AVC/AIT et double AAP
- Indications -

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20 juin 2019
6ème journée régionale de l'AVC

AVC Normandie

1. AIT et Infarctus cérébraux mineurs

AHA/ASA Guideline

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

In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**LEVEL B** Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	New recommendation.

The generalizability of this intervention in non-Asian populations remains to be established, and a large phase III multicenter trial in the United States, Canada, Europe, and Australia is ongoing.[195]

CHANCE

- Randomisé
- Objectif : évaluer l'efficacité de la double AAP Aspirine + plavix 21 J sur le pronostic des patients IC mineur ou AIT
- 5170 patients (Chine)
- Critères d'inclusion :
  - >40 ans
  - AIT ABCD 2 ≥4, infarctus mineur NIHSS ≤3
  - Ttt débuté <24 h

Wang et al. N Engl J Med 2013;369:11-19.

CHANCE

- Critères d’exclusion : spt isolés sensitifs/trouble visuel/vertige; candidats à TAC, rtPA, endarteriectomie, mRS >2, TAC avant randomisation, AIT ou IC post procédure endovasculaire
- CJP: AVC (i+h) à 90 j

Wang et al. N Engl J Med 2013;369:11-19.

CHANCE

Simple AAP	Double AAP 21J
Aspi 75mg à 300 mg J1	Aspi 75mg à 300 mg J1 + PLAVIX 300 mg J1
Aspi 75mg 90 J + Placebo 21J	Plavix 75mg 90J + Aspi 75mg/j 21J

Wang et al. N Engl J Med 2013;369:11-19.

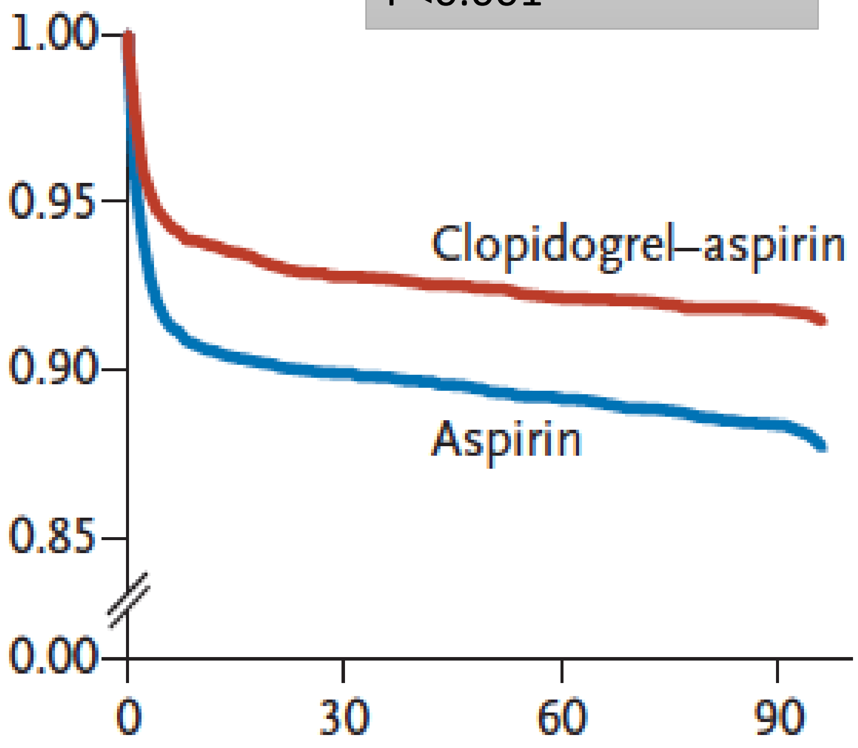
CHANCE

Outcome	Aspirin (N=2586)		Clopidogrel and Aspirin (N=2584)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%	*no.*	%		
Primary outcome						
Stroke	303	11.7	212	8.2	0.68 (0.57–0.81)	<0.001
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	307	11.9	216	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	295	11.4	204	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98

Wang et al. N Engl J Med 2013;369:11-19.

CHANCE

HR=**0.68** (0.57-0.81)
P<0.001



Probability of Survival Free of Stroke.

Wang et al. N Engl J Med 2013;369:11-19.

CHANCE

Outcome	Aspirin (N=2586)		Clopidogrel and Aspirin (N=2584)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%	*no.*	%		
Safety outcomes						
Bleeding*						
Severe	4	0.2	4	0.2	0.94 (0.24–3.79)	0.94
Moderate	4	0.2	3	0.1	0.73 (0.16–3.26)	0.68
Mild	19	0.7	30	1.2	1.57 (0.88–2.79)	0.12
Any bleeding	41	1.6	60	2.3	1.41 (0.95–2.10)	0.09
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98

Wang et al. N Engl J Med 2013;369:11-19.

POINT

- Randomisé
- Objectif : évaluer l'efficacité de la double AAP aspirine + Plavix dans une population internationale
- 4881 patients (75% caucasiens, 20% ethnie noire, 3% asiatiques)
- Critères d'inclusion :
  - >18 ans,
  - AIT $ABCD^2 \geq 4$, infarctus mineur NIHSS ≤ 3;
  - randomisés dans les 12 h, dose de charge le plus rapidement après randomisation

Claiborne Johnston et al. N Engl J Med july 2018;379:215-25.

POINT

- Critères d'exclusion : candidats à TAC, rtPA, thrombectomie, <u>endartériectomie</u>, spt isolés : paresthésies/trouble visuel/vertige
- CJP: (AVCi, IDM, mort vasculaire ischémique à J90)

Claiborne Johnston et al. N Engl J Med july 2018;379:215-25.

POINT

Simple AAP	Double AAP 3 mois
Aspi 50mg à 325 mg J1	Aspi 50mg à 325 mg J1 + Plavix 600 mg J1
Aspi 50 à 325 mg 90 J + Placebo 90J	Aspi 50mg à 325 mg 90J + Plavix 75mg/j 90J

Wang et al. N Engl J Med 2013;369:11-19.

POINT

Outcome	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary efficacy outcome				
Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes	121 (5.0)	160 (6.5)	0.75 (0.59–0.95)	0.02
Secondary efficacy outcomes				
Ischemic stroke	112 (4.6)	155 (6.3)	0.72 (0.56–0.92)	0.01*
Myocardial infarction	10 (0.4)	7 (0.3)	1.44 (0.55–3.78)	0.46*
Death from ischemic vascular causes	6 (0.2)	4 (0.2)	1.51 (0.43–5.35)	0.52*
Ischemic or hemorrhagic stroke	116 (4.8)	156 (6.4)	0.74 (0.58–0.94)	0.01*
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	141 (5.8)	167 (6.8)	0.84 (0.67–1.05)	0.13*

POINT

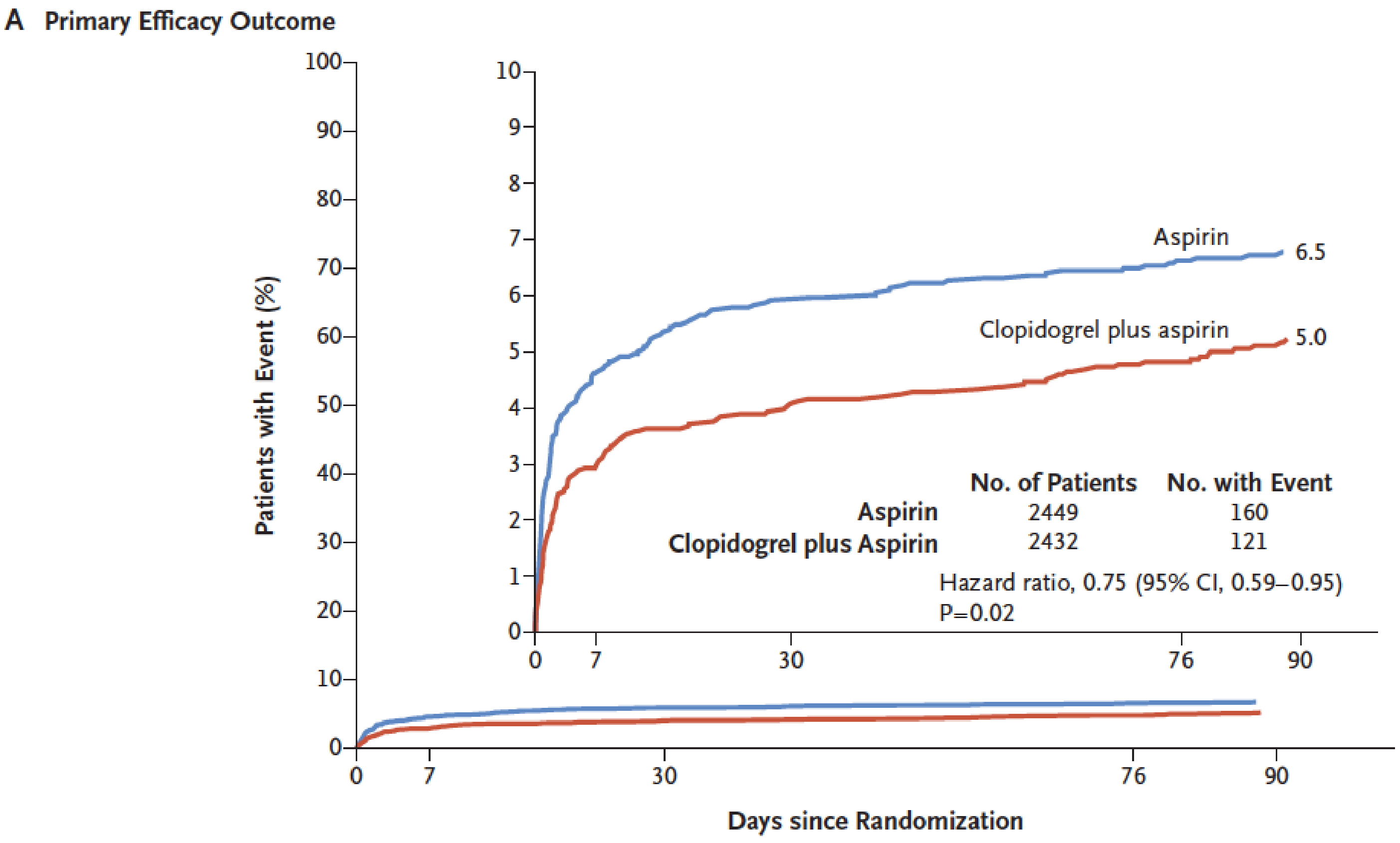
Outcome	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary safety outcome				
Major hemorrhage	23 (0.9)	10 (0.4)	2.32 (1.10–4.87)	0.02
Other safety outcomes				
Hemorrhagic stroke	5 (0.2)	3 (0.1)	1.68 (0.40–7.03)	0.47
Symptomatic intracerebral hemorrhage	2 (0.1)	2 (0.1)	1.01 (0.14–7.14)	0.99
Other symptomatic intracranial hemorrhage	2 (0.1)	0		0.16
Major hemorrhage other than intracranial hemorrhage	17 (0.7)	7 (0.3)	2.45 (1.01–5.90)	0.04
Minor hemorrhage	40 (1.6)	13 (0.5)	3.12 (1.67–5.83)	<0.001
Death from any cause	18 (0.7)	12 (0.5)	1.51 (0.73–3.13)	0.27

Hémorragies fatales : 3-2 ; 0,1%-0,1%

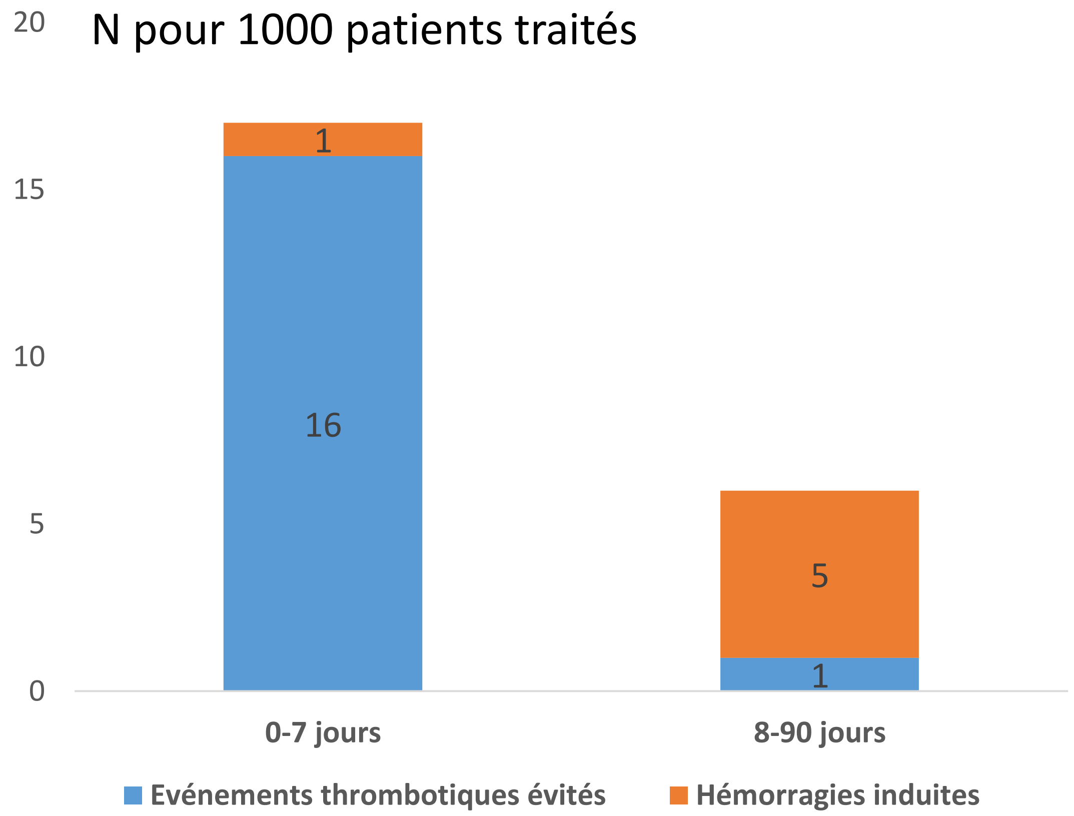
POINT

Bénéfice absolu surtout dans les 7 premiers jours

Risque hémorragique constant au cours du temps et un peu accru au-delà du 8^{e} jour



No. at Risk						
Aspirin	2449	2269	2153	2105	1365
Clopidogrel plus aspirin	2432	2279	2178	2113	1445



Optimal Duration of Aspirin Plus Clopidogrel After Ischemic Stroke or Transient Ischemic Attack

A Systematic Review and Meta-Analysis

Hammad Rahman, MD; Safi U. Khan, MD; Fahad Nasir, MD; Tehseen Hammad, MBBS; Michael A. Meyer, MD; Edo Kaluski, MD

10 essais randomisés

Stroke avril 2019

15 434 patients AIT ou IC

A+C vs A seule

Durée variable : ≤1 mois; ≤3 mois; >3 mois

CJP efficacité : IC

CJP sécurité : hémorragie majeure

Optimal Duration of Aspirin Plus Clopidogrel After Ischemic Stroke or Transient Ischemic Attack

A Systematic Review and Meta-Analysis

Hammad Rahman, MD; Safi U. Khan, MD; Fahad Nasir, MD; Tehseen Hammad, MBBS; Michael A. Meyer, MD; Edo Kaluski, MD

Efficacité :

Double AAP ≤1 mois : RR CJP 0,53 (IC 0,37-0,78)

Double AAP ≤3 mois : RR CJP 0,68 (0,60-0,78)

Double AAP >3 mois : RR CJP 0,81 (IC 0,63-1,04)

Sécurité :

Double AAP ≤1 mois : RR 1,82 (IC 0,91-3,62)

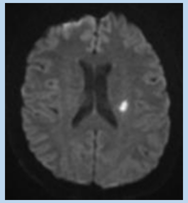
Double AAP ≤3 mois : RR 2,58 (1,19-5,6)

Double AAP >3 mois : RR 1,87 (IC 1,36-2,56)

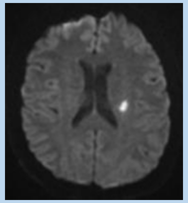
Durée optimale : <1 mois :

- supérieur en prévention du risque ischémique
- pas plus risqué sur le plan hémorragique

2. Infarctus lacunaires



2. Infarctus lacunaires

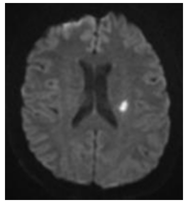


=> Pas de recommandation ; ni en phase aigue ni en prévention secondaire

… Mais des arguments pour une double AAP <u>brève</u> en <u>phase aigue ;</u>

en cas d’aggravation neurologique initiale

- Prévention secondaire : SPS 3 trial : Secondary Prevention of Small Subcortical Strokes



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

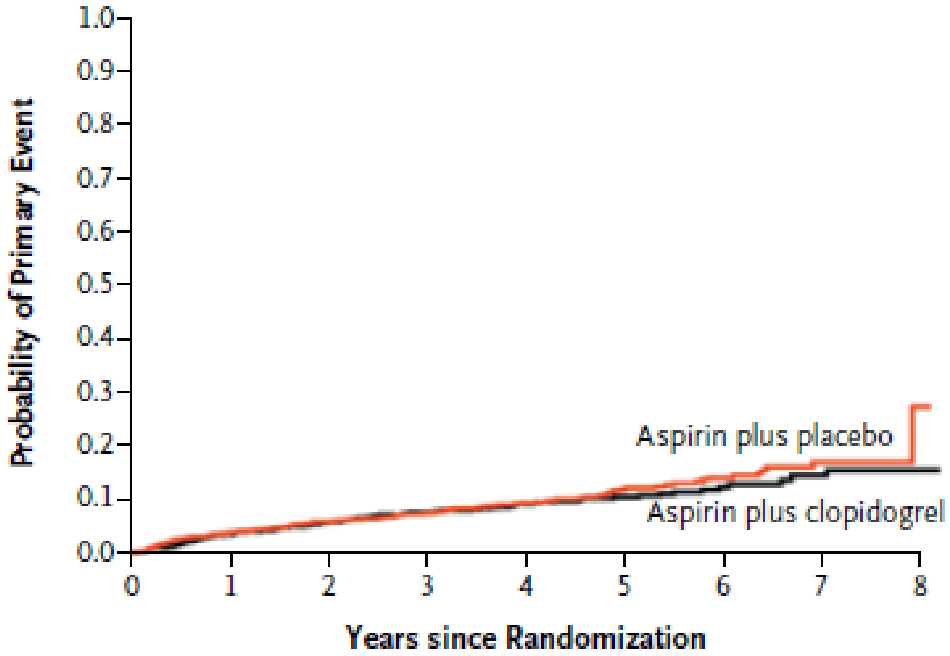
30 aout 2012

. 3020 infarctus lacunaires <6 mois

. Randomisée

. 325 mg aspirine +/- 75 mg clopidogrel

. CJP : récidive d’AVC



No. at Risk

Aspirin plus placebo	1517	1272	1027	788	574	355	189	83	3
Aspirin plus clopidogrel	1503	1288	1030	802	589	371	205	90	5

Figure 1. Probability of the Primary Outcome.

The hazard ratio for the primary outcome, recurrent stroke, was 0.92 (95% CI, 0.72 to 1.2).

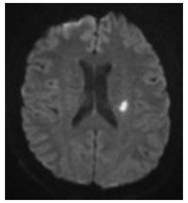
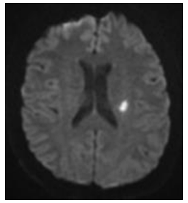


Table 2. **Primary Efficacy Outcomes.***

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	*rate (%/yr)*	*no.*	*rate (%/yr)*		
All strokes (ischemic and hemorrhagic)	138	2.7	125	2.5	0.92 (0.72–1.16)	0.48
Ischemic stroke	124	2.4	100	2.0	0.82 (0.63–1.09)	0.13
Intracranial hemorrhage	13	0.25	21	0.42	1.65 (0.83–3.31)	0.15
Unknown†	1	0.02	4	0.08	3.97 (0.44–35.47)	0.22
Disabling or fatal stroke‡	40	0.78	42	0.84	1.06 (0.69–1.64)	0.79
Transient ischemic attack without stroke	39	0.78	28	0.57	0.73 (0.45–1.18)	0.19
Myocardial infarction	38	0.71	31	0.59	0.84 (0.52–1.35)	0.47
Other thromboembolic events§	12	0.22	21	0.40	1.81 (0.89–3.68)	0.10
Major vascular event¶	174	3.4	153	3.1	0.89 (0.72–1.11)	0.29
All deaths	77	1.4	113	2.1	1.52 (1.14–2.04)	0.004
Vascular causes	19	0.35	27	0.51	1.46 (0.81–2.64	0.20
Cerebral	9	0.17	10	0.19	1.13 (0.46–2.78)	0.79
Noncerebral	10	0.18	17	0.32	1.77 (0.81–3.87)	0.15
Probable vascular causes	6	0.11	18	0.34	3.09 (1.23–7.80)	0.02
Nonvascular causes	31	0.57	39	0.73	1.31 (0.82–2.10)	0.26
Uncertain	21	0.39	29	0.55	1.41 (0.82–2.52)	0.21



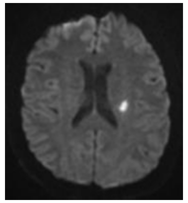
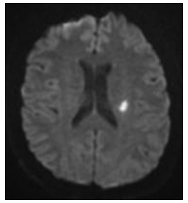


Table 3. Safety Outcomes.*

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	*rate (%/yr)*	*no.*	*rate (%/yr)*		
All major hemorrhages	56	1.1	105	2.1	1.97 (1.41–2.71)	<0.001
Intracranial hemorrhages†	15*	0.28	22	0.42	1.52 (0.79–2.93)	0.21
Intracerebral	8	0.15	15	0.28	1.92 (0.82–4.54)	0.14
Subdural or epidural	6	0.11	7	0.13	1.23 (0.41–3.64)	0.72
Other	4	0.07	2	0.04	0.53 (0.10–2.89)	0.46
Extracranial bleeding	42	0.79	87	1.7	2.15 (1.49–3.11)	<0.001
Gastrointestinal‡	28	0.52	58	1.1	2.14 (1.36–3.36)	<0.001
Fatal hemorrhages	4	0.07	9	0.17	2.29 (0.70–7.42)	0.17
Intracranial	4	0.07	7	0.13	1.78 (0.52–6.07)	0.36
Extracranial	0	0	2	0.04	—	—

- Phase aigue



Dual Antiplatelet Therapy Improves Functional Outcome in Patients With Progressive Lacunar Strokes

Anne Berberich, MD; Christine Schneider, MD; Tilman Reiff, MD; Christoph Gumbinger, MD; Peter Arthur Ringleb, MD

Stroke, 1er avril 2019

. 458 infarctus lacunaires

. Rétrospective

. Aggravation neurologique précoce ≥3 pts de NIHSS, ≥2 pts NIHSS moteur, dans les 5 jours

. Double AAP selon habitudes locales

. CJP : NIHSS à la sortie ≤NIHSS entrée

Dual Antiplatelet Therapy Improves Functional Outcome in Patients With Progressive Lacunar Strokes

Anne Berberich, MD; Christine Schneider, MD; Tilman Reiff, MD;
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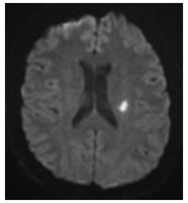
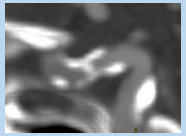
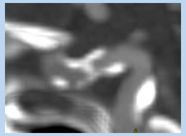


	All Patients (n=130) (28%)			Patients With Thrombolysis (n=32)			Patients Without Thrombolysis (n=98)		
End Points	(75%) DAPT (n=97)	No DAPT (n=33)	*P* Value	DAPT (n=17)	No DAPT (n=15)	*P* Value	DAPT (n=80)	No DAPT (n=18)	*P* Value
Fulfilled primary end point	66 (68%)	12 (36%)	0.0019	14 (82%)	8 (53%)	0.13	52 (65%)	4 (22%)	0.0013
Fulfilled secondary end points									
Rankin Scale score	78 (80%)	24 (73%)	0.46	16 (94%)	9 (60%)	0.03	62 (78%)	15 (83%)	0.76
No further fluctuation	77 (79%)	11 (33%)	<0.001	15 (88%)	9 (60%)	0.1	62 (78%)	2 (11%)	<0.001
No bleeding complications	97	33	…	17	15	…	80	18	…

3. Sténose athéromateuse intra-crânienne



Sténose athéromateuse intra-crânienne



AHA/ASA Guideline 2014

Intracranial atherosclerosis	For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable *(Class IIb; Level of Evidence B)*.	New recommendation

CLASS IIb

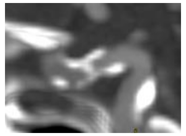
Benefit ≥ Risk
Additional studies with broad objectives needed; additional registry data would be helpful

Procedure/Treatment
MAY BE CONSIDERED

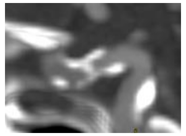
LEVEL B

Limited populations evaluated*

Data derived from a single randomized trial or nonrandomized studies



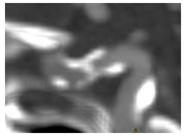
- Aucune étude randomisée comparant des traitements AAP avec un CJP clinique!
- CJP radiologiques ou doppler



ETUDES COMPARANT LES ANTIPLAQUETTAIRES

- ASA +/- Cilostazol : moins de progression en ARM à 6 mois, pas d'AVC
- Aspirine +/- PLAVIX : (Etude randomisée, en ouvert), sténose CI intra ou extra cranienne, IC ou AIT <7J; CJP : microemboles au DTC; groupe sténose intracranienne : moins de microemboles dans le groupe double AAP

Kwon et al Stroke 2005; 36:782-786
Wang et al Int J Stroke 2011;42:2883-2890

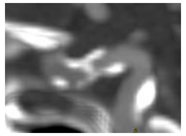


WASID

- randomisée
- Aspirine 1300 mg vs COUMADINE
- 569 patients
- Sténose intracranienne symptomatique >50%
- CJP AVC ou DC

Chimowitz et al NEJM 2005;352:1305-1316

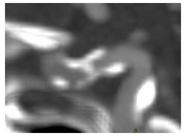
WASID



- Stoppée en raison d'un sur-risque hémorragique et de décès dans le groupe COUMADINE
- CJP 22% à 1,8 ans de suivi dans les 2 bras
- AVC à 1an : 12% dans le groupe ASA; 11% groupe COUMADINE
- AVC à 1 an dans le sous groupe sténose >70% (bras combinés) : 18%

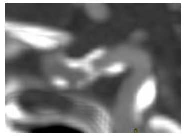
Chimowitz et al NEJM 2005;352:1305-1316

SAMMPRIS



- 451 patients
- Ttt médical agressif (dont double AAP) +/- STENTING
- Sténose intracranienne symptomatique >70%
- CJP AVC ou DC
- 20% vs 12,2% à 1 an

Chimowitz et al NEJM 2011;365:993-1003



SAMMPRIS

Traitement médical intensif

(double AAP + PEC intensive FDRV)

12%

WASID

Aspirine ou coumadine + PEC FDR

standard sous groupe >70%

comparable:

25%

Risque AVC ou DC à 1 an

Chimowitz et al NEJM 2011;365:993-1003

CONCLUSION

Double AAP

Recommandée pour :

1. **AIT ou IC mineur**

    - si **débutée dans les 24h**

    - pour une **durée de 3 semaines**

CONCLUSION

Posologies dose de charge ?

=> Plavix 4cp (CHANCE) ou 8 cp (POINT) + aspirine 75 à 300 mg

Posologies ensuite?

=> 75/75 (CHANCE) ou Plavix 75/Aspirine 50 à 325 (POINT) ?

Quel AAP après les 3 semaines?

=> CHANCE : Plavix

CONCLUSION

Double AAP

Recommandée pour :

2. **Sténose intracrânienne symptomatique**

- si **vu dans les 30 J**
- pour une **durée de 3 mois**

Aspirine + Plavix 75 mg

CONCLUSION

Double AAP

<u>Probablement utile mais sans recommandation :</u>

Claudication des infarctus lacunaires à la phase aigue

- si aggravation dans les 5 jours

- pour une **durée de 5 jours**

Et les thrombi flottants carotidiens ?

AHA/ASA Guideline 2018

The optimal medical management of patients with AIS and radiologic evidence of nonocclusive, intraluminal thrombus (eg, cervical carotid, vertebrobasilar arteries) remains uncertain. Several small observational studies have suggested the safety of short-term IV heparin or LMWH in this setting,[203,204] but further research is required to establish safety and efficacy.