Impact des microbleeds dans les traitements de phase aiguë et de prévention secondaire de l'ischémie cérébrale

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Impact des microsaignements sur la prise en charge des patients à la phase aiguë de l'infarctus cérébral

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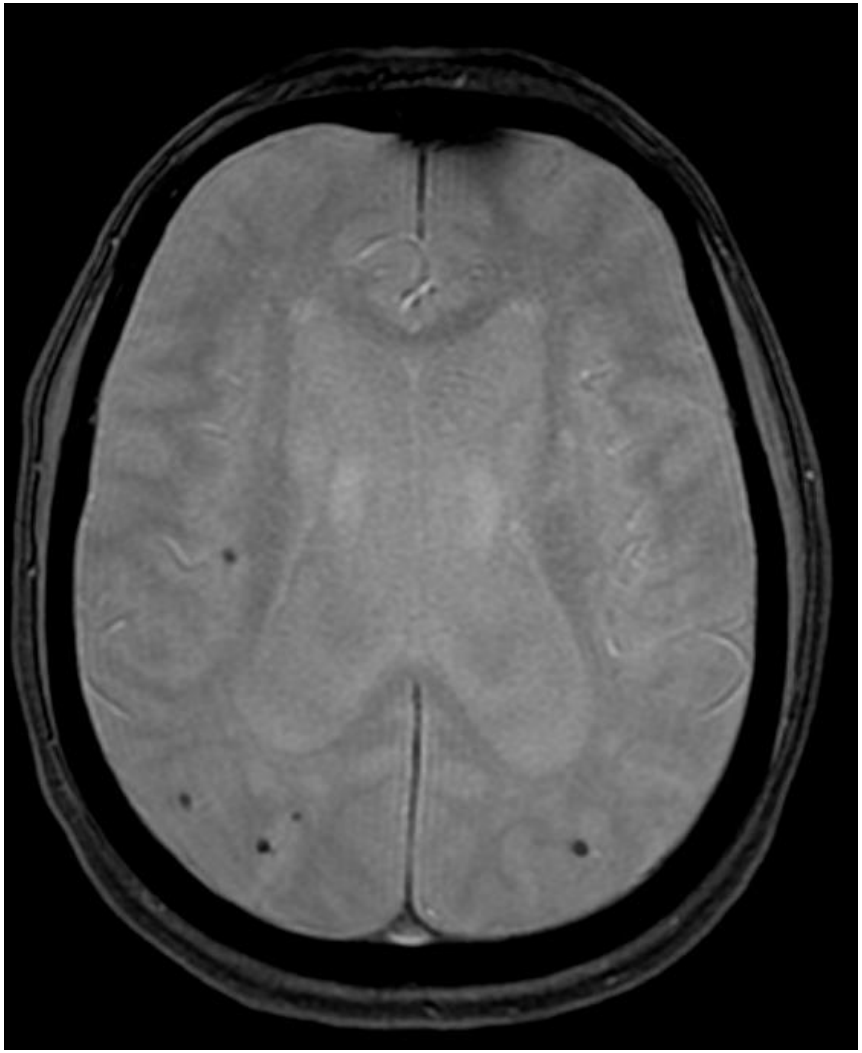
Contexte

- Essais randomisés ayant évalué thrombolyse (IVT) et thrombectomie:
  pas d'information sur l'impact des microsaignements ou d'une hémosidérose focale pour la prise de décision en phase aiguë

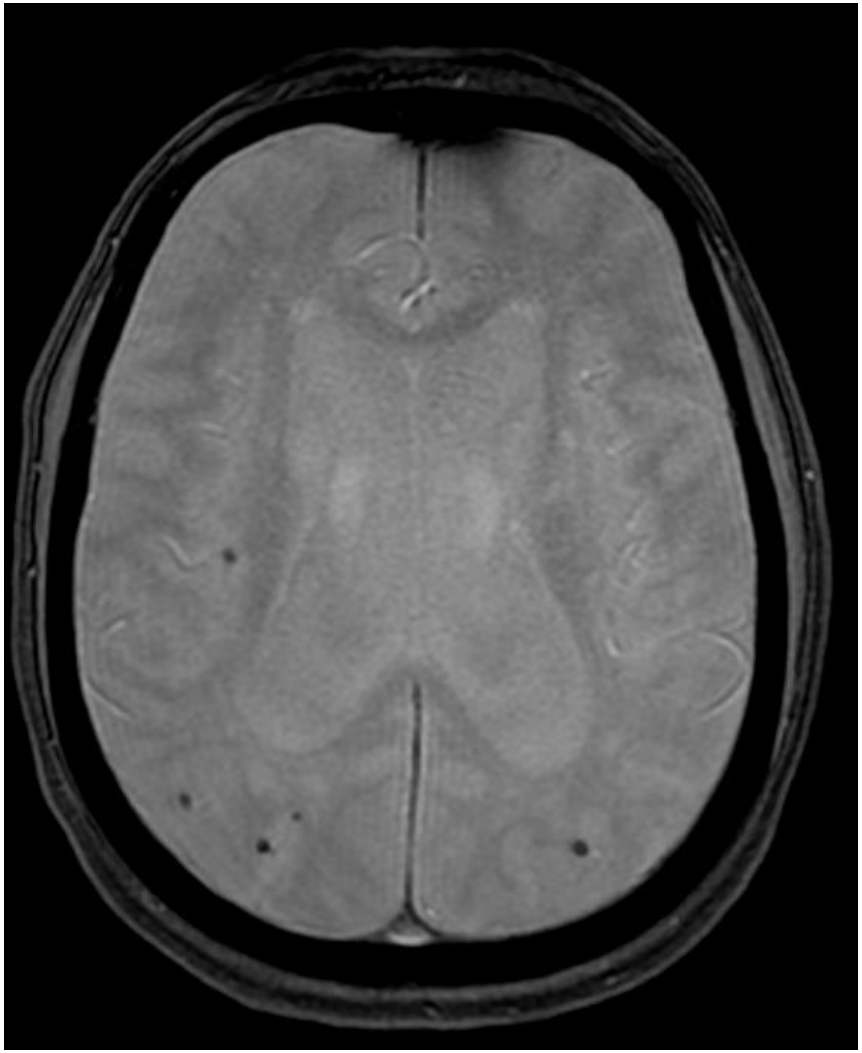
- Données observationnelles uniquement:
  - Surtout concernant microsaignements et IVT



Questions pragmatiques

- Augmentation du risque d'hémorragie intracrânienne symptomatique (sICH) après IVT?
- Augmentation du risque de mauvais pronostic à long terme ?

- Si oui:
  - Est-ce un prédicteur indépendant ?
  - Rapport bénéfice/risque de la thrombolyse défavorable chez certains patients?



Résultats contrastés… 2 exemples

Etude Berlinoise

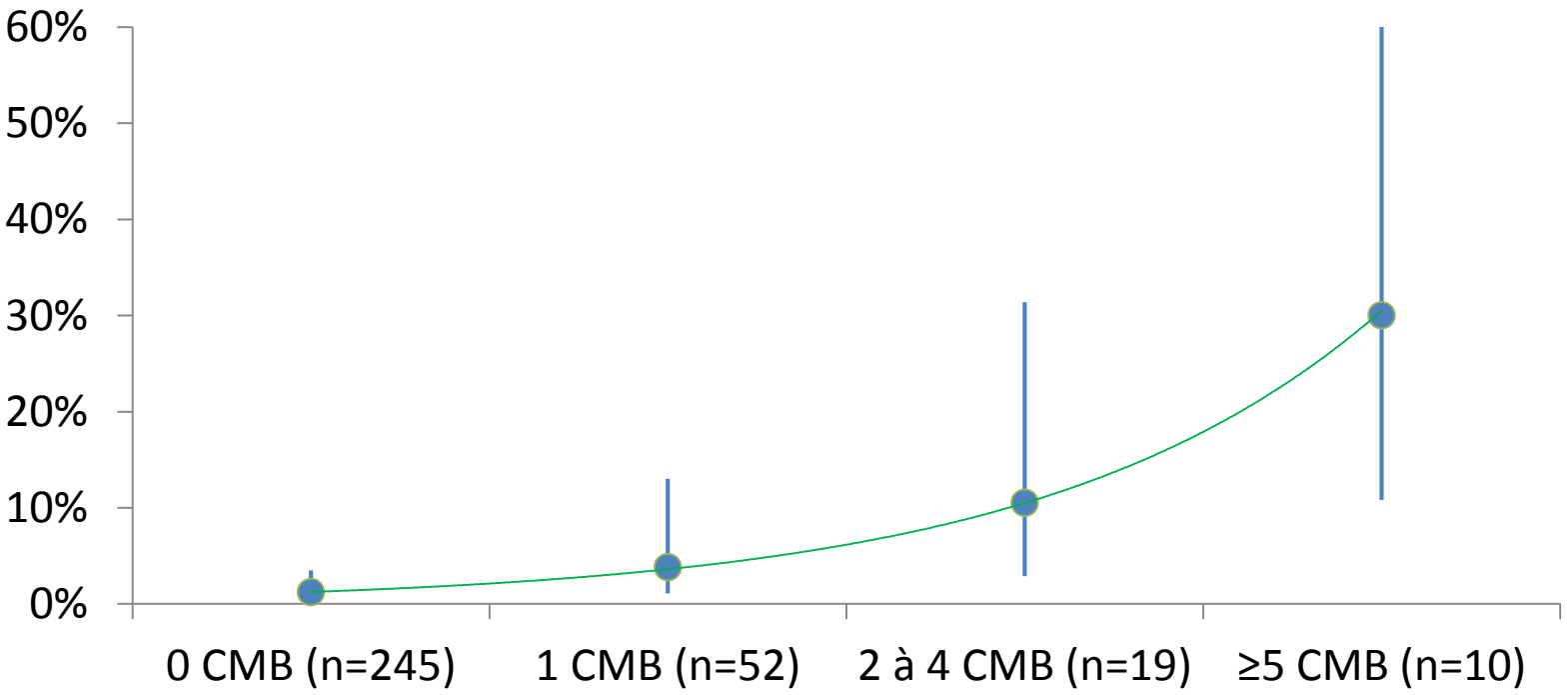
- Etude prospective, monocentrique, N=326, IVT ≤4h30
- T2*/ 3T, Prévalence microsaignement(s): 25%
- Prévalence sICH (ECASS-3): 3,1% (n=10)

- Association entre présence de microsaignement(s) et sICH:
  - Prévalence sICH: 8,6% vs; 1,2%
  - OR=7,63 (IC95% :1,68-46,49)

Dannenberg et al., Stroke 2014

Etude Berlinoise

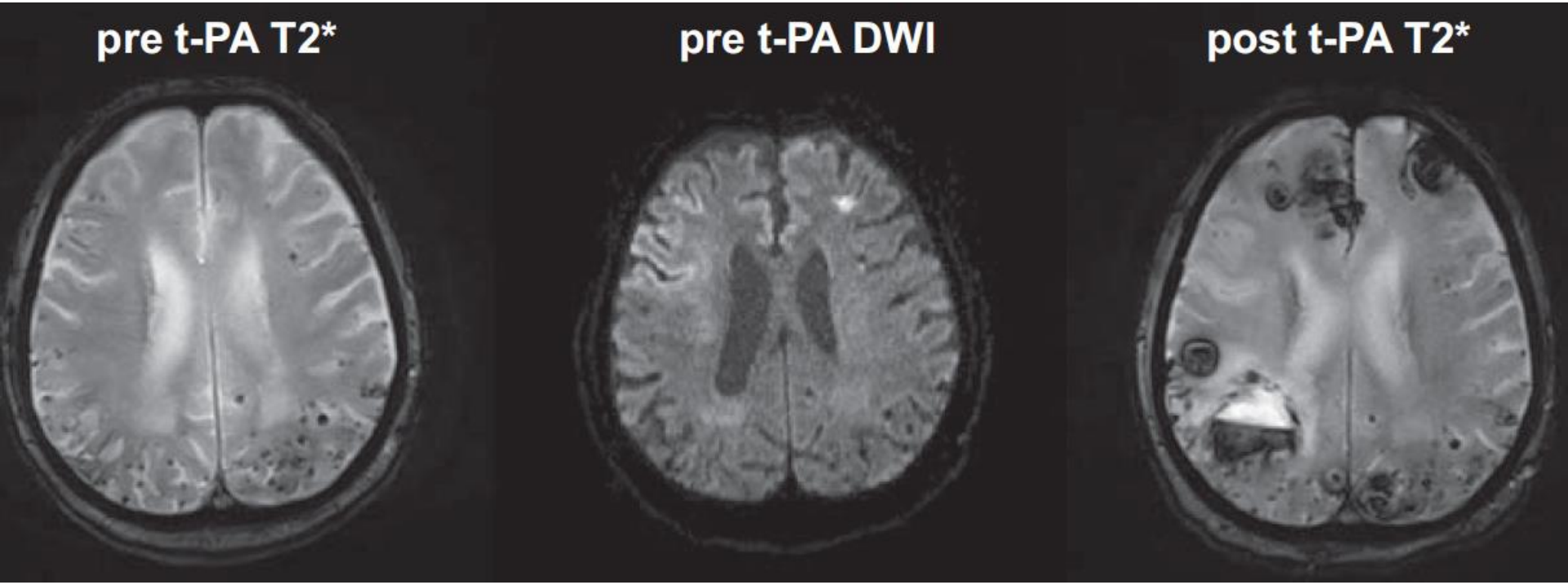
- Incidence sICH en fonction du nombre de microsaignements:



  - Pour chaque augmentation d'un microsaignement: OR=1,19 (IC95% 1,07-1,33)
  - Association persistante après ajustement sur âge, leucopathie, PA systolique, FA…

D'après Dannenberg et al., Stroke 2014

Etude Berlinoise



Dannenberg et al., Stroke 2014

Etude collaborative Sainte-Anne/Lille

- IC traités par TIV seule ≤4h30, après IRM cérébrale
- A Lille (2009-2014) ou Sainte-Anne (2003-2013)
- Cotation des microsaignements selon l'échelle MARS

- Analyse des relations entre microsaignements et:
  - mRS à 3 mois (critère de jugement principal)
  - sICH

Turc et al., Stroke 2015

Description de la population

N=717 (Lille: 375, Ste-Anne: 342)

Variable		Valeur
Age, médiane (IQR)		74 (60-83)
Hypertension artérielle, n (%)		63%
Diabète, n (%)		16%
NIHSS initial, médiane (IQR)		11 (6-18)
Nb de microsaignements, n (%)		
	0	567 (79)
	1	92 (13)
	2-4	33 (5)
	≥5	25 (3)
mRS à 3 mois, médiane (IQR)		2 (1-4)
sICH selon NINDS, n (%)		65 (9)
sICH selon ECASS-3, n (%)		27 (4)

Turc et al., Stroke 2015

Relations entre microsaignements et mRS ou sICH

Critère de jugement	**Charge lésionnelle en microsaignements** (par pas de 1 microsaignement)			
	Analyse univariable		**Analyse multivariables** (ajustement sur âge, HTA, FA)	
	OR brut (IC95%)	P	OR ajusté (IC95%)	P
Analyse ordinale du mRS: Plus mauvais pronostic à 3 mois	1,07 (1,00-1,15)	0,049	1,03 (0,96-1,11)	0,37
mRS à 3 mois >2	1,05 (0,96-1,16)	0,29	1,02 (0,93-1,12)	0,69
sICH (définition NINDS)	1,09 (0,99-1.19)	0,09	1,07 (0,97-1,17)	0,20
sICH (définition ECASS-3)	1,04 (0,89-1,22)	0,62	1,02 (0,86-1,21)	0,83

- Pas d'influence significative de la physiopathologie présumée des microsaignements sur le mRS ou le risque de sICH

Turc et al., Stroke 2015

Microsaignements et sICH post-IVT: revue systématique et méta-analyse (09/2016)

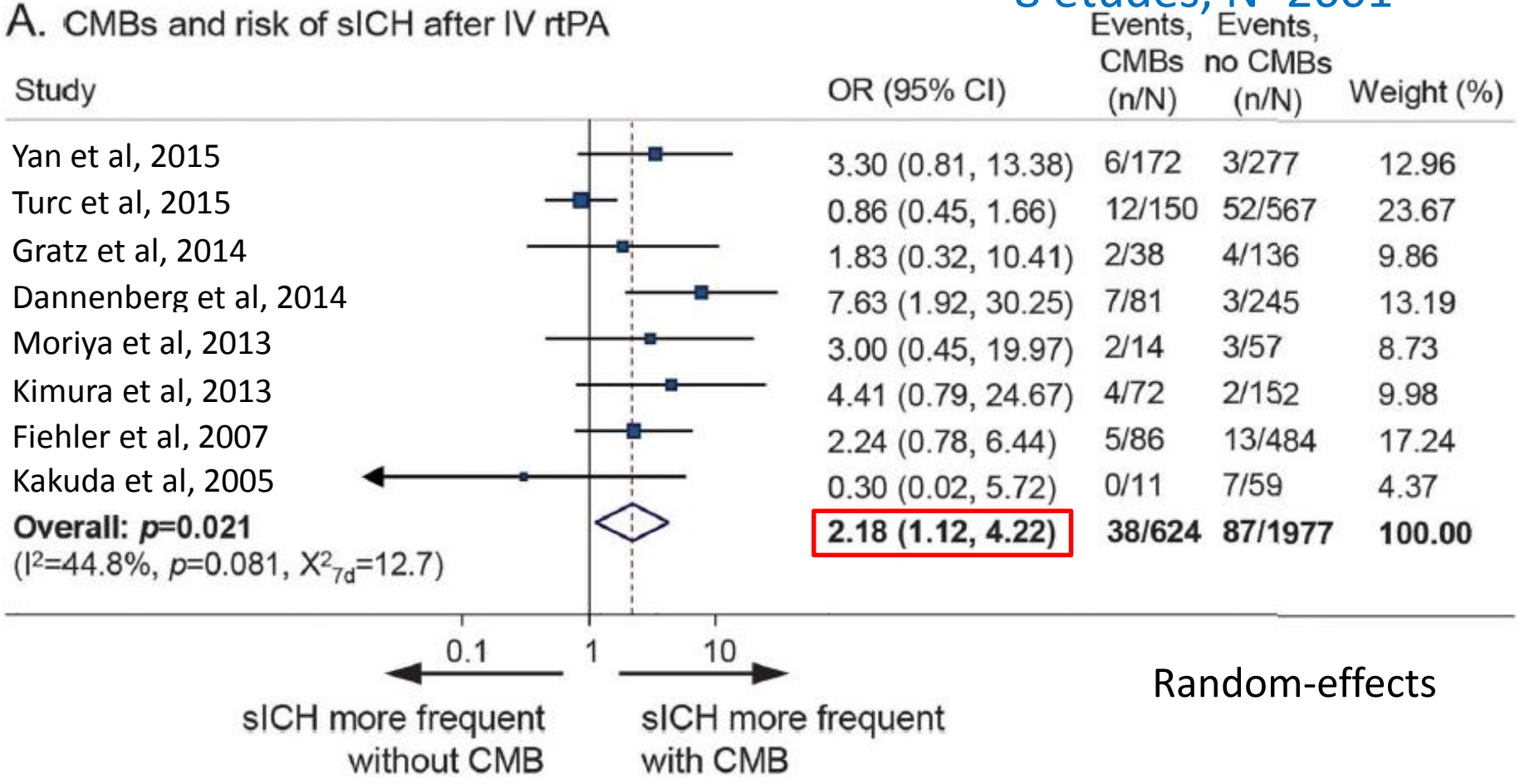
8 études, N=2601

- Méta-analyse sur données agrégées
- Prévalence des microsaignements chez thrombolysés: 24% (18-30%)
- SWI pour 2 études, T2* pour les 6 autres
- Définition sICH: hétérogène; le plus souvent proche d'ECASS-2
- Incidence sICH post-IVT:
  - 5% (4-7%) chez patients avec au moins 1 microsaignement
  - 3% (2-5%) chez patients sans microsaignement

Charidimou et al., Neurology 2016

Microsaignements et sICH post-IVT: revue systématique et méta-analyse (09/2016)

8 études, N=2601

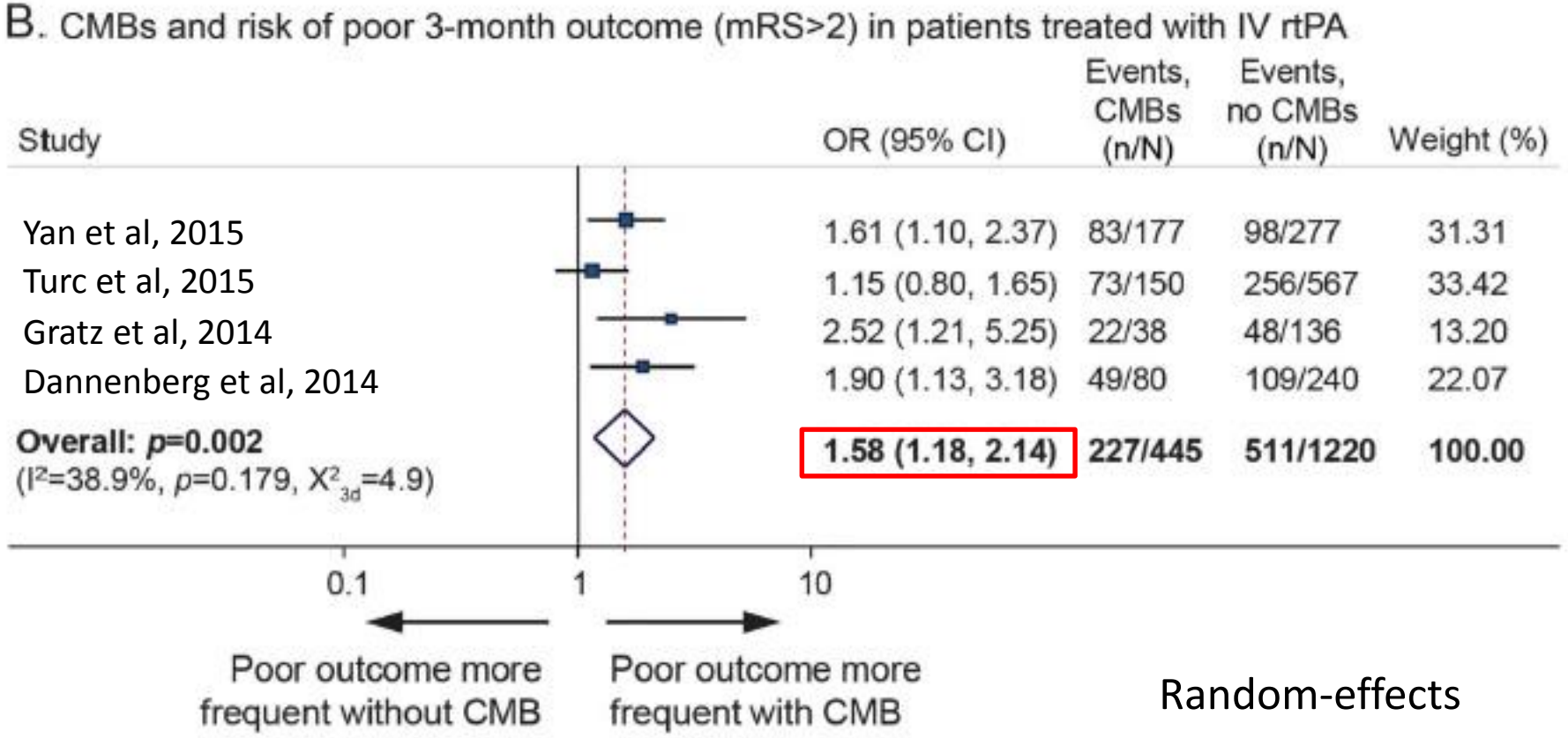


Random-effects

Charidimou et al., Neurology 2016

Microsaignements et mRS>2 post-TIV: revue systématique et méta-analyse (09/2016)

4 études, N=1665



Random-effects

Charidimou et al., Neurology 2016

Microsaignements: est-il possible de définir un seuil « critique » ?

Seuil de 10 microsaignements et sICH post-IVT: méta-analyse sur données agrégées

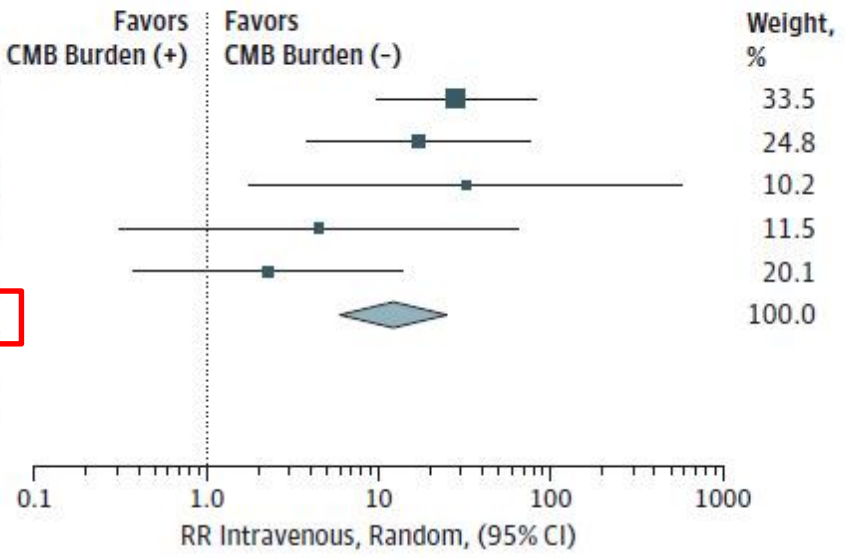
5 études, N=1808

B Patients with 0 to 10 CMBs

Study or Subgroup	>10 CMBs Events	>10 CMBs Total	0-10 CMBs Events	0-10 CMBs Total	RR Intravenous, Random, (95% CI)	Weight, %
Dannenberg et al[20]	3	5	7	321	27.51 (9.88-76.62)	33.5
Fiehler et al[22]	1	2	17	568	16.71 (3.87-72.14)	24.8
Goyal et al[10]	1	1	0	20	31.50 (1.82-546.26)	10.2
Gratz et al[23]	0	2	6	172	4.44 (0.32-62.18)	11.5
Turc et al[26]	1	5	63	712	2.26 (0.39-13.25)	20.1
Total (95% CI)		**15**		**1793**	**12.10 (4.36-33.57)**	100.0
Total events	6		93			

Heterogeneity: $\tau^2 = 0.54$; $\chi^2 = 6.84$, $df = 4$ ($P = .14$); $I^2 = 41\%$

Test for overall effect: $Z = 4.79$ ($P < .001$)



<1% des patients ont >10 microsaignements…

Tsivgoulis et al., JAMA Neurology 2016

Limites de ces méta-analyses sur données agrégées

- Données observationnelles
  - Pas de groupe(s) contrôle(s): non traités; TIV vs. Thrombectomie seule
- Hétérogénéité (protocoles IRM, définition sICH…)
- Analyse binaire (0 vs. ≥1 microbleeds)
  - Importance de la charge lésionnelle ?
  - Peut-on définir un seuil critique ?... En fonction du type de séquence IRM
- Analyse univariable
  - Pas de prise en compte des facteurs de confusion:
    - Age
    - Hypertension artérielle / PA initiale
    - Leucopathie vasculaire / autres marqueurs de maladies des petites artères cérébrales
    - Antithrombotiques…
- Pas de prise en compte de la physiopathologie sous-jacente
  - Maladie des petites artères cérébrales de l'hypertendu
  - Angiopathie amyloïde suspectée

Seuil de 10 microsaignements et sICH post-TIV: méta-analyse sur données individuelles

Table 2. Univariable and Multivariable Logistic Regression on the Risk of Symptomatic Intracerebral Hemorrhage in the Patients Included in the Individual-Patient Meta-analysis

3 études, N=521

	Univariable Analysis OR (95% CI)	*P* Value	Multivariable Analysis OR (95% CI)	*P* Value
Age, per 1-y increase	1.06 (1.02-1.11)	.007	1.05 (0.99-1.12)	.10
Male sex	1.88 (0.76-4.69)	.17	NA	NA
NIHSS score at admission, per 1-point increase	1.01 (0.94-1.08)	.80	NA	NA
HTN	1.41 (0.41-4.92)	.59	NA	NA
AF	2.42 (0.90-6.46)	.08	2.35 (0.70-7.92)	.17
DM	1.21 (0.43-3.40)	.72	NA	NA
Smoking	1.18 (0.38-3.62)	.77	NA	NA
CAD	0.80 (0.17-3.70)	.76	NA	NA
OTT, per 1-min increase	1.01 (0.99-1.01)	.05	1.01 (1.00-1.02)	.03
Glucose level	1.00 (0.99-1.01)	.97	NA	NA
High CMB burden[a] (>10 CMBs)	31.06 (7.12-135.44)	<.001	18.17 (2.39-138.22)	.005
SWI	0.85 (0.32-2.25)	.74	NA	NA
3-T MRI	1.11 (0.44-2.84)	.82	NA	NA

(4/8 pts avec >10 microsaignements ont une sICH)

Tsivgoulis et al., JAMA Neurology 2016

Impact des microsaignements sur la prise en charge thérapeutique en prévention secondaire des accidents ischémiques cérébraux

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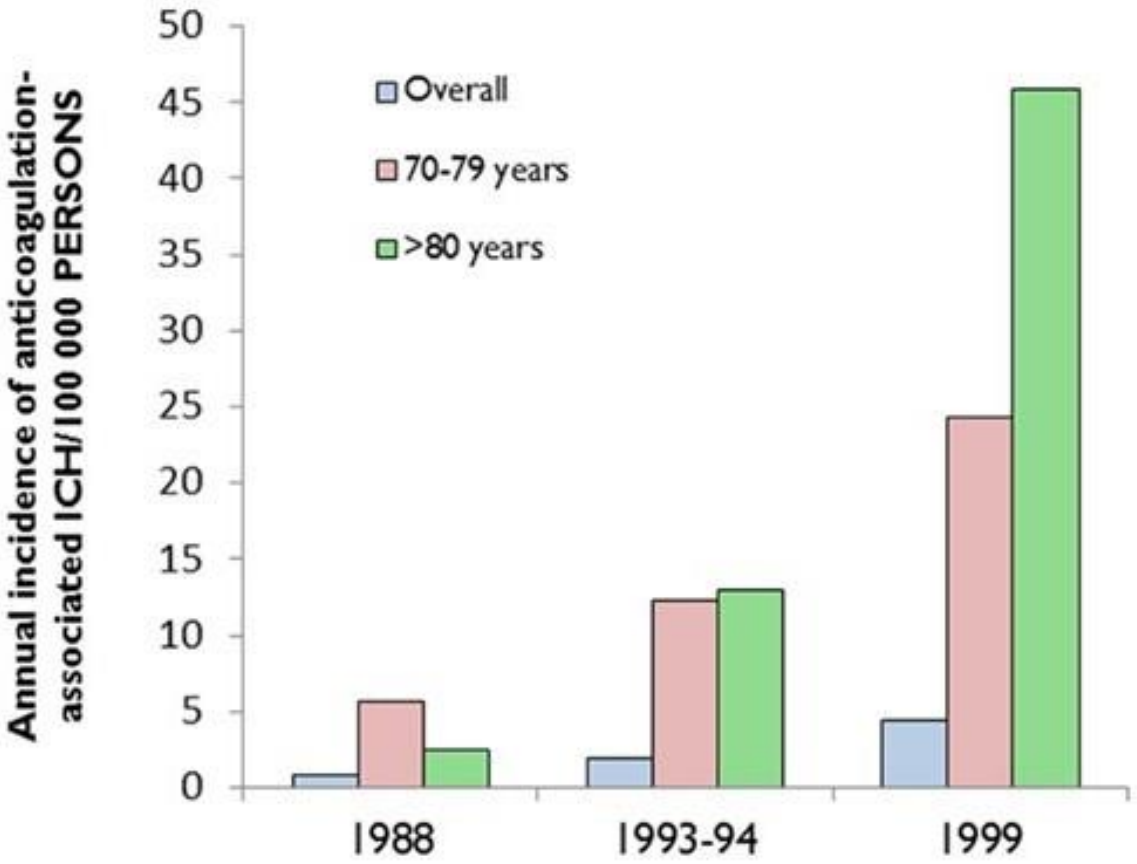
The increasing incidence of anticoagulant-related ICH

Flaherty et al, Neurology 2006



Now accounts for 10-15% of all « spontaneous » ICH

Under-use of anticoagulation in real life

- AC in 49% of older patients with AF with no relationship between AC use and stroke risk (Sandhu, Heart 2011)

- Risk stratification score to predict warfarin-associated hemorrhage
  - HEMORR2HAGES (Am Hear J, 2006)
  - ATRIA bleeding risk score
  - HAS-BLED
  - Modest performance in predicting relevant bleeding (JACC 2012)
  - Poorly validated in stroke patients

Ischemic stroke and TIA population

Recurrent stroke risk and microbleed burden in ischemic stroke and TIA

Wilson, Neurology 2016

- Meta-analysis
- 5,068 patients from 15 studies (3,111 Eastern cohorts)
- Prospective studies of patients with IS or TIA
- Risk of IS (recurrent) and ICH
- Median (IQR) follow-up 18 months (11-30)
- Treatments
  - Antiplatelet agents: 79%
  - Anticoagulants: 15%

ICH risk in ischemic stroke and TIA according to presence of CMBs

Wilson, Neurology 2016

	Intracerebral hemorrhage				
CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
CMB presence	49/1,142 (4.3)	3.8	6.3	3.5	11.4

- CMBs (+) 49/1,142 (4.3%)
- CMBs (-) 17/2,912 (0.6%)

ICH risk in ischemic stroke and TIA according to presence of CMBs

Wilson, Neurology 2016

	Intracerebral hemorrhage				
CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
CMB presence	49/1,142 (4.3)	3.8	6.3	3.5	11.4
1 CMB	8/354 (2.3)	1.7	4.6	1.9	10.7
2–4 CMBs	9/383 (2.3)	1.8	5.6	2.4	13.3
≥5 CMBs	24/274 (8.8)	8.2	14.1	6.9	29.0

ICH risk in ischemic stroke and TIA according to presence of CMBs

Wilson, Neurology 2016

	Intracerebral hemorrhage				
CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
Strictly lobar	12/332 (3.6)	3.2	10.5	4.5	24.3
Strictly deep	6/437 (1.4)	1	3.3	1.3	8.5
Mixed	25/411 (6.1)	5.7	11.1	5.5	22.6

Recurrent ischemic stroke risk in ischemic stroke and TIA according to presence of CMBs

Wilson, Neurology 2016

	Ischemic stroke				
CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
CMB presence	115/1,284 (9)	3.4	1.8	1.4	2.5

- CMBs (+) 115/1,284 (9.6%)
- CMBs (-) 212/3,781 (5.6%)

Recurrent ischemic stroke risk in ischemic stroke and TIA according to presence of CMBs

Wilson, Neurology 2016

	Ischemic stroke				
CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
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Recurrent stroke risk in ischemic stroke and TIA according to presence of CMBs

Wilson, Neurology 2016

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CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
CMB presence	115/1,284 (9)	3.4	1.8	1.4	2.5
1 CMB	31/433 (7.2)	1.8	1.8	1.0	3.1
2-4 CMBs	44/433 (10.2)	4.8	2.4	1.3	4.4
≥5 CMBs	34/342 (10.5)	5.1	2.7	1.5	4.9

Recurrent stroke risk in ischemic stroke and TIA according to presence of CMBs

Wilson, Neurology 2016

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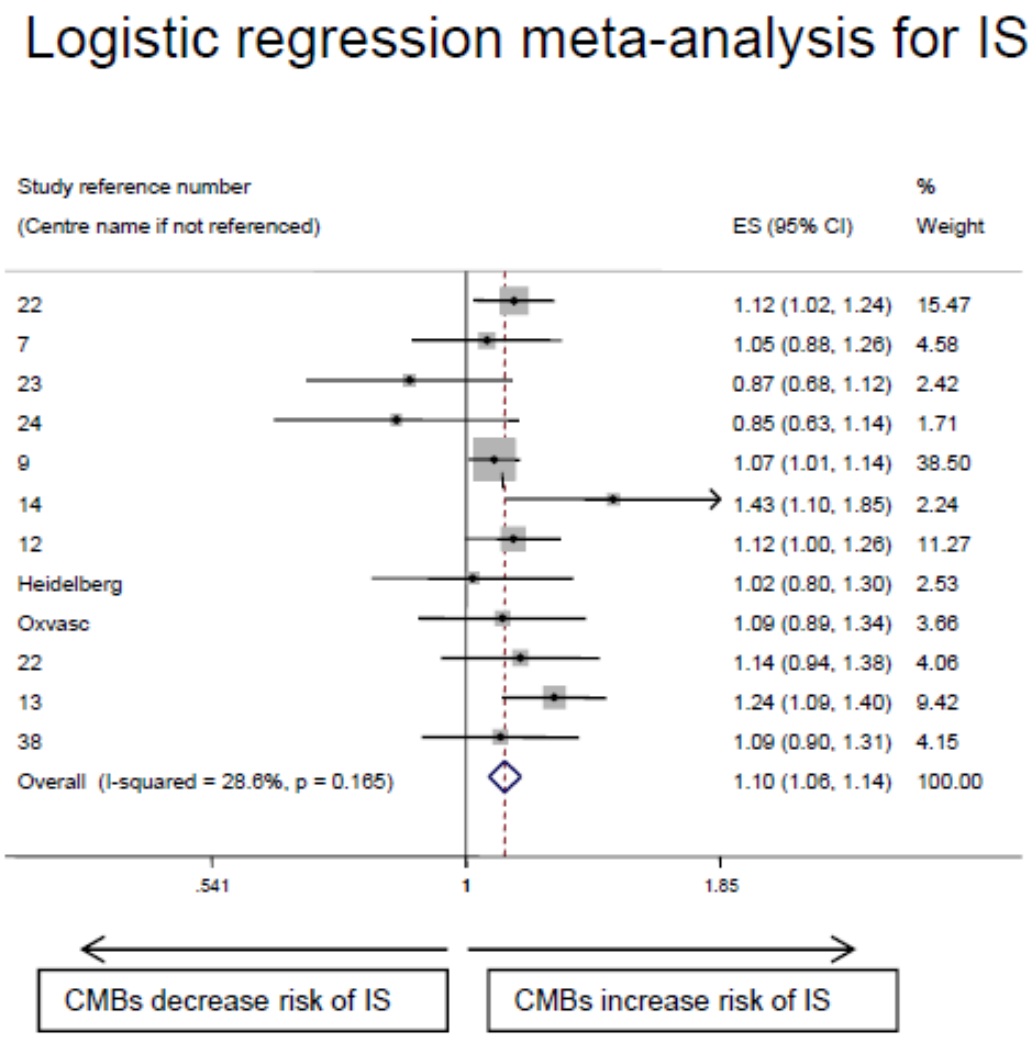
CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
Strictly lobar	31/332 (9.3)	3.9	2.0	1.4	2.9
Strictly deep	29/437 (6.6)	1.2	1.6	1.0	2.7
Mixed	44/411 (10.7)	5.3	2.6	1.5	4.3

But heterogeneity between studies



Effect on heterogeneity of each variable for the association between IS and CMB presence

Variable	Reduction in I^2 %	p value of regression coefficient in meta-regression
Ethnicity (East compared to West)	8.3	0.17
Patient year follow up	4.9	0.23
Age (year)	2.3	0.33
Hypertension %	14.8	0.08
Anticoagulant use %	4.3	0.13
Antiplatelet use %	3.4	0.15

Study (primary author or name) Ref	Number of patients	Average follow up (months)	Ethnicity	Cohort	Age (mean)	HTN (%)	Gender (% Male)	Antiplatelets (%)	Anticoagulants (%)	Field strength (Tesla)	Echo time (ms)	T2*/SWI
Boulanger (11)	236	18	Western	IS/TIA	NA	60	55	NA	NA	3	20	T2*
CROMIS-1 (e1)*	68	24	Western	IS/TIA	66	60	66	81	16	1.5	Variable	T2*
Fan (25)	121	27	Eastern	IS	68	69	68	80	6	1.5	30	T2*
Fluri (14)	176	3	Western	TIA	71	72	61	77	12	1.5	15	T2*
Heidelberg*	265	12	Western	IS	65	80	67	78	20	3	19.7	SWI
Huang (21)	636	14	Eastern	IS	60	67	68	100	0	1.5	NA	T2*
Imaizumi (07)	138	22	Eastern	IS	66	73.2	66	33	2	1.5	26	T2*
Kwa (22)	397	46	Western	IS	65	55	59	90	10	1.5	27.6	T2*
Lim (13)	500	3	Eastern	TIA	65	66	58	91	15	NA	15-25	T2*
Mok (26)	75	60	Eastern	IS	71	85	52	96	0	1.5	NA	T2*
Naka (23)	183	18	Eastern	IS	67	70	63	93	2	1	26	T2*
OXVASC*	323	35	Western	IS/TIA	72	63	75	83	11	1.5	14	T2*
Song (24)	550	30	Eastern	IS	70	77	59	35	87	3	16	T2*
Soo (9)	908	11	Eastern	IS	68	68	58	93	3	1.5	30	T2*
Thijs (12)	487	20	Western	IS/TIA	72	64	61	73	27	Variable	Variable	T2*

Legend: IS-* denoted unpublished study, Ischemic stroke; TIA- transient ischemic attack, HTN –hypertension SWI- susceptibility weighted imaging

Study (primary author or name) Ref	Number of patients	Average follow up (months)	Ethnicity	Cohort	Age (mean)	HTN (%)	Gender (% Male)	Antiplatelets (%)	Anticoagulants (%)	Field strength (Tesla)	Echo time (ms)	T2*/SWI
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Lim (13)	500	3	Eastern	TIA	65	66	58	91	15	NA	15-25	T2*
Mok (26)	75	60	Eastern	IS	71	85	52	96	0	1.5	NA	T2*
Naka (23)	183	18	Eastern	IS	67	70	63	93	2	1	26	T2*
OXVASC*	323	35	Western	IS/TIA	72	63	75	83	11	1.5	14	T2*
Song (24)	550	30	Eastern	IS	70	77	59	35	87	3	16	T2*
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Legend: IS-* denoted unpublished study, Ischemic stroke; TIA- transient ischemic attack, HTN –hypertension SWI -susceptibility weighted imaging

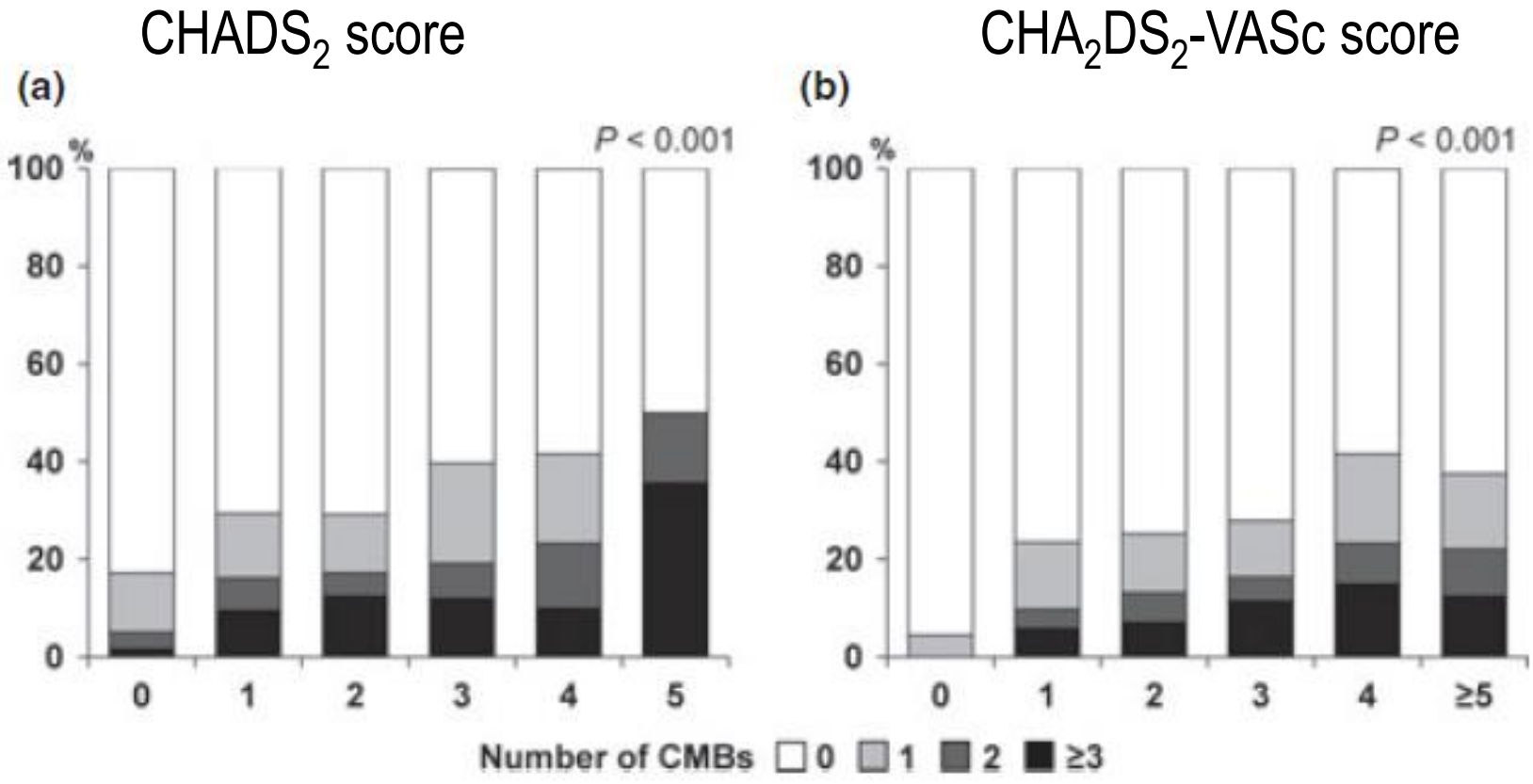
CMBs in AF-ischemic stroke patients

Song, Eur J Neurol2013

- 550 Ischemic stroke patients with non-valvular AF
- From January 2005 to November 2011, CMBs on MRI
- Median follow-up: 3.1 y
- Mean age 70 y, 59% male
- Prevalence CMBs: 31.5%

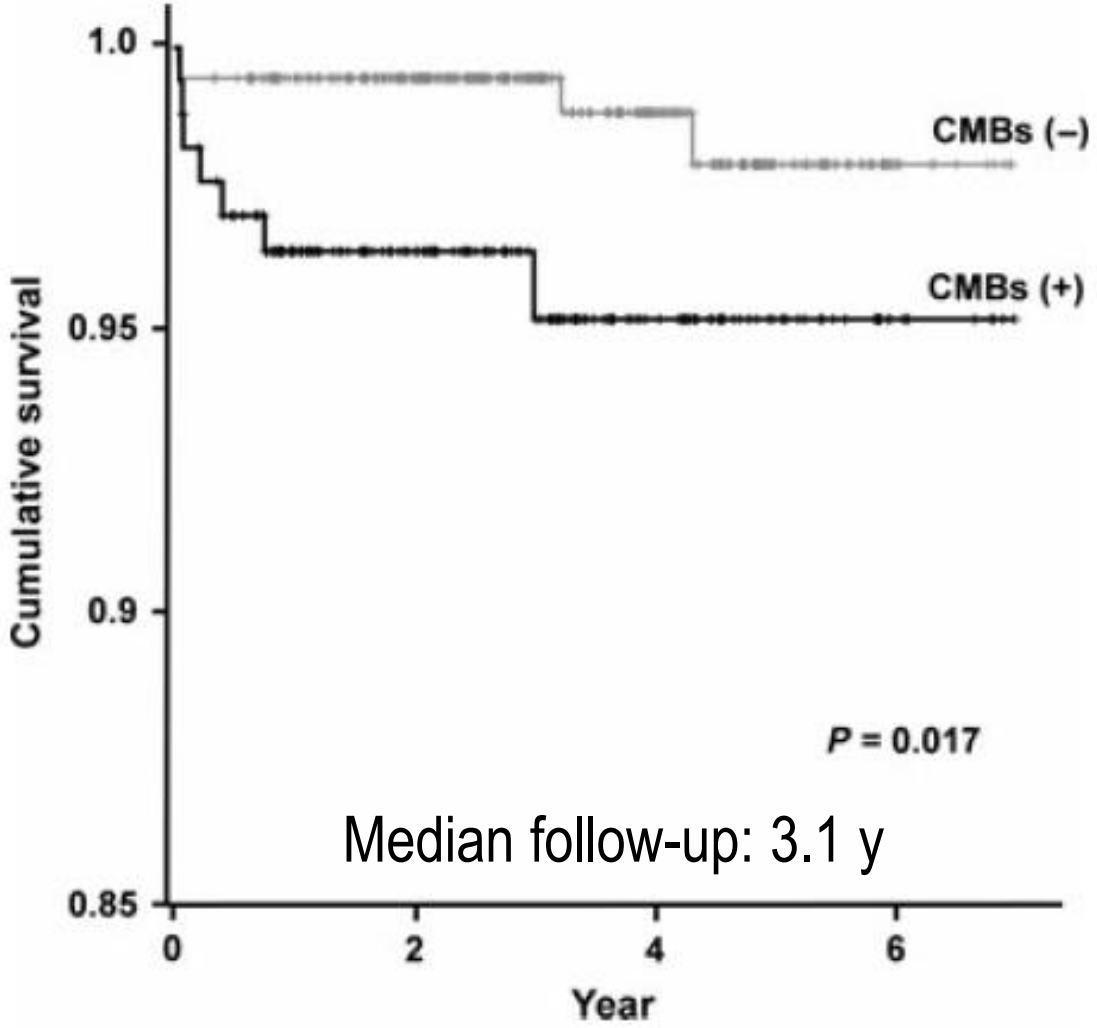
CMBs and $CHADS_2$ scores in AF stroke patients

Song, Eur J Neurol2013



CMBs and risk of ICH

Song, Eur J Neurol2013



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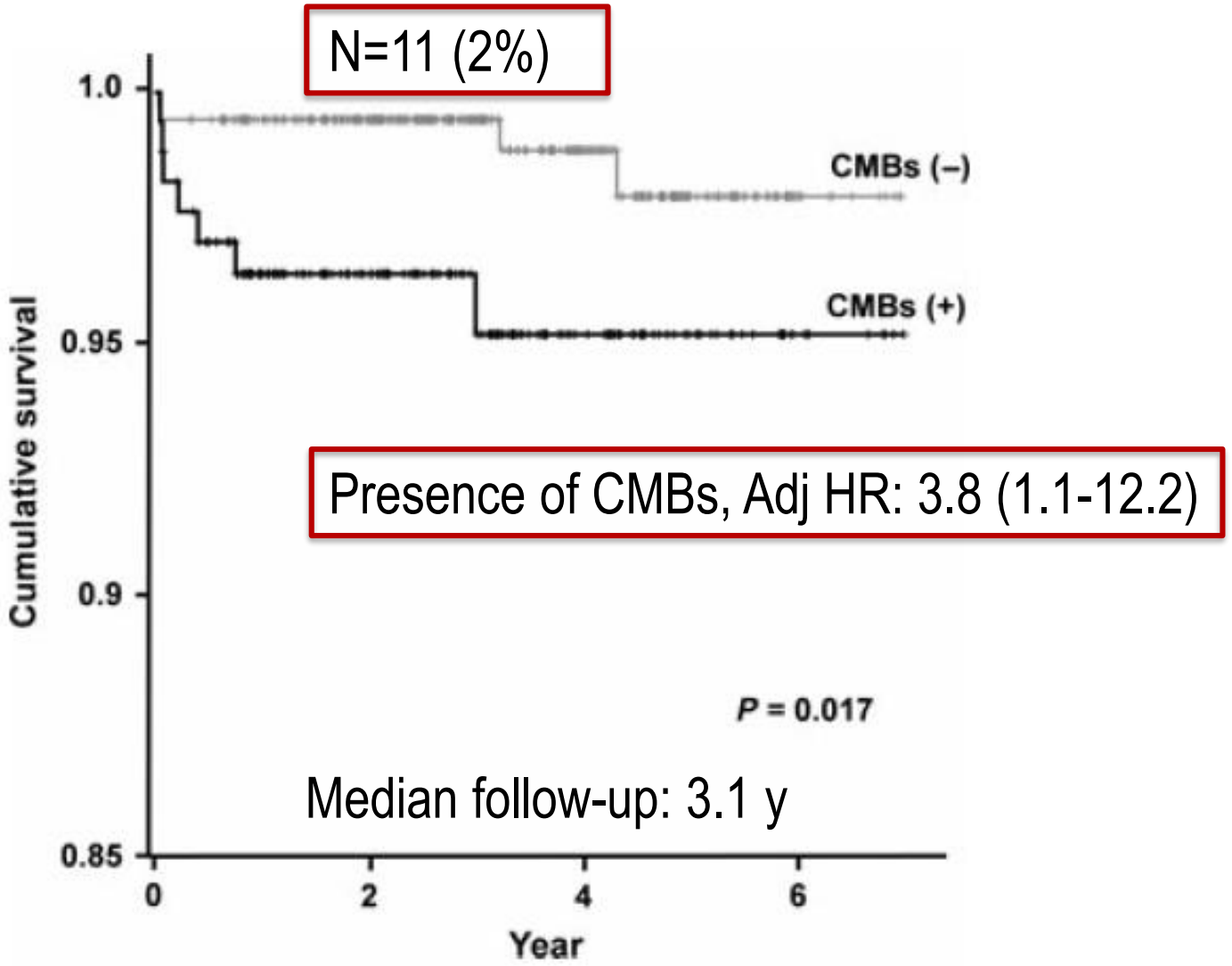


Ischemic stroke patients with atrial fibrillation

Mauro Silva, unpublished

- From November 2013 to December 2015
- 1597 consecutive patients with IS : 385 with AF
- Brain MRI in 349 (91%)
  - CMB
  - Infarct topography
  - White matter hyperintensity of presumed vascular origin
- ASCOD classification
- Mean follow-up: 15 months (±10.6)

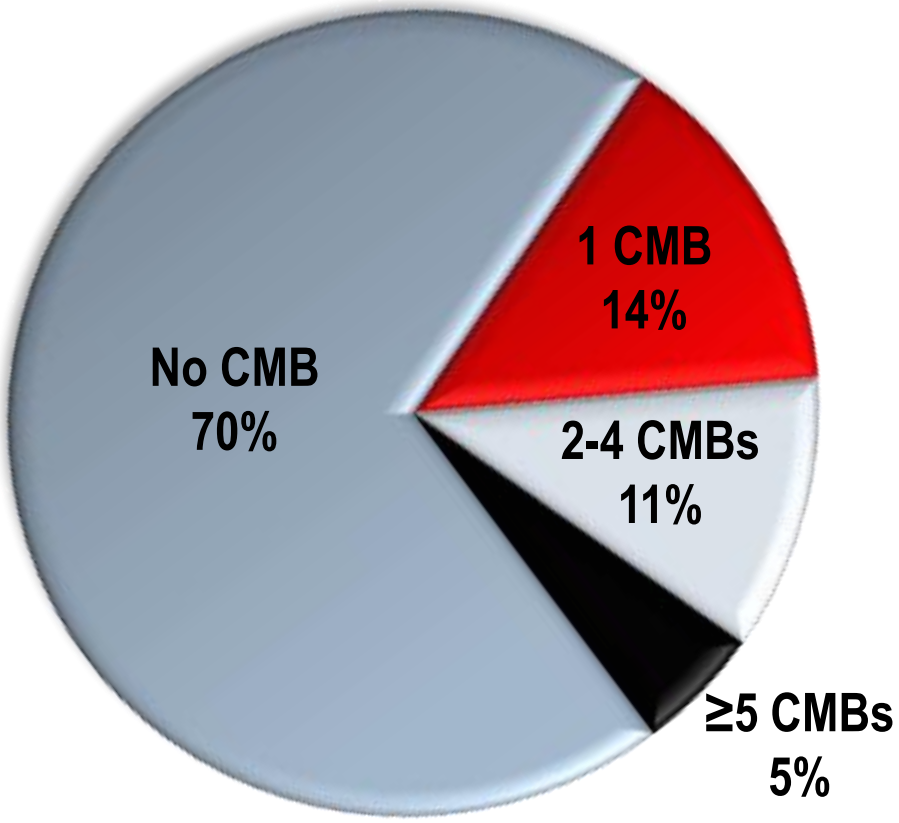
Characteristics of AF-stroke patients

- Mean age: 80
- Female 53%
- HTA: 72%
- Dyslipidemia: 41%
- Previous IS: 13%
- Previous TIA: 9%
- ICH:3%

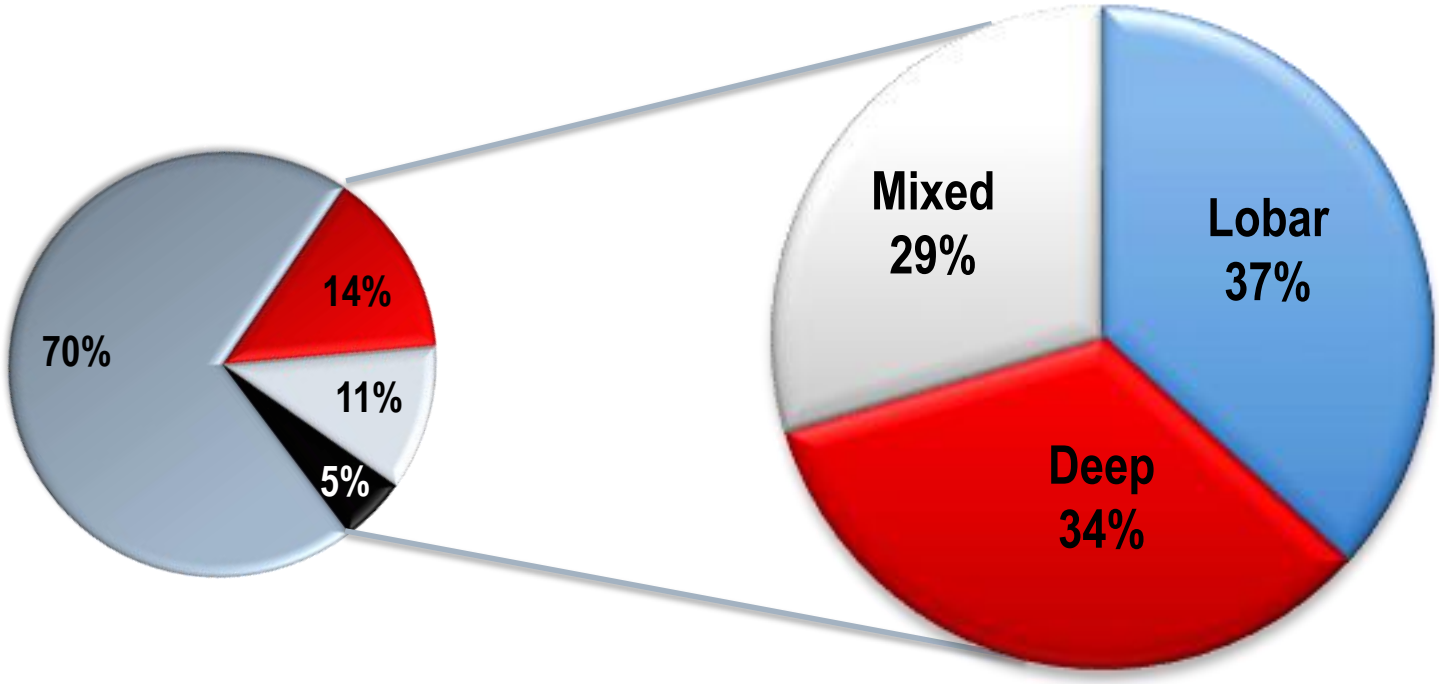
- Paroxysmal AF: 60%
- Known before stroke: 57%
  - 51% under anticoagulant (VKA 38%, DOAC 13%)
  - VKA patients: 24% INR on target

Prevalence of CMBs in AF-stroke patients (n=349)

- At least one CMB : 30.2% (25.2-35.2)

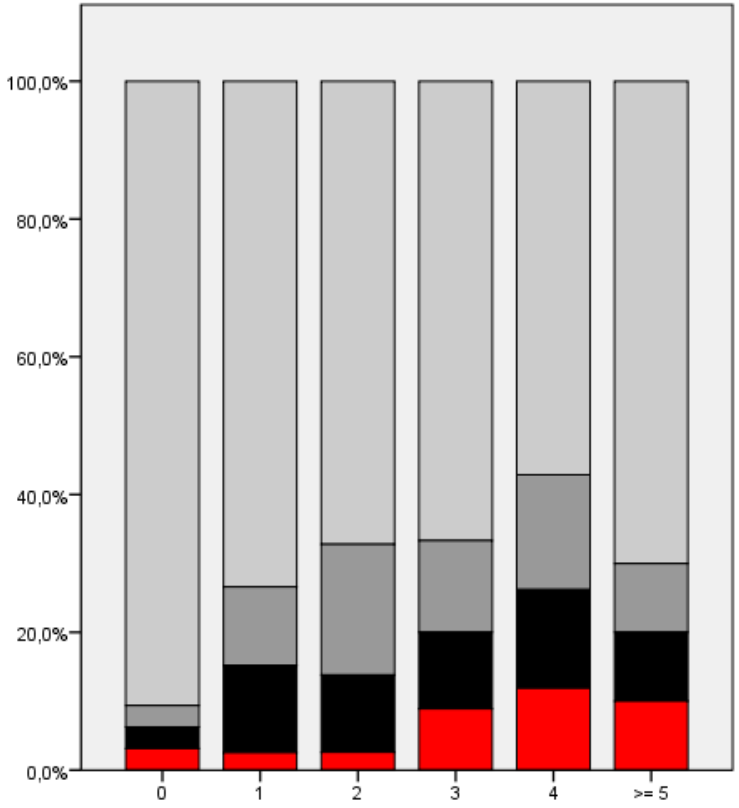


CMBs location in AF-stroke patients

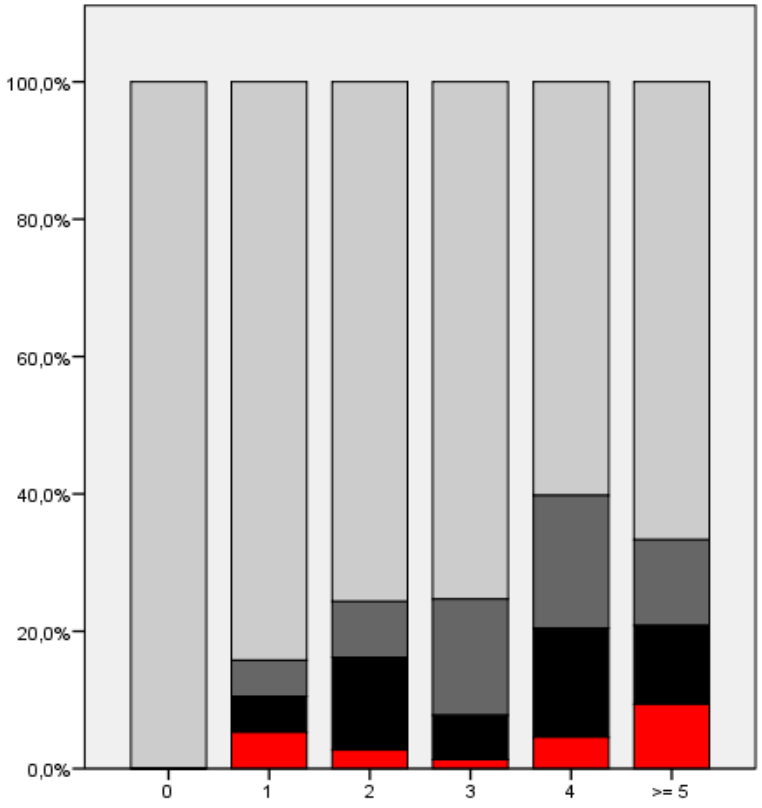


CMBs and $CHADS_2$ scores in AF stroke patients

$CHADS_2$ score
(p for trend 0.006)



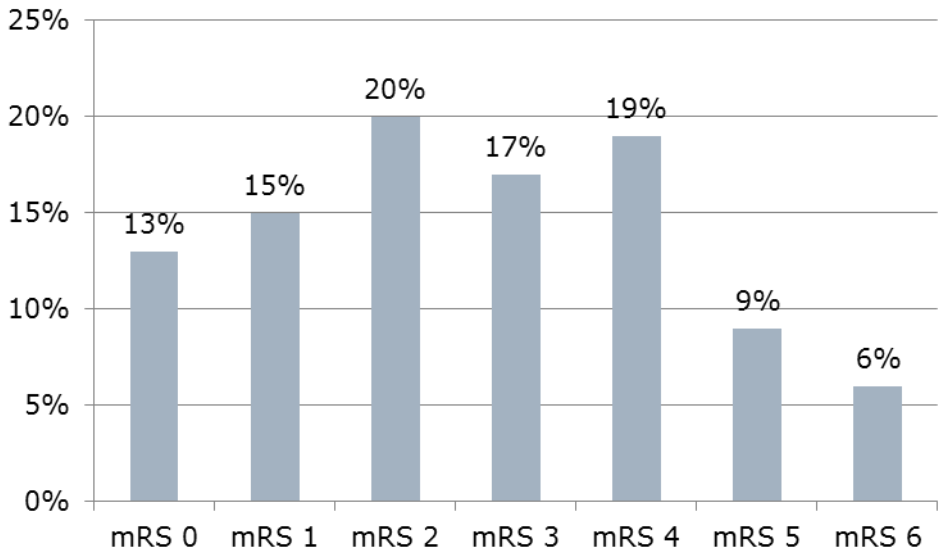
CHA_2DS_2-VASc score
(p for trend 0.02)



Number of CMBs
0 1 2-4 >=5

Discharge treatment

Modified Rankin Score at discharge



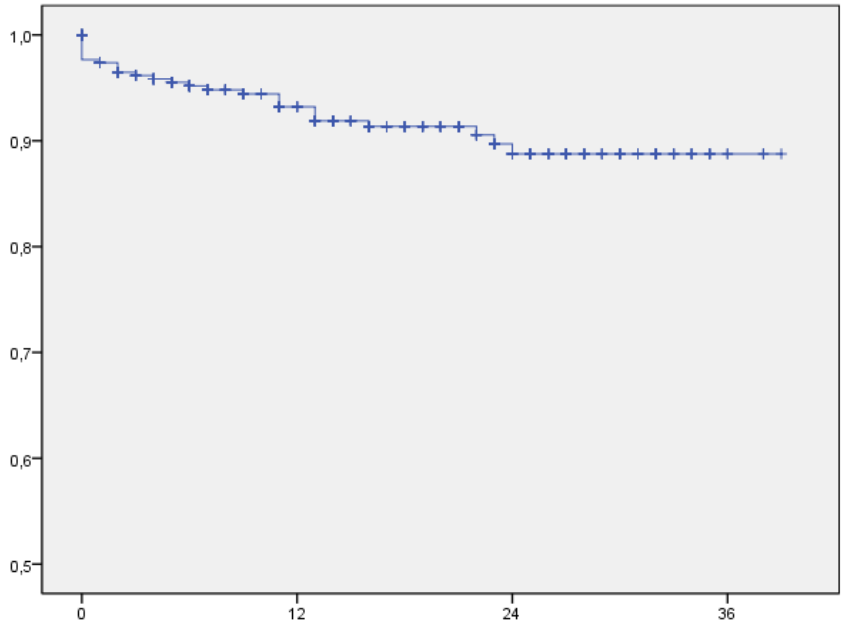
- Anticoagulation : 62%
  - VKA : 24%
  - DOAC : 36%
  - Heparin : 2%
- Antiplatelet : 37%
- None : 1%

Discharge treatment

- Anticoagulation : 62%
  - VKA : 24%
  - DOAC : 36%
  - Heparin : 2%
- Antiplatelet : 37%
  - Delayed ACO : 84%
  - Contraindication : 5%
  - Unknown : 11%
- None : 1%

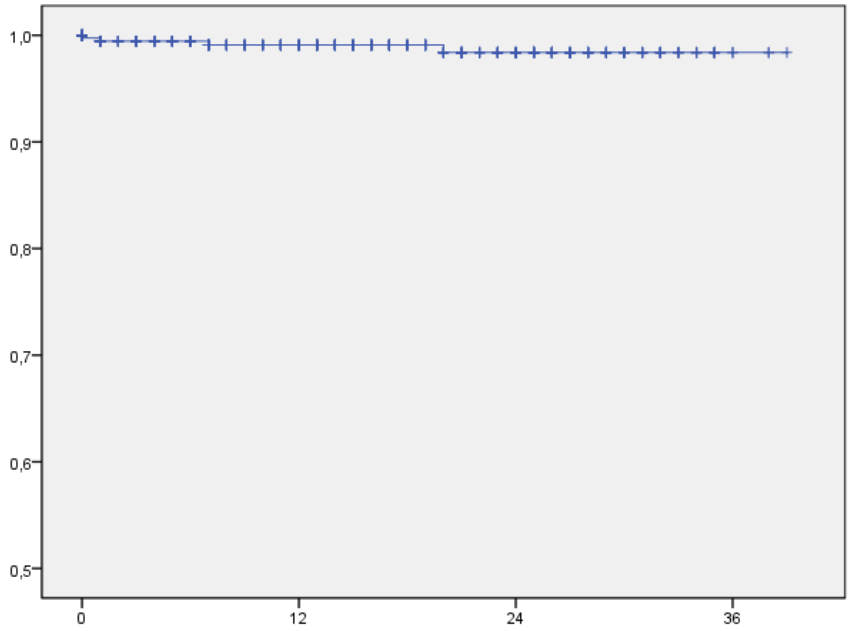
Recurrent IS and ICH during follow-up

Recurrent IS, n=29



- Absolute risk of recurrent IS
  - 6.8% (4.1-9.5) at 1-y
  - 11.2% (6.9-15.5) at 2-y

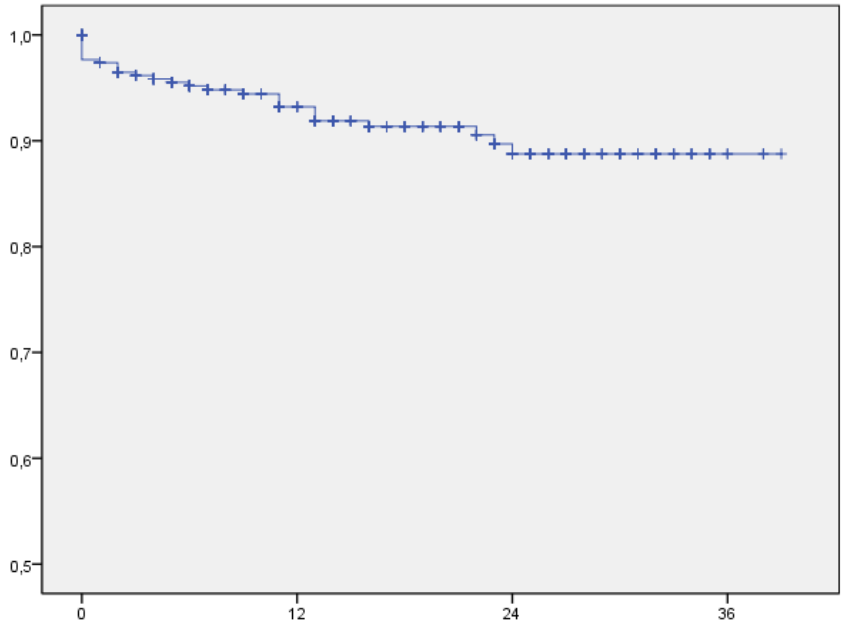
ICH, n=4

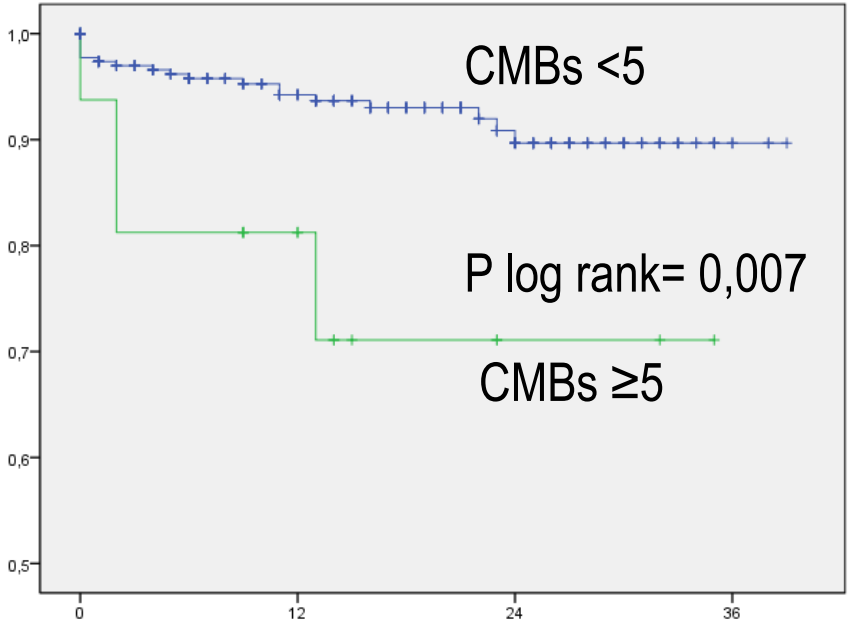


- Absolute risk of ICH
  - 0.9% (0-1.9) at 1-y
  - 1.6% (0-3.4) at 2-y

Recurrent IS according to number of CMBs

Recurrent IS: n=29





- Absolute risk of recurrent IS
  - 6.8% (4.1-9.5) at 1-y
  - 11.2% (6.9-15.5) at 2-y

- Recurrent IS
  - Anticoagulant n=16 (45%)
  - Antiplatelet n=13 (45%)

Ischemic stroke and TIA population

Cerebral microbleeds <5

Risk of ICH

Risk of ischemic stroke

Antithrombotic treatment according to current guidelines

Ischemic stroke and TIA population

Cerebral microbleeds ≥ 5

Risk of ICH

Risk of ischemic stroke

- Absolute risk of IS ≈ Absolute risk of ICH
- If indication for anticoagulation, to favour DOAC
- Left atrial appendage occlusion might be an option (if lobar?)

Ischemic stroke and TIA population

Cerebral microbleeds ≥ 5

Risk of ICH

Risk of ischemic stroke

HAS conclusions for LAA

- ☐ Contraindication to anticoagulation
  - Strict and permanent
  - Absence of alternative
- ☐ CHA_2DS_2-VASc ≥ 4