D'Amelio M. et al. 2014; Fiorelli M. et al. 1999).

Chapter 3. Anticoagulation in secondary stroke prevention

3.1 Anticoagulation

Oral anticoagulant therapy (OAC) is the treatment of choice for secondary prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF). The currently approved OACs are vitamin K antagonists (VKAs) and non vitamin K-based antagonist oral anticoagulants (NOACs).

Atrial fibrillation is the most common cause of cardioembolic stroke, but there are other potential cardiac sources of embolism for which anticoagulation therapy may be indicated in select cases. Among them:

- Mechanical heart valves and a subpopulation of high-risk patients with bioprosthetic valves
- Left ventricular thrombus
- Dilated cardiomyopathy with reduction of ejection fraction
- Rheumatic valve disease
- Recent myocardial infarction in high-risk patients

Long-term anticoagulation with warfarin, dabigatran, rivaroxaban, apixaban or edoxaban is highly effective in reducing the rate of ischemic recurrence after an index ischemic stroke in AF patients. However, their use is also associated with an increased risk of major bleeding.

3.1.1 Warfarin

A pooled analysis of six randomized trials on patients with stroke and AF demonstrated that aspirin alone does not adequately protect against ischemic recurrence, with a stroke risk of approximately 10% per year (van Walraven C. et al. 2002); while, treatment with adjusted-dose warfarin (with target international normalized ratio 2 to 3) reduced this risk to 4% per year.

Another analysis from the European Atrial Fibrillation Trial (EAFT) and Stroke Prevention in Atrial Fibrillation (SPAF) III of 834 patients with prior nondisabling ischemic stroke at study entry found similar results; in particular this analysis found that the long-term risk of recurrent stroke was lower in patients with a prior TIA than in those with a completed ischemic stroke (Hart RG. et al. 2004), and that the reduction in stroke recurrence risk with warfarin therapy was lower than the risk with aspirin in both groups: 3% versus 7% per year with aspirin in patients with a TIA and 4% versus 11% per year in ischemic stroke.

3.1.2 Dabigatran

Dabigatran is a direct thrombin (factor II of the coagulation cascade) inhibitor and was the first drug, among non vitamin-K anticoagulants, approved in NVAF patients.

The drug was compared with adjusted-dose warfarin in a trial of non-inferiority involving over 18,000 AF patients, the RE-LY study (Connolly SJ. et al. 2009) with two dosages: 110 mg twice a day and 150 mg twice a day.

Dabigatran, at the dosage of 110 mg, resulted non-inferior to warfarin in the prevention of ischemic stroke, and safer in respect to major extra and intracranial bleedings; at the dosage of 150 mg it resulted superior to warfarin, with a comparable risk of hemorrhage. The two tested dosages are currently approved for secondary prevention of stroke in NVAF patients.

3.1.3 Rivaroxaban

Rivaroxaban is an inhibitor of the activated factor X of the coagulation cascade (Xa), and was compared with adjusted-dose warfarin in the ROCKET AF trial of over 14,000 patients. The drug was found to be non-inferior (1.7 versus 2.2 percent per year, respectively) with regard to the primary composite end point of stroke or non-central nervous systemic embolism (Patel MR. et al. 2011).

Similar to the entire cohort, there was no significant difference in the primary composite outcome between rivaroxaban and in the subgroup of patients (52%) with prior stroke (2.79% versus 2.96% per year) (Hankey GJ. et al. 2012).

3.1.4 Apixaban

Apixaban is an Xa inhibitor which was tested in a non-inferiority trial against warfarin in the ARISTOTLE trial involving over 18,000 patients.

Apixaban resulted being superior to warfarin in preventing stroke or systemic embolism (1.3% versus 1.6%), and caused less major bleeding (2.1% versus 3.1%), resulting in a lower overall mortality (3.5% versus 3.9%) (Granger CB. et al. 2011).

Among the 3,436 subjects with a prior stroke or TIA, there was no significant difference in stroke and systemic embolism between apixaban and warfarin (apixaban 2.5% versus warfarin 3.2%).

3.1.5 Edoxaban

Edoxaban, the most recent Xa inhibitor currently approved for secondary prevention of stroke in NVAF, was compared to warfarin in the ENGAGE TIMI 48 trial of over 21,000 patients (Giugliano RP. et al. 2013). Edoxaban was found to be non-inferior to warfarin with regard to the primary efficacy endpoint, and caused less bleeding. Outcomes were similar in the subgroup of patients with prior stroke or transient ischemic attack as in the entire cohort.

3.2 Differences between vitamin k-based and direct oral anticoagulants

Warfarin and other vitamin k-based oral anticoagulants (VKAs) are slower than NOACs in reaching the therapeutic target dose, and their efficacy is measured through international normalized ratio (INR), as the effect is reached through an inhibition of vitamin-K dependent coagulation factors, which causes a prolongation of prothrombin time (PT). Different factors, including genetic ones (i.e. enzymatic polymorphisms) and environmental ones (i.e. diets, gastrointestinal flora) influence the bioavailability of warfarin, and thus its dosage and the rapidity in reaching the therapeutic INR.

On the other hand, 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 1-2 hours) and their fast reversal, similar to heparin in that respect. Moreover, their standard dosages do not require titration, whereas VKAs do.

3.3 Heparin in acute ischemic stroke

The use of heparin in acute ischemic stroke has a controversial story. After empiric use of unfractioned heparin (UFH), the International Stroke Trial (IST, 1997) and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST, 1998) evaluated the use of heparin in the acute phase of stroke. In the IST trial, patients were randomized to receive low-dose heparin (5000 mg twice daily) or medium-dose heparin (12,500 mg twice daily) and either aspirin (300 mg daily) or placebo for 14 days or until discharge; it was observed that patients

on heparin had significantly fewer recurrent ischemic strokes within 14 days but also a significant increase in hemorrhagic transformation.

Subsequent large randomized trials confirmed the results of the IST (Bath PM et al. 2001; Wong KS et al. 2007; Diener HC et al. 2001) and a Cochrane review on 11 trials with over 2000 patients demonstrated an increased risk for fatal intracranial hemorrhages in patients treated with acute anticoagulation (Sandercock PAG et al. 2009).

A recent meta-analysis on seven trials evaluated patients with acute cardioembolic stroke who received anticoagulation (either UFH, LMWH, or heparinoid) within 48 h of stroke onset, and found a non-significant reduction in early stroke recurrence (within 7–14 days), but a significant increase in the risk of symptomatic brain hemorrhage, and no significant difference in death or disability at 3 months. Moreover, in the same meta-analysis, patients taking aspirin in the first 14 days after stroke had a reduced risk of death and disability in comparison to those under heparin (Paciaroni M. et al. 2007).

Current international guidelines do not recommend any kind of heparin or heparinoid in acute stroke care (ASA/AHA 2018; ESO 2008).

With regard of cardioembolic stroke due to atrial fibrillation, a subgroup analysis of the IST trial found that heparin reduced ischemic stroke recurrence, but also increased the risk of hemorrhagic transformation, without adding a benefit in 6-month functional outcome (Saxena R. et al. 2001), and both the TOAST and TAIST trials found no difference in outcome between patients with acute anticoagulation and those without (TOAST, 1998; Bath PM et al. 2001).

However, it can be argued that some subgroups of patients at high risk could benefit from immediate anticoagulation; for example those with a visible left atrial appendage thrombus, reduced atrial appendage emptying velocities, or spontaneous contrast on their echocardiogram, indicating high thrombotic potential (The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography, 1998; Mügge A. et al. 1994; Black IW et al. 1991; Vincelj J. 2002), or those who have other factors associated to AF, such as left ventricle thrombus or mechanical heart valves (Ruff IM. et al. 2015).

3.4 When to start anticoagulation after ischemic stroke

The relatively high risk of early ischemic recurrence (see chapter 2) in the first days after ischemic stroke in AF patients addresses the issue of the correct time to start or resume oral anticoagulation; on the other side, the same patients also have an increased risk of early hemorrhagic transformation (see chapter 2).

An analysis retrospectively conducted on the VISTA database confirmed that the early use of anticoagulants within 2–3 days after stroke were associated with a significant reduction of stroke recurrence over the following weeks, without an increased risk of symptomatic intracerebral bleedings; this was also true for antiplatelet therapy, but with a minor effect (5).

The guidelines of European Society of Cardiology (ESC) empirically suggest to introduce oral anticoagulant therapy between 1 and 12 days after an ischemic stroke, considering stroke severity (Heidbuchel H. et al. 2013). In case of TIA (confirmed by negative DWI at brain MRI), anticoagulation can be started immediately or continued in previously treated patients. In case of mild stroke (NIHSS <8) anticoagulation can be started after 72 hours; in case of moderate stroke (NIHSS 8 – 15) after 6 days, and in case of severe stroke (NIHSS ≥16) after 12 days. In the case of moderate or severe strokes, ESC guidelines also suggest to perform a control brain imaging (preferably MRI) at day 6 or 12, respectively, to evaluate the presence of HT before starting anticoagulation (Kirchhof P. et al. 2016).

In the absence of large randomized trials, the optimal time to start oral anticoagulation has been addressed by two recent prospective, observational studies, RAF and RAF NOACs.

3.4.1 The RAF study

The Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation (RAF) trial (Paciaroni M. et al. 2015) was an international prospective multicentric study which enrolled 1029 patients with acute ischemic stroke and AF. The aims of the study were to evaluate at 90 days from the acute event the following endpoints:

(1) the risk of recurrent ischemic embolic event and severe bleeding (both intra and extracranial);

(2) the risk factors associated with ischemic stroke recurrence, systemic embolism, and symptomatic cerebral bleeding;

(3) the risk of recurrence and bleeding associated with anticoagulant therapy and its timing.

Of the 1,029 enrolled patients, 123 had 128 events (12.6%). Of these events, 77 (7.6%) were ischemic strokes or transient ischemic attack or systemic embolism; 37 (3.6%) were symptomatic cerebral bleeding, and 14 (1.4%) major extracranial bleeding.

Using the adjusted Cox regression analysis, the RAF study found that starting anticoagulants 4 to 14 days after stroke onset was associated with a significant reduction in primary study outcome, compared with treatment started before 4 or after 14 days, with a hazard ratio of 0.53 (95% confidence interval 0.30–0.93).

The RAF study also observed that high CHA_2DS_2-VASc score, higher NIHSS at admission, large ischemic lesions; and type of anticoagulant administered were all independent factors for a greater risk of both ischemic recurrence and bleedings.

Finally, it was observed that, patients treated with oral anticoagulants alone had better outcomes compared with patients treated with low molecular weight heparins alone or before oral anticoagulants.

3.4.2 The RAF NOACs study

In the RAF study, <10% of the patients were treated with NOACs. Since the use of NOACs is becoming more frequent, and these drugs appear to be safer than VKAs with respect to warfarin (see above), another trial focused on its use after ischemic stroke.

The Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants (RAF-NOACs) was an international, prospective, observational, multicentric study in patients with acute stroke and AF treated with NOACs (Dabigatran, Rivaroxaban and Apixaban; Edoxaban was not yet available for commercial use at the time of enrolment) for secondary prevention (Paciaroni M. et al. 2017). Like the RAF study, the RAF NOACs study evaluated, the following endpoints at 90 days:

(1) the rates of recurrence of ischemic embolic events and severe bleedings (both intra- and extracranial) and their timing;

(2) the risk factors associated with ischemic stroke recurrence, systemic embolism, symptomatic intracranial bleeding, and severe extracerebral hemorrhage.

The study enrolled 1,127 patients: 381 (33.8%) were treated with dabigatran, 366 (32.5%) with rivaroxaban, and 380 (33.7%) with apixaban.

32 patients (2.8%) had an early ischemic recurrence, and 27 (2.4%) had a major bleeding. The study observed that patients who started NOACs within 2 days after acute stroke had a composite rate of ischemic recurrence and major bleeding of 12.4%, versus 2.1% of patients who initiated NOACs between 3 and 14 days and 9.1% of those who initiated >14 days after acute stroke.

Chapter 4. Experimental work

4.1 Introduction

Oral anticoagulant therapy (OAC) is the treatment of choice for secondary prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF). The currently approved OACs are vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs). VKAs are slower than NOACs in reaching the therapeutic target dose, and their efficacy is measured through international normalized ratio (INR), as the effect is reached through an inhibition of vitamin-K dependent coagulation factors, which causes a prolongation of prothrombin time (PT) and INR. In some cases, temporary therapy with full-dose low molecular weight heparin (LMWH) can be given alongside warfarin until the therapeutic INR level is achieved; in this way, bridging therapy may protect against a transient prothrombotic effect during initiation of OAC treatment (Douketis JD et al. 2012).

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 (Paciaroni M. et al. 2007) in particular in the presence of atrial fibrillation (Whiteley WN. et al. 2013), there are still anecdotal reports of its use in selected

patients (Al-Sadat A. et al. 2002; Caplan LR. 2003). Mostly, acute heparin treatment is used as bridging therapy until the therapeutic range of OACs is achieved, so-called bridging therapy (Douketis JD et al. 2012).

By using data from the prospective RAF (Paciaroni M. et al. 2015) and RAF-NOACs (Paciaroni M. et al. 2017) studies, we aimed to evaluate 1) clinical profiles of patients who underwent and who did not undergo bridging therapy; 2) any differences in overall group outcomes; 3) any differences between overall group outcomes according to type of OAC prescribed.

4.2 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 (Paciaroni M. et al. 2015 and 2017). 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 (James PA. et al. 2014), 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 (European Stroke Organisation (ESO) Executive Committee. 2008; Powers WJ. Ee al. 2015; Jauch EC. et al. 2013). 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) (Fuster V. et al. 2006).

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) (Wolpert SM. et al. 1993; Paciaroni M. et al. 2008). 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 (Hacke W. et al. 2008). The sites and sizes of the qualifying infarcts were determined based on standard templates (Tatu L. et al. 1996 and 1998) as: 1) small, when a lesion was ≤1.5 cm in the anterior or posterior circulation; 2) medium, when a lesion was in a cortical superficial 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 cortical superficial 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 ≥1.5 cm in the brain stem or cerebellum (Paciaroni M. et al. 2008).

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 with or before VKAs, in order to cover the time needed by the latter to reach the therapeutic effect (Douketis JD et al. 2012), or as any full-dose (for at least 24 hours) of LMWH prior to the use of a NOAC.

4.2.1 Risk factors

Data on stroke risk factors were collected as previously described (Paciaroni M. et al. 2015 and 2017): age, gender, history of hypertension (blood

pressure of ≥140/90 mm Hg at least twice before stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting glucose level ≥126 mg/dL preprandial on 2 examinations, glucose level ≥200 mg/dL postprandial, or HbA1c≥6.5%, or under antidiabetic treatment), current cigarette smoking, past smoking (cessation less than 5 years ago), hyperlipidemia (total cholesterol ≥200 mg/dL or triglyceride ≥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 (≥300 g per week), obesity (body mass index ≥30 kg/m2), 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 ≥5 mm according to published criteria) were investigated (Wahlund LO. et al. 2001). 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, prior to admission, at baseline and during the follow-up period, were recorded. The CHA_2DS_2-VASc score was calculated before and after the index event (Lip GY et al. 2010).

4.2.2 Evaluation of Outcomes

Patients were followed-up prospectively by 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 (Paciaroni M. et al. 2015 and 2017). 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 haemoglobin 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 (Schulman S. and Kearon C. 2005).

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.

4.3 Statistical analysis

Differences in patient characteristics between the two groups (bridging vs non-bridging therapy) were assessed by means of the Chi square test. Univariate 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.

Multivariate 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_2DS_2VASc score after the event, as well as the histories of previous stroke or TIA, smoking habit, congestive heart failure and/or myocardial infarction.

Univariate 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.

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

4.4 Results

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

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

OAC was initiated with warfarin for 561/1,780 patients (31.52%) and NOACs were started for 1,219/1,780 (68.48%). Mean NIHSS at admission was 7.2±6.3 in the bridging group and 7.7±6.2 in the non-bridging group (p = ns).

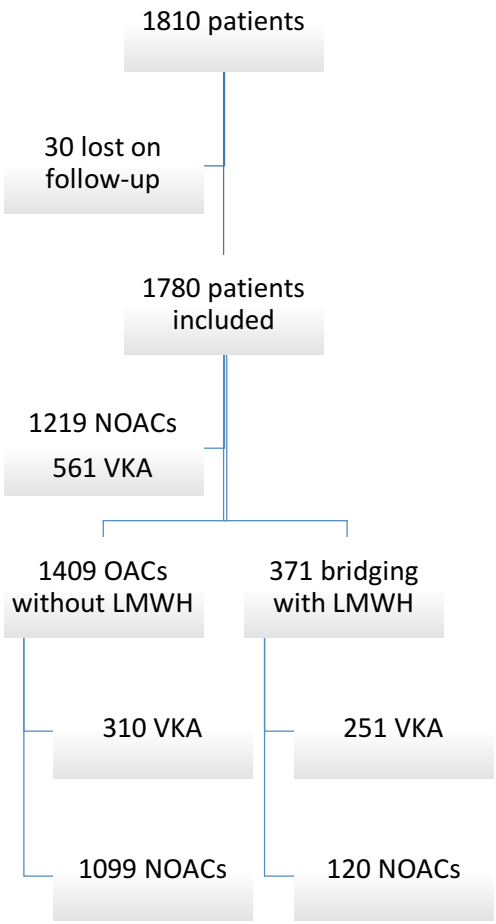


Figure 1: *patients selection. VKA = vitamin k antagonists; NOACs = non-vitamin k oral anticoagulants; LMWH = low molecular weight heparin.*

4.4.1 Clinical characteristics of the bridging and non-bridging groups

The bridging and non-bridging groups differed for age, sex, percentage of medium-sized lesions, of large anterior circulation lesions, and for the presence of leukoaraiosis (Table 1).

clinical characteristics of patients (n = 1810)			
	Bridging therapy (n = 371)	*No bridging therapy (n = 1439)*	*p*
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 (median + IQR)	5 (IQR 9)	5 (IQR 10)	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_2DS_2-VASc after >4	255 (68.7%)	1094 (76.0%)	p=0.03
Lesion features			
Small lesion	153 (41.2%)	582 (40.4%)	n.s.
Medium lesion	153 (41.2%)	469 (32.6%)	0.010
Large anterior circulation lesion	41 (11.1%)	232 (16.1%)	0.006
Large posterior circulation lesion	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 =*

The mean ages were 73.0±9.7 years vs 76.1±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).

At multivariate 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 2).

logistic regression		
	OR (95% CI)	*p*
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_2DS_2-VASc after	1.18 (1.00 - 1.40)	n.s.

Table 2: *clinical features of patients correlated to the use of bridging therapy with LMWH at multivariate analysis.*

4.4.2 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

event, respectively. Major bleedings occurred in 19/42 patients (45.23%, 5.1% of all outcomes) in the bridging group and in 32/72 (44.44%, 2.3% of all outcomes) in the non-bridging group (p=0.08) (Table 3).

Univariate analysis (n = 1780)			
	Bridging (n = 371)	*Non bridging (n = 1409)*	*p*
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 3: *univariate analysis; differences in outcomes at 90 days between patients treated with bridging with LMWH and those without bridging therapy.*

In the multivariate analysis, bridging therapy was associated with combined outcome (OR 2.88; 95% CI 1.87-4.43, p < 0.0001), ischemic event (OR 3.08; 95% CI 1.83-5.19, p < 0.0001) and hemorrhagic event (OR 2.86; 95% CI 1.52-5.37, p = 0.0001) (Table 4).

Logistic regression		
	OR (95% CI)	*p*
Bridging therapy (combined outcome)	2.88 (1.87 - 4.43)	<0.0001
Bridging therapy (ischemic outcome)	3.08 (1.83 - 5.19)	<0.0001
Bridging therapy (hemorrhagic outcome)	2.86 (1.52 - 5.37)	0.001

Table 4: *Multivariate analysis; differences in outcomes at 90 days between patients treated with bridging with LMWH and those without bridging therapy.*

Figure 2 plots the cumulative hazard rates for the combined outcome, in respect to treatment group, according to Cox regression model (HR 1.62; 95% CI 1.02-2.60; p = 0.042).

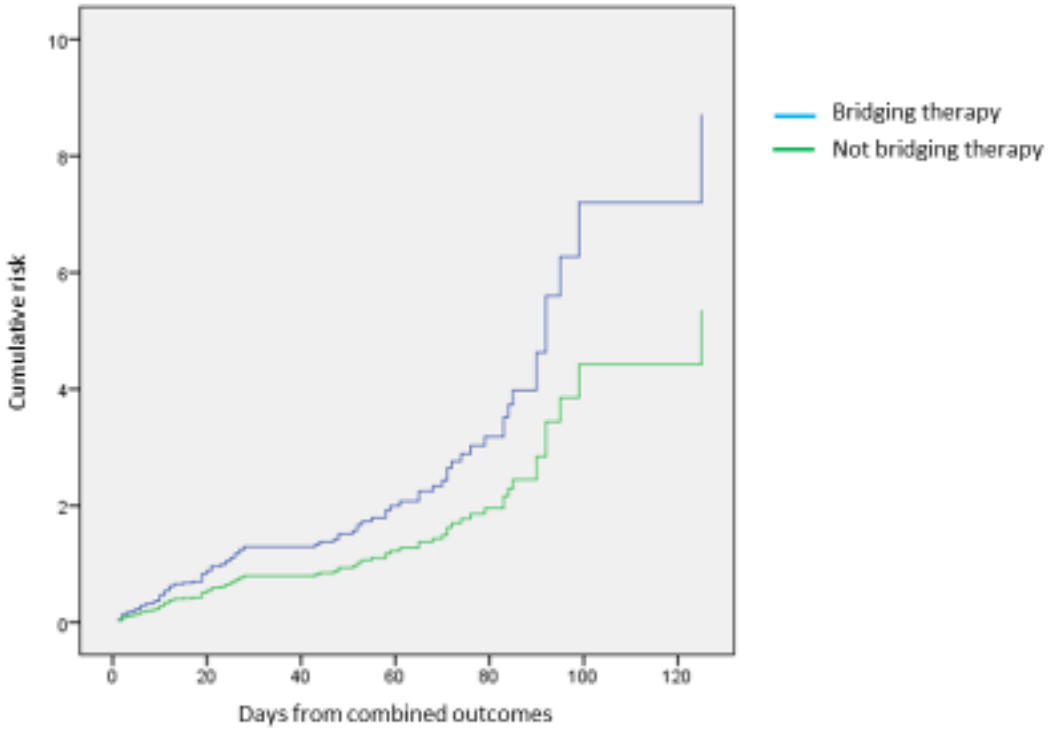


Figure 2: *Cumulative risk of combined outcome according to Cox regression model. Blue line: patients treated with bridging therapy with LMWH. Green line: patients treated without bridging therapy. HR 1.62; 95% CI 1.02-2.60; p = 0.042.*

4.4.3 Outcomes according to 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. Sixty-two (5.1%) and 52 (9.3%) patients, respectively, reached the combined outcome (p = 0.01); 35/1,219 (2.9%) and 38/561 (6.8%) had an ischemic outcome (p = 0.0001). The NOACs and VKAs groups did not differ for hemorrhagic events: 29/1,219 (2.4%) and 22/561 (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.

4.5 Discussion

This combined analysis of the RAF and RAF NOAC studies suggests that full-dose LMWH, as a bridging therapy, resulted in an overall higher risk of early ischemic recurrence and intracranial symptomatic bleeding, independently of the type of OAC administered. However, we were not able to distinguish between either early or late symptomatic HTs, or new symptomatic intracranial bleedings; although it is reasonable to assume that the majority of hemorrhagic outcomes were HTs of the ischemic lesion.

In patients receiving VKAs, the time needed to reach the therapeutic effect and the possibility to rapidly reverse the anticoagulant effect by stopping LMWH, may lead to the perception that LMWH is a safer and more efficacious option in subacute cardioembolic stroke patients. However, previous studies have reported on the risky profile of heparin in acute stroke patients (Paciaroni M. et al. 2007; Whiteley WN. et al. 2013), and it seems that its use is to be considered only in selected types of patients, not including cardioembolic stroke (Ruff IM. et al. 2015).

Regarding NOACs, there is no need for bridging therapy as their pharmacodynamic profiles are similar to heparin, and yet, in our analysis 9.8% of patients treated with NOACs had received a LMWH bridging therapy. This was despite the fact that the same investigators had already access to the results of the RAF study, where patients treated with bridging therapy seemed to be having more combined outcome events (12.3% vs 7%) (Paciaroni M. et al. 2015).

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.

An analysis of the patient profiles, indicated that older patients (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 (Tan S. et al. 2014; Kalinin MN. et al. 2017; Fierini F. et al. 2017), both spontaneous (Tan S. et al. 2014) and after thrombolytic therapy (Liu Y. et al. 2018). Our data were obtained from a real world setting, suggesting that clinical treatment strategies do not always comply with current international guidelines on this topic.

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 points of LWMH and OAC initiation, nor when INR reached 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.

In conclusion, this analysis of 1,780 patients strongly suggests that, in agreement with current international guidelines, following an acute ischemic stroke in patients with AF, bridging therapy with full-dosage LMWH is not to be recommended. Our data argue for avoiding bridging therapy completely in these patients.

1.

Aknowledgements

Il presente studio è stato possibile grazie ai dati forniti da tutti i centri partecipanti agli studi RAF e RAF NOACs, a cui va la mia gratitudine per l'enorme lavoro svolto e per la possibilità di accesso ai dati per la loro analisi.

I miei più sentiti ringraziamenti sono rivolti al prof. Maurizio Paciaroni ed alla prof.ssa Valeria Caso della Stroke Unit di Perugia, che sono la mente e l'anima e dietro al presente studio.

Entrambi sono stati per me maestri preziosi e insostituibili, che hanno saputo trasmettere il rigore e la passione per il metodo scientifico nella ricerca clinica, tollerare i miei errori e spronarmi costantemente al miglioramento. Sono stati guide sempre presenti e modelli di ideale cui tendere, perchè mi hanno mostrato cosa vuol dire saper coniugare l'eccellenza scientifica del Ricercatore all'umanità e alla dedizione del lavoro di Medico.

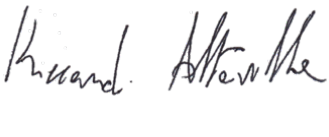
Infine, vorrei ringraziare il prof. Fabrizio Vernieri, che mi ha seguito e supportato lungo tutto il mio percorso universitario, dalla tesi di Laurea fino ad oggi. I miei primi incerti passi nella Clinica Neurologica e nel laboratorio di ricerca sono stati sotto la sua guida, e senza di lui non sarebbero stati possibili.

Bibliography

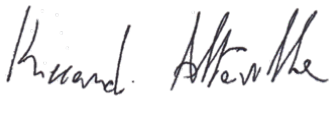
Chapter 1

- Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Jul;44(7):2064-89.
- Furlan M, Marchal G, Viader F, Derlon JM, Baron JC. Spontaneous neurological recovery after stroke and the fate of the ischemic penumbra. Ann Neurol. 1996;40:216–226.
- Olivot JM, Albers GW. Using advanced MRI techniques for patient selection before acute stroke therapy. Curr Treat Options Cardiovasc Med. 2010;12:230–239.
- Brazzelli M, Sandercock P, Chappell F, Celani M, Righetti E, Arestis N, Wardlaw J, Deeks J. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane Database Syst Rev. 2009;(4):CD007424.
- Harmsen P, Lappas G, Rosengren A, Wilhelmsen L. Long-term risk factors for stroke: twenty-eight years of follow-up of 7457 middle-aged men in Göteborg, Sweden. Stroke 2006; 37:1663.
- Hankey GJ. Potential new risk factors for ischemic stroke: what is their potential? Stroke 2006; 37:2181.
- Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. Neurol Clin 2008; 26:871.
- O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 2016; 388:761.
- Jerrard-Dunne P, Cloud G, Hassan A, Markus HS. Evaluating the genetic component of ischemic stroke subtypes: a family history study. Stroke 2003; 34:1364.
- Jood K, Ladenvall C, Rosengren A, et al. Family history in ischemic stroke before 70 years of age: the Sahlgrenska Academy Study on Ischemic Stroke. Stroke 2005; 36:1383.
- Meschia JF, Worrall BB, Rich SS. Genetic susceptibility to ischemic stroke. Nat Rev Neurol 2011; 7:369.
- Howard VJ. Reasons underlying racial differences in stroke incidence and mortality. Stroke 2013; 44:S126.
- Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. Curr Cardiol Rep 2010; 12:6.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45:1545.
- Arnao V, Acciarresi M, Cittadini E, Caso V. Stroke incidence, prevalence and mortality in women worldwide. Int J Stroke. 2016 Apr;11(3):287-301.
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991; 22:312.
- Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360:1903.

- Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet 2014; 383:1899.
- Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010; 375:895.
- Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 2010; 375:938.
- Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007; 6:611.
- Prabhakaran S, Wright CB, Yoshita M, et al. Prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study. Neurology 2008; 70:425.
- Das RR, Seshadri S, Beiser AS, et al. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. Stroke 2008; 39:2929.
- Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. Lancet 2011; 377:1681.
- PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358:1033.
- Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008; 359:1225.
- Liu L, Wang Z, Gong L, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. Hypertens Res 2009; 32:1032.
- Arima H, Chalmers J. PROGRESS: Prevention of Recurrent Stroke. J Clin Hypertens (Greenwich) 2011; 13:693.
- Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. Circulation 1997; 96:3243.
- Kawachi I, Colditz GA, Stampfer MJ, et al. Smoking cessation and decreased risk of stroke in women. JAMA 1993; 269:232.
- Kurth T, Kase CS, Berger K, et al. Smoking and risk of hemorrhagic stroke in women. Stroke 2003; 34:2792.
- Wilson PW, Hoeg JM, D'Agostino RB, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. N Engl J Med 1997; 337:516.
- Li C, Engström G, Hedblad B, et al. Risk factors for stroke in subjects with normal blood pressure: a prospective cohort study. Stroke 2005; 36:234.
- Wolf PA, D'Agostino RB, Kannel WB, et al. Cigarette smoking as a risk factor for stroke. The Framingham Study. JAMA 1988; 259:1025.
- Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. Stroke 2013; 44:2821.
- Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and the risk of stroke in middle-aged men. JAMA 1995; 274:155.
- Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology 2006; 67:1960.
- Janghorbani M, Hu FB, Willett WC, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study. Diabetes Care 2007; 30:1730.
- Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010; 375:2215.



- Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 2012; 11:261.
- Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet 2014; 383:1973.
- Vitelli LL, Shahar E, Heiss G, et al. Glycosylated hemoglobin level and carotid intimal-medial thickening in nondiabetic individuals. The Atherosclerosis Risk in Communities Study. Diabetes Care 1997; 20:1454.
- Jørgensen L, Jenssen T, Joakimsen O, et al. Glycated hemoglobin level is strongly related to the prevalence of carotid artery plaques with high echogenicity in nondiabetic individuals: the Tromsø study. Circulation 2004; 110:466.
- Yaghi S, Elkind MS. Lipids and Cerebrovascular Disease: Research and Practice. Stroke 2015; 46:3322.
- Leppälä JM, Virtamo J, Fogelholm R, et al. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. Stroke 1999; 30:2535.
- Zhang X, Patel A, Horibe H, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol 2003; 32:563.
- Kurth T, Everett BM, Buring JE, et al. Lipid levels and the risk of ischemic stroke in women. Neurology 2007; 68:556.
- Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. Stroke 2002; 33:1863.
- Tirschwell DL, Smith NL, Heckbert SR, et al. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology 2004; 63:1868.
- Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2003; 34:623.
- Bots ML, Elwood PC, Nikitin Y, et al. Total and HDL cholesterol and risk of stroke. EUROSTROKE: a collaborative study among research centres in Europe. J Epidemiol Community Health 2002; 56 Suppl 1:i19.
- Corvol JC, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. Arch Intern Med 2003; 163:669.
- North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325:445.
- MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991; 337:1235.
- de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, Rosvall M, Sitzer M, Buskens E, Bots ML: Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke 2010;41:1294–1297.
- Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO: Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke 1999;30: 2513–2516.
- Marquardt L, Geraghty OC, Mehta Z, Rothwell PM: Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. Stroke 2010;41:e11–e17.
- North American symptomatic carotid endarterectomy trial. Methods, patient characteristics, and progress. Stroke 1991;22:711–720.
- Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European carotid surgery trial (ECST). Lancet 1998;351:1379–1387.



- Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR: Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans affairs cooperative studies program 309 trialist group. JAMA 1991;266:3289–3294.
- Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists' Collaboration: Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361:107–116.
- Endarterectomy for asymptomatic carotid artery stenosis. Executive committee for the asymptomatic carotid atherosclerosis study. JAMA 1995;273:1421–1428.
- Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group: Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491–1502.
- Hobson RW 2nd, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, Wright CB: Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The veterans affairs cooperative study group. N Engl J Med 1993;328:221–227.
- Singh TD, Kramer CL, Mandrekar J, Lanzino G, Rabinstein AA. Asymptomatic Carotid Stenosis: Risk of Progression and Development of Symptoms. Cerebrovasc Dis. 2015;40(5-6):236-43.
- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129:e28–e292.
- Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in Stroke. 2011;42:e26]. Stroke. 2011;42:517–584.
- Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxys- mal atrial fibrillation by 30-day event monitoring in cryptogenic isch- emic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. Stroke. 2012;43:2788–2790.
- Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–2870.
- Lip GY, Nieuwlatt 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.
- Furie KL, Goldstein LB, Albers GW, Khatri P, Neyens R, Turakhia MP, Turan TN, Wood KA; on behalf of the American Heart Association Stroke Council, Council on Quality of Care and Outcomes Research, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advi- sory for healthcare professionals from the American Heart Association/ American Stroke Association [published corrections appear in Stroke. 2013;44:e20 and Stroke. 2012;43:e181]. Stroke. 2012;43:3442–3453.
- The STroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fbrillation. Neurology. 2007;69:546–554.
- EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fbrillation after transient ischaemic attack or minor stroke. Lancet. 1993;342:1255–1262.

- January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014; 130:2071.
- Rizos T, Guntner J, Jenetzky E, Marquardt L, Reichardt C, Becker R, Reinhardt R, Hepp T, Kirchhof P, Aleynichenko E, Ringleb P, Hacke W, Veltkamp R. Continuous stroke unit electrocardiographic monitoring versus 24-hour Holter electrocardiography for detection of paroxysmal atrial fbrillation after stroke. Stroke. 2012;43:2689–2694.
- Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fbrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. Stroke. 2012;43:2788–2790.
- Tayal AH, Callans DJ. Occult atrial fibrillation in ischemic stroke: seek and you shall find. Neurology. 2010;74:1662–1663.
- Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011; 57:223.
- Fuster V, Ryden LE, Cannom DS, et al. 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.
- American College of Cardiology Foundation, American Heart Association, European Society of Cardiology, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation 2013; 127:1916.
- Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37:2893.
- Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285:2370.
- Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375:1695.
- Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA 2013; 309:2480.
- Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 2012; 379:2364.
- Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014; 384:1929.
- Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: a systematic review. JAMA 2015; 313:1451.
- Whiteley WN, Emberson J, Lees KR, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. Lancet Neurol 2016; 15:925.
- Lees KR, Emberson J, Blackwell L, et al. Effects of Alteplase for Acute Stroke on the Distribution of Functional Outcomes: A Pooled Analysis of 9 Trials. Stroke 2016; 47:2373.

- Whiteley WN, Slot KB, Fernandes P, et al. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke 2012; 43:2904.
- Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372:11.
- Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372:1019.
- Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015; 372:2285.
- Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015; 372:1009.
- Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015; 372:2296.
- Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med 2018; 378:11.
- Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med 2018; 378:708.
- Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med. 2018 May 16.

Chapter 2

- Anderson DC, Kappelle LJ, Eliasziw M, et al. Occurrence of hemispheric and retinal ischemia in atrial fibrillation compared with carotid stenosis. Stroke 2002; 33:1963.
- Harrison MJ, Marshall J. Atrial fibrillation, TIAs and completed strokes. Stroke 1984; 15:441.
- Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009; 40:2276.
- Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996; 27:1760.
- Jørgensen HS, Nakayama H, Reith J, et al. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke 1996; 27:1765.
- Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke 2001; 32:392.
- Ezekowitz MD, James KE, Nazarian SM, et al. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Circulation 1995; 92:2178.
- Kempster PA, Gerraty RP, Gates PC. Asymptomatic cerebral infarction in patients with chronic atrial fibrillation. Stroke 1988; 19:955.
- Cullinane M, Wainwright R, Brown A, et al. Asymptomatic embolization in subjects with atrial fibrillation not taking anticoagulants: a prospective study. Stroke 1998; 29:1810.
- Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003; 349:1019.
- Lei C, Wu B, Liu M, Chen Y. Asymptomatic hemorrhagic transformation after acute ischemic stroke: is it clinically innocuous? J Stroke Cerebrovasc Dis. 2014;23:2767–72.
- Sussman ES, Connolly ES Jr. Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke. Front Neurol. 2013;4:69.

- Zhang J, Yang Y, Sun H, Xing Y. Hemorrhagic transformation after cerebral infarction: current concepts and challenges. Ann Transl Med. 2014;2:81.
- Jaillard A, Cornu C, Durieux A, et al. Hemorrhagic transformation in acute ischemic stroke. The MAST-E study. MAST-E Group. Stroke 1999;30:1326-32.
- Kidwell CS, Saver JL, Carneado J, et al. Predictors of hemorrhagic transformation in patients receiving intraarterial thrombolysis. Stroke 2002;33:717-24.
- Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA Stroke Study Group. Stroke 1997;28:2109-18.
- Paciaroni M, Agnelli G, Corea F, et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008;39:2249-56.
- Valentino F, Gentile L, Terruso V, Mastrilli S, Aridon P, Ragonese P, et al. Frequency and determinants for hemorrhagic transformation of posterior cerebral stroke: Posterior ischemic stroke and hemorrhagic transformation. BMC Res Notes. BioMed Central; 2017 Nov 13;10(1):592.
- Lee M, Saver JL, Alger JR, Hao Q, Starkman S, Ali LK, Kim D, Ovbiagele B, Vespa PM, Froehler MT, Tenser MS, Salamon N, Villablanca JP, Jahan R, Duckwiler GR, Tateshima S, Gonzalez N, Vinuela F, Liebeskind DS. Blood–brain barrier permeability derangements in posterior circulation ischemic stroke: frequency and relation to hemorrhagic transformation. J Neurol Sci. 2012;313:142–6.
- Zhang J, Yang Y, Sun H, Xing Y. Hemorrhagic transformation after cerebral infarction: current concepts and challenges. Ann Transl Med. 2014 Aug;2(8):81.
- Tan S, Wang D, Liu M, et al. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. J Neurol 2014;261:905-12.
- Terruso V, D'Amelio M, Di Benedetto N, et al. Frequency and determinants for hemorrhagic transformation of cerebral infarction. Neuroepidemiology 2009;33:261-5.
- Wang BG, Yang N, Lin M, et al. Analysis of Risk Factors of Hemorrhagic Transformation After Acute Ischemic Stroke: Cerebral Microbleeds Do Not Correlate with Hemorrhagic Transformation. Cell Biochem Biophys 2014;70:135-42.
- Kerenyi L, Kardos L, Szász J, et al. Factors influencing hemorrhagic transformation in ischemic stroke: a clinicopathological comparison. Eur J Neurol 2006;13:1251-5.
- Nogueira RG, Gupta R, Jovin TG, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. J Neurointerv Surg 2014. [Epub ahead of print].
- Lee JH, Park KY, Shin JH, et al. Symptomatic hemorrhagic transformation and its predictors in acute ischemic stroke with atrial fibrillation. Eur Neurol 2010;64:193-200.
- Tu HT, Campbell BC, Christensen S, et al. Worse stroke outcome in atrial fibrillation is explained by more severe hypoperfusion, infarct growth, and hemorrhagic transformation. Int J Stroke 2013.
- Kidwell CS, Saver JL, Carneado J, et al. Predictors of hemorrhagic transformation in patients receiving intraarterial thrombolysis. Stroke 2002;33:717-24.
- Xing Y, Jiang X, Yang Y, et al. Hemorrhagic transformation induced by acute hyperglycemia in a rat model of transient focal ischemia. Acta Neurochir Suppl 2011;111:49-54. 18.
- Paciaroni M, Agnelli G, Caso V, et al. Acute hyperglycemia and early hemorrhagic transformation in ischemic stroke. Cerebrovasc Dis 2009;28:119-23.
- Nardi K, Leys D, Eusebi P, et al. Influence of lipid profiles on the risk of hemorrhagic transformation after ischemic stroke: systematic review. Cerebrovasc Dis Extra 2011;1:130-41. 21.
- Bang OY, Saver JL, Liebeskind DS, et al. Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. Neurology 2007;68:737-42. 22.
- D'Amelio M, Terruso V, Famoso G, et al. Cholesterol levels and risk of hemorrhagic transformation after acute ischemic stroke. Cerebrovasc Dis 2011;32:234-8.
- Prodan CI, Stoner JA, Cowan LD, et al. Lower coatedplatelet levels are associated with early hemorrhagic transformation in patients with non-lacunar brain infarction. J Thromb Haemost 2010;8:1185-90.
- Kablau M, Kreisel SH, Sauer T, et al. Predictors and early outcome of hemorrhagic transformation after acute ischemic stroke. Cerebrovasc Dis 2011;32:334-41.
- D'Amelio M, Terruso V, Famoso G, et al. Early and late mortality of spontaneous hemorrhagic transformation of ischemic stroke. J Stroke Cerebrovasc Dis 2014;23:649-54.

- Fiorelli M, Bastianello S, von Kummer R, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke 1999;30:2280-4.

Chapter 3

- van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA 2002; 288:2441.
- Hart RG, Pearce LA, Koudstaal PJ. Transient ischemic attacks in patients with atrial fibrillation: implications for secondary prevention: the European Atrial Fibrillation Trial and Stroke Prevention in Atrial Fibrillation III trial. Stroke 2004; 35:948.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883.
- Hankey GJ, Patel MR, Stevens SR, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol 2012; 11:315.
- Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365:981. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093.
- The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997; 349: 1569–81. 5.
- Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. JAMA. 1998;279: 1265– 72.
- Bath PM et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. Lancet. 2001;358:702–10. 7.
- Wong KS et al. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. Lancet Neurol. 2007;6:407–13. 8.
- Diener HC et al. Treatment of acute ischemic stroke with the lowmolecular-weight heparin certoparin: results of the TOPAS trial. Therapy of Patients with Acute Stroke (TOPAS) Investigators. Stroke J Cereb Circ. 2001;32:22–9. 9.
- Sandercock PAG, Gibson LM, Liu M. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. Cochrane Database Syst Rev. 2009; CD000248.
- Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. Stroke J Cereb Circ. 2001;32:2333–7.
- Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke a metaanalysis of randomized controlled trials. Stroke. 2007;38:423–30.
- Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; 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 Mar;49(3):e46-e110.
- European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507.
- Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Ann Intern Med. 1998; 128: 639–47.
- Mügge A et al. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. J Am Coll Cardiol. 1994;23:599– 607.

- Black IW, Hopkins AP, Lee LC, Walsh WF. Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis. J Am Coll Cardiol. 1991;18:398–404.
- Vincelj J, Sokol I, Jaksić O. Prevalence and clinical significance of left atrial spontaneous echo contrast detected by transesophageal echocardiography. Echocardiography. 2002;19:319–24.
- Ruff IM, Jindal JA. Use of Heparin in Acute Ischemic Stroke: Is There Still a Role? Curr Atheroscler Rep. 2015 Sep;17(9):51.
- Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P; European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013 May;15(5):625-51.
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct 7;37(38):2893-2962.

Chapter 4

- 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 Feb;38(2):423-30.
- Whiteley WN, Adams HP Jr, Bath PM, Berge E, Sandset PM, Dennis M, Murray GD, Wong KS, Sandercock PA. 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 Jun;12(6):539-45.
- Al-Sadat A, Sunbulli M, Chaturvedi S. Use of intravenous heparin by North American neurologists. Stroke 2002; 33: 1574–77.
- Caplan LR. Resolved: heparin may be useful in selected patients with brain ischemia. Stroke 2003; 34: 230–31
- Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. 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 Feb;141(2 Suppl):e326S-e350S.
- Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, Rueckert C, Pezzini A, Poli L, Padovani A, Csiba L, Szabó L, Sohn SI, Tassinari T, Abdul-Rahim AH, Michel P, Cordier M, Vanacker P, Remillard S, Alberti A, Venti M, Scoditti U, Denti L, Orlandi G, Chiti A, Gialdini G, Bovi P, Carletti M, Rigatelli A, Putaala J, Tatlisumak T, Masotti L, Lorenzini G, Tassi R, Guideri F, Martini G, Tsivgoulis G, Vadikolias K, Liantinioti C, Corea F, Del Sette M, Ageno W, De Lodovici ML, Bono G, Baldi A, D'Anna S, Sacco S, Carolei A, Tiseo C, Acciarresi M, D'Amore C, Imberti D, Zabzuni D, Doronin B, Volodina V, Consoli D, Galati F, Pieroni A, Toni D, Monaco S, Baronello MM, Barlinn K, Pallesen LP, Kepplinger J, Bodechtel U, Gerber J, Deleu D, Melikyan G, Ibrahim F, Akhtar N, Mosconi MG, Bubba V, Silvestri I, Lees KR. 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 Aug;46(8):2175-82.
- Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, Chondrogianni M, Bovi P, Carletti M, Cappellari M, Zedde M, Ntaios G, Karagkiozi E, Athanasakis G, Makaritsis K, Silvestrelli G, Lanari A, Ciccone A, Putaala J, Tomppo L, Tatlisumak T, Abdul-Rahim AH, Lees KR, Alberti A, Venti M, Acciarresi M, D'Amore C, Becattini C, Mosconi MG, Cimini LA, Soloperto R, Masotti L, Vannucchi V, Lorenzini G, Tassi R, Guideri F, Acampa M, Martini G, Sohn SI, Marcheselli S, Mumoli N, De Lodovici ML, Bono G, Furie KL, Tadi P, Yaghi S, Toni D, Letteri F, Tassinari T, Kargiotis O, Lotti EM, Flomin Y, Mancuso M, Maccarrone M, Giannini N, Bandini F, Pezzini A, Poli L, Padovani A, Scoditti U, Denti L, Consoli D, Galati F, Sacco S, Carolei A, Tiseo C, Gourbali V, Orlandi G, Giuntini M, Chiti A, Giorli E, Gialdini G, Corea F, Ageno W, Bellesini M, Colombo G, Monaco S, Maimone Baronello M, Karapanayiotides T, Caso V. 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 Nov 29;6(12).
- European Stroke Organisation (ESO) Executive Committee. Guidelines for management of ischemic stroke and transient ischemic attack. Cerebrovasc Dis. 2008;25:457–507.

- James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 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 Feb 5;311(5):507-20.
- Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, Johnston KC, Johnston SC, Khalessi AA, Kidwell CS, Meschia JF, Ovbiagele B, Yavagal DR; American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:3020–3035.
- Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri F, McMullan PW JR, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H. 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. 2013;44:870–947.
- Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL; 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 Aug 15;114(7):e257-354. Erratum in: Circulation. 2007 Aug 7;116(6):e138.
- 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.
- Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, Caso V, Micheli S, Bertolani L, Venti M, Palmerini F, Biagini S, Comi G, Previdi P, Silvestrelli G. 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.
- Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–1329.
- Tatu L, Moulin T, Bogousslavsky J, Duvemoy H. Arterial territories of the human brain: cerebral hemispheres. Neurology. 1998;50:1699–1708.
- Tatu L, Moulin T, Bogousslavsky J, Duvemoy H. Arterial territories of the human brain: brainstem and cerebellum. Neurology. 1996;47:1125–1135.
- Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin A, Sjogren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32:1318–1322.
- 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.
- 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.
- 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.

- 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 Sep 7;17(1):177.
- Fierini F, Poggesi A, Pantoni L. Leukoaraiosis as an outcome predictor in the acute and subacute phases of stroke. Expert Rev Neurother. 2017 Oct;17(10):963-975.
- 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 Feb 15;1681:28-33.
- Ruff IM, Jindal JA. Use of Heparin in Acute Ischemic Stroke: Is There Still a Role? Curr Atheroscler Rep. 2015 Sep;17(9):51.