

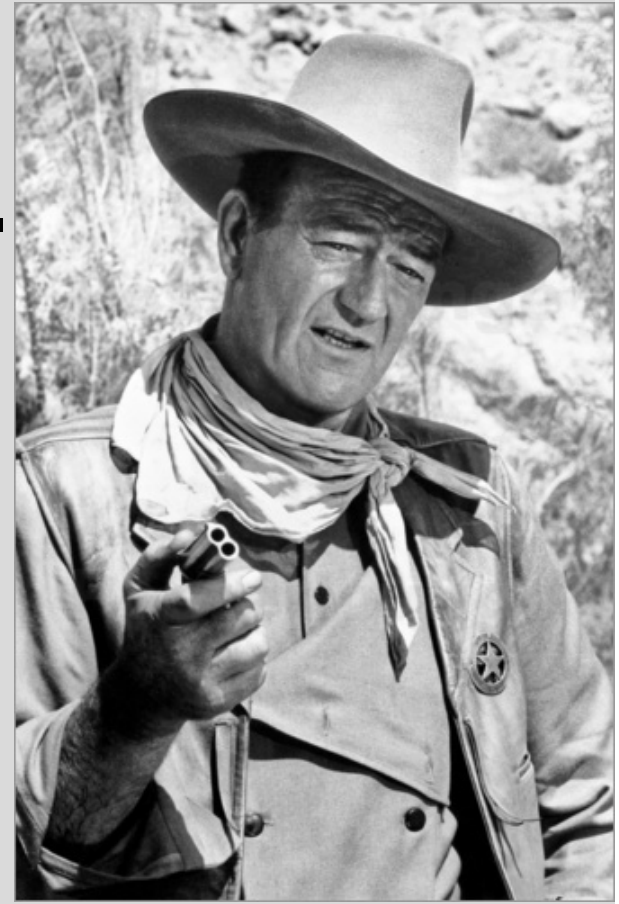


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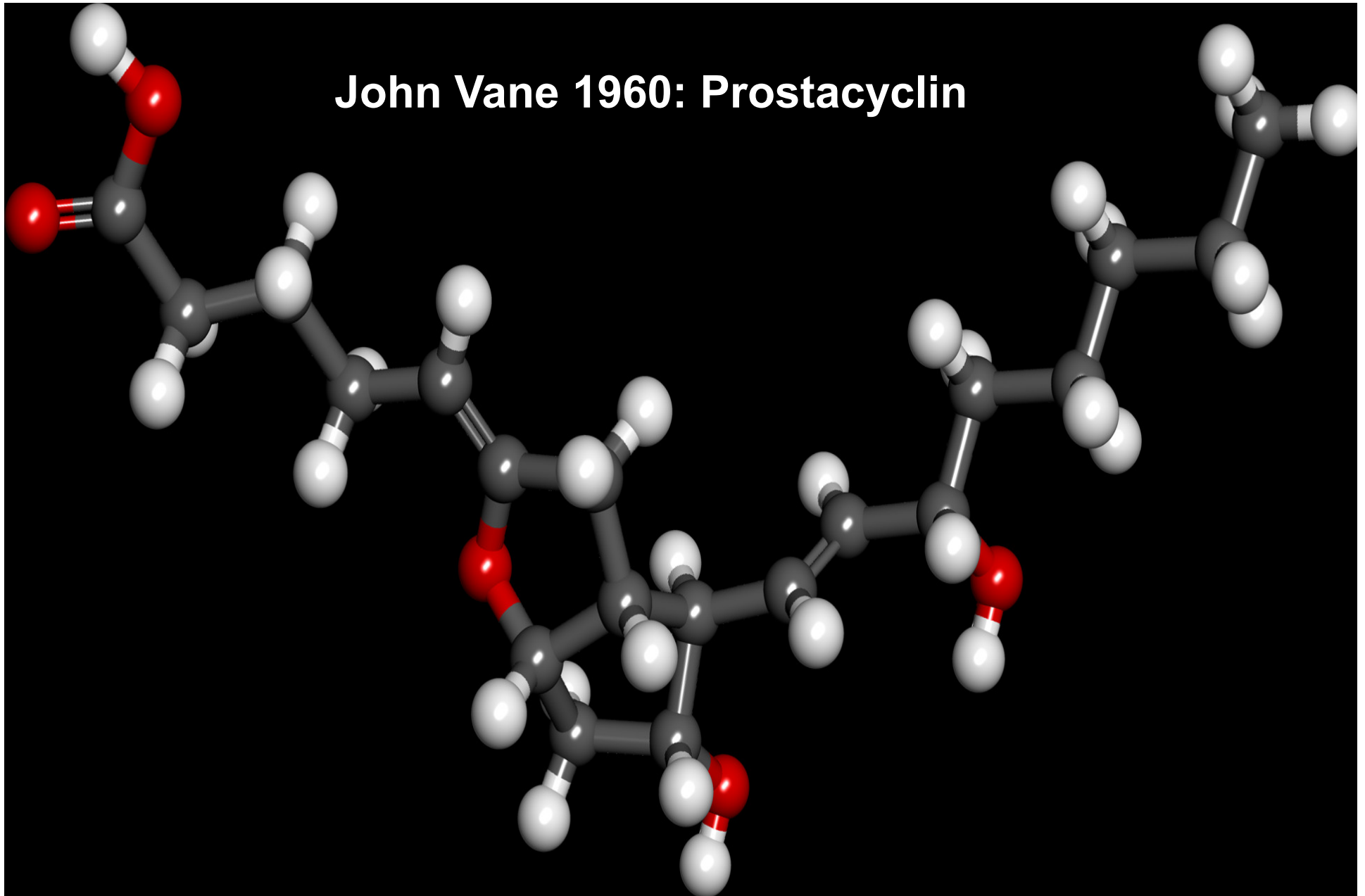
Ilomedin et autres..

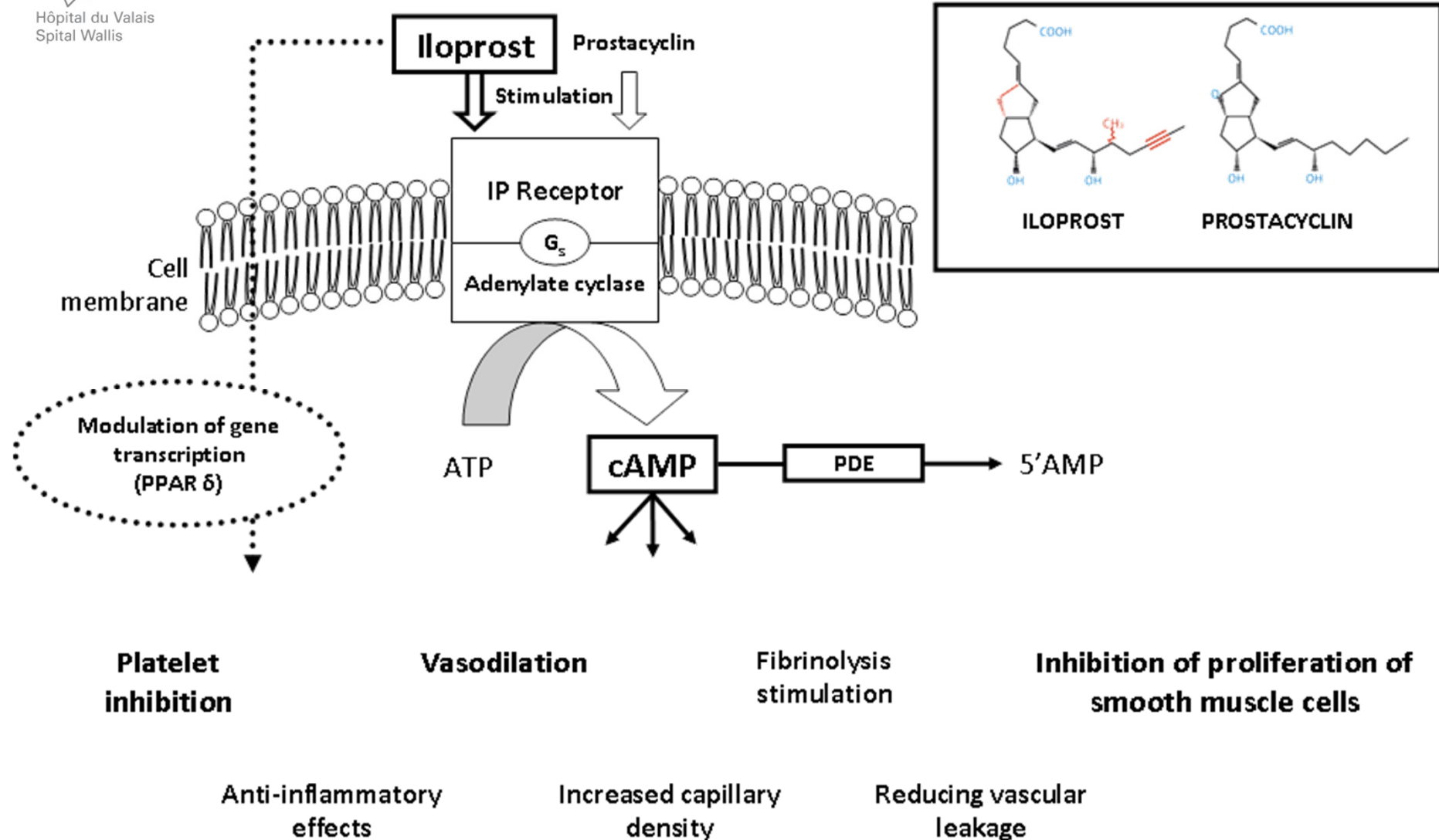
D Danzer

Service de chirurgie vasculaire



John Vane 1960: Prostacyclin



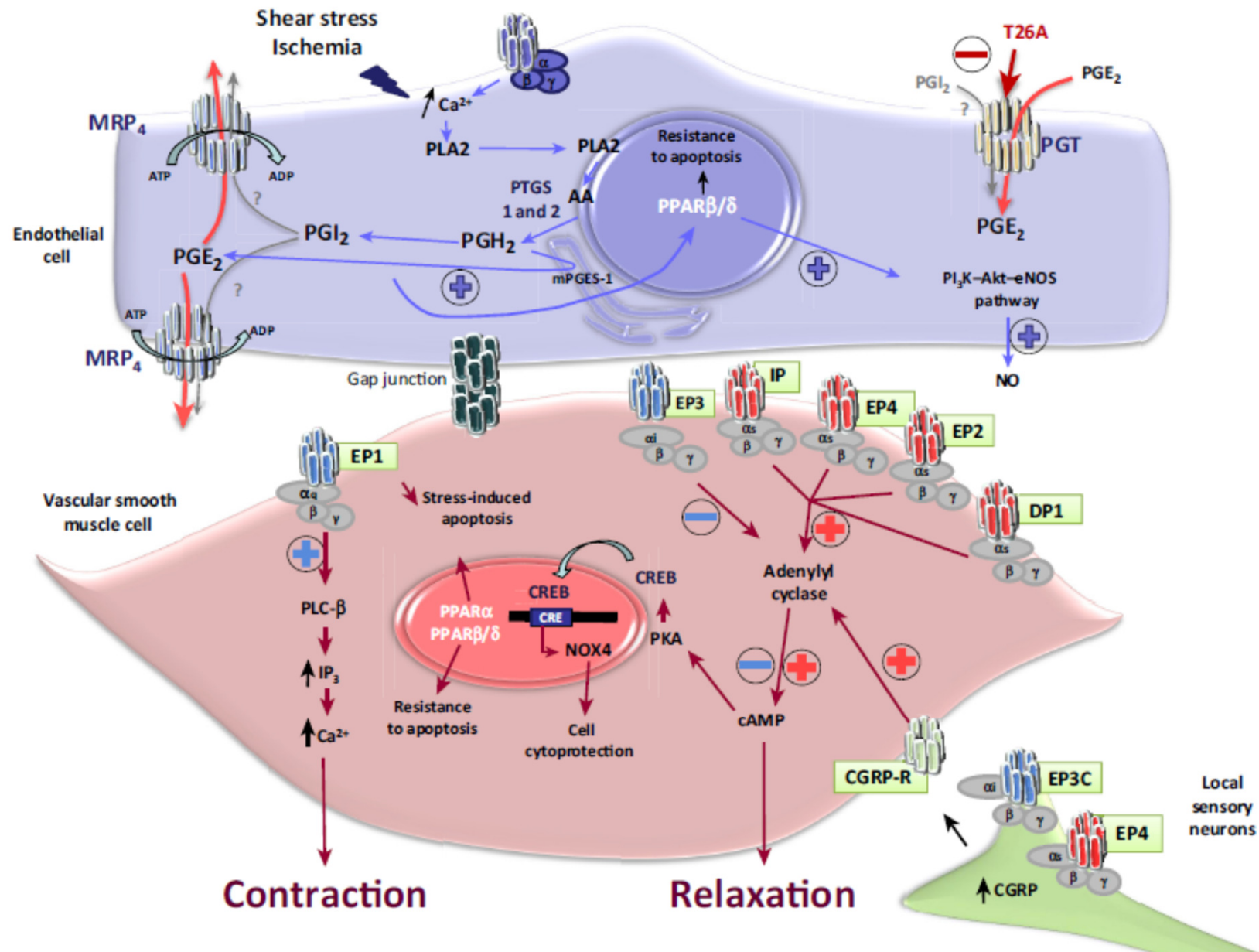


Prostacyclin effect		Mechanism	Cellular response
Classical functions	Vessel tone	↑cAMP, ↓ET-1 ↓Ca ²⁺ , ↑K ⁺	↓SMC proliferation ↑Vasodilation
	Antiproliferative	↑cAMP ↑PPARgamma	↓Fibroblast growth ↑Apoptosis
	Antithrombotic	↓Thromboxane-A2 ↓PDGF	↓Platelet aggregation ↓Platelet adherence to vessel wall
Novel functions	Antiinflammatory	↓IL-1, IL-6 ↑IL-10	↓Proinflammatory cytokines ↑Antiinflammatory cytokines
	Antimitogenic	↓VEGF ↓TGF-β	↓Angiogenesis ↑ECM remodeling

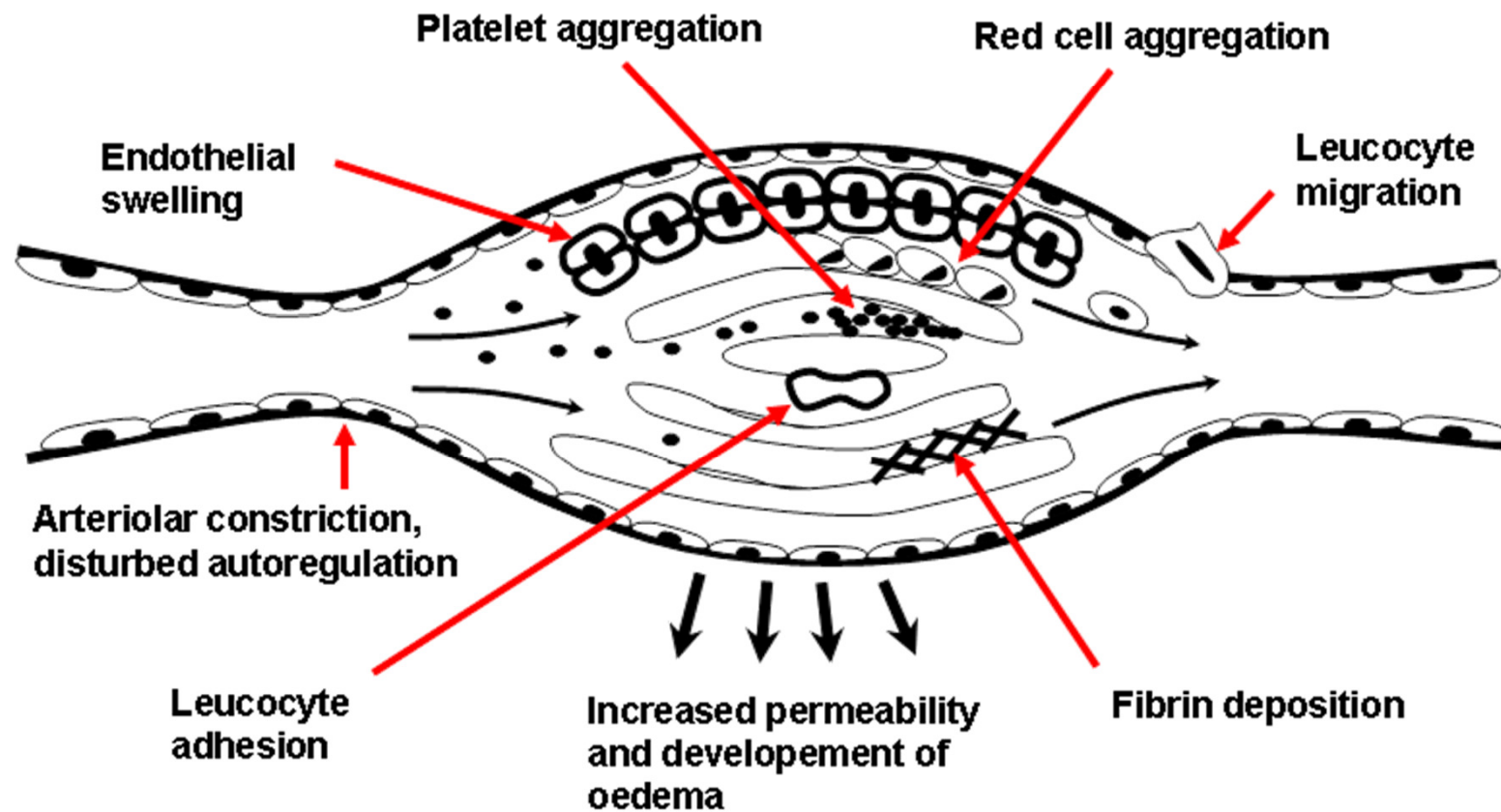
Ilomedin® (Iloprost)

- L'iloprost : dérivé synthétique de la prostacycline (PGI_2).
 - Inhibition de l'agrégation et de l'adhésion plaquettaires, ainsi que de la réaction de libération des thrombocytes.
 - Dilatation des artérioles et des veinules.
 - Augmentation de la densité capillaire et diminution de la perméabilité vasculaire augmentée dans la microcirculation.
 - Stimulation du potentiel fibrinolytique endogène.
 - Actions anti-inflammatoires, telles qu'inhibition de l'adhésion des leucocytes lors de lésions de l'endothélium et de l'accumulation des leucocytes dans le tissu lésé, ainsi que diminution de la libération du facteur de nécrose tumorale.
 - Protection contre l'apoptose des cellules musculaires lisses
 - Stimule la néoangiogenèse
- Pluchart et al, Trends in Pharmacology 2017

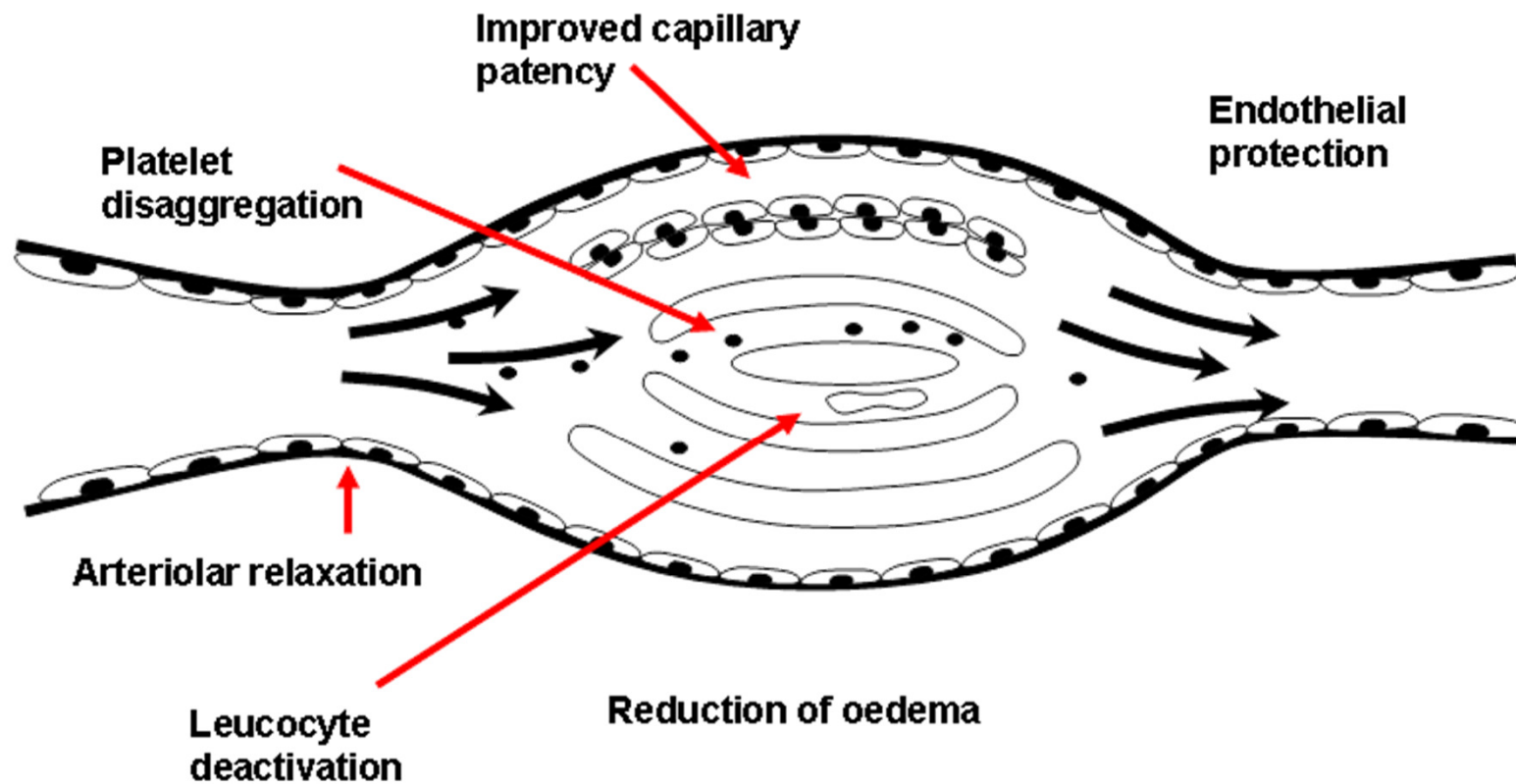
Prostacyclin Pathways in the Systemic Circulation



ALTERED MICROCIRCULATION: IMPAIRED AND IRREGULAR PERFUSION



RESTORED MICROCIRCULATION: IMPROVED PERFUSION



Effets secondaires

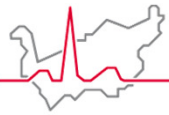
- Fréquent ($>10\%$): céphalées ($>50\%$), un flushing ($>50\%$), des nausées, des vomissements, hyperhidrose, ($>1/100$) hypotension, tachycardie, angine de poitrine, dyspnée
- Occasionnel ($1/1000-1/100$): accident vasculaire cérébral, infarctus du myocarde, embolie pulmonaire, insuffisance cardiaque aiguë, convulsions, asthme, oedème pulmonaire

Utilisation en cas de vasculopathie périphérique

- **Perfusion intraveineuse sur 6h/j pdt 1-4sem**
- **0.5-2ng/kg/min par palier de 30min**
 - Tachyphylaxie (thrombocyte)
 - Effet rebond sur l'aggrégation plaquettaire

Indications

- **Frost bite (Helsinki protocol)**



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Frostbite

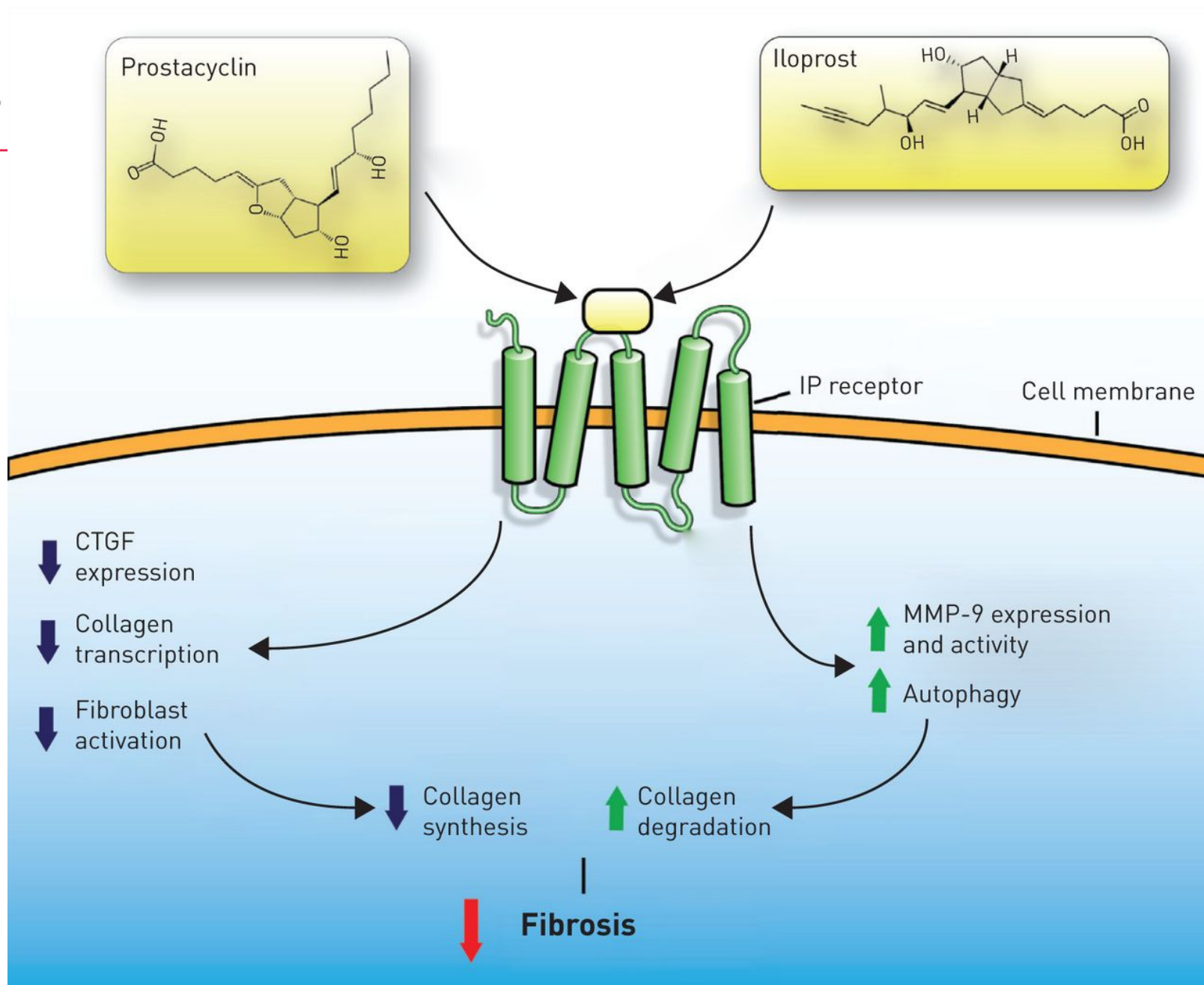


Indications

- **Frost bite (Helsinki protocol)**
- **Synd de Raynaud (Ilre, Sclerodermie)**
 - Activité sur la production de cytokine (Th17)

Scleroderme





Syndrome de Raynaud primaire-temporaire

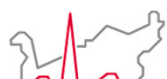


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Indications

- **Frost bite (Helsinki protocol)**
- **Synd de Raynaud (Ilre, Sclerodermie)**
 - Activité sur la production de cytokine (Th17)
- **Mal. De Buerger**





Maladie de Buerger

Patient or population: patients with Buerger's disease

Settings: hospital and community

Intervention: intravenous prostacyclin analogue (Iloprost)

Comparison: oral aspirin

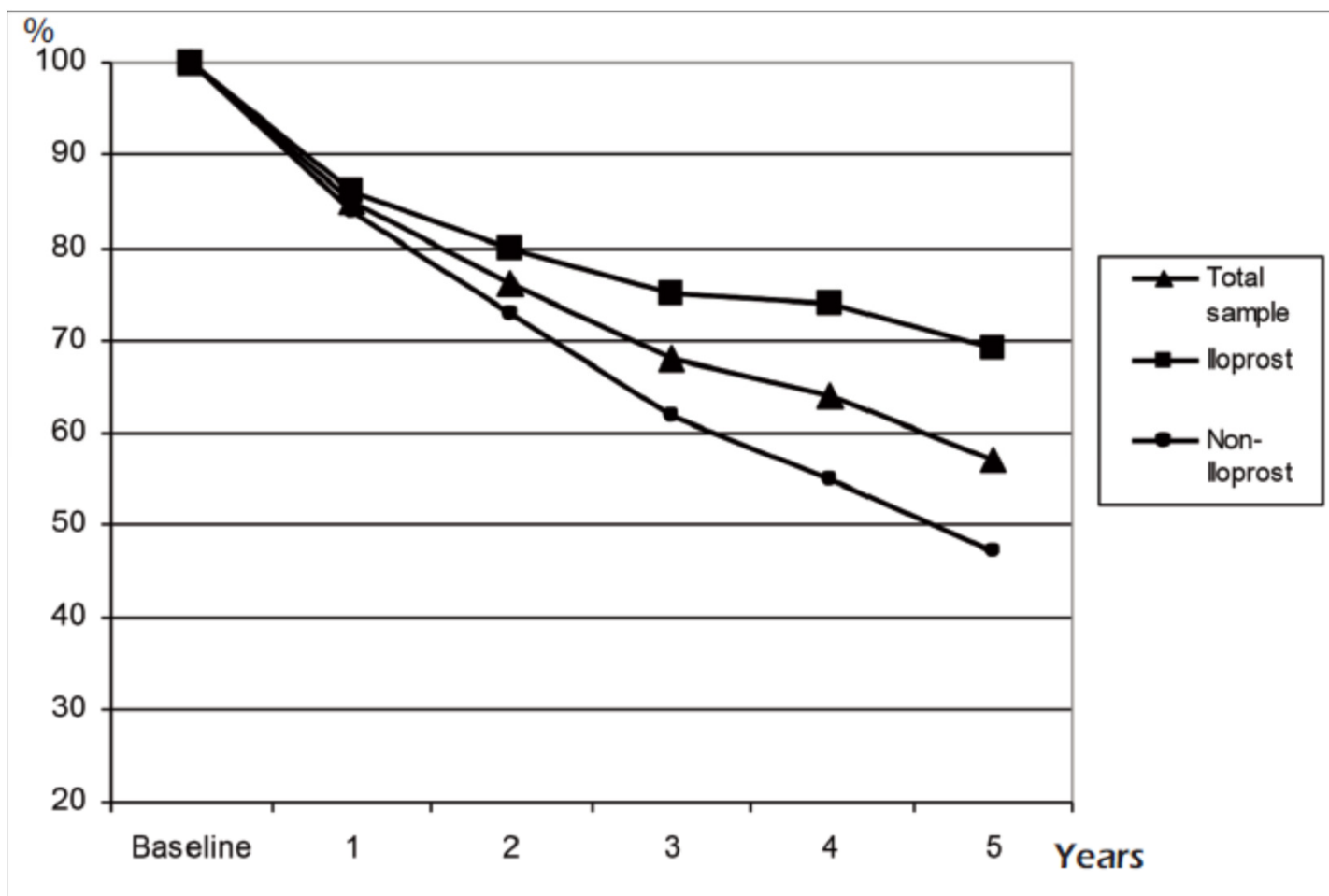
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	oral aspirin	intravenous prostacyclin analogue			
Ulcer healing Follow-up: 28 days	Study population		RR 2.65 (1.15 to 6.11)	98 (1 RCT)	⊕⊕⊕⊖ ^{1,2} moderate
	130 per 1000	346 per 1000 (150 to 797)			
Ulcer healing Follow-up: 6 months	Study population		RR 4.03 (1.24 to 13.10)	95 (1 RCT)	⊕⊕⊕⊖ ^{1,2} moderate
	68 per 1000	275 per 1000 (86 to 893)			
Complete relief of rest pain Follow-up: 28 days	Study population		RR 2.28 (1.48 to 3.52)	133 (1 RCT)	⊕⊕⊕⊖ ^{1,2} moderate
	277 per 1000	631 per 1000 (410 to 975)			
Rate of amputation Follow-up: 6 months	Study population		RR 0.32 (0.09 to 1.15)	95 (1 RCT)	⊕⊕⊕⊖ ^{1,2} moderate
	182 per 1000	58 per 1000 (16 to 209)			

Cacione et al Cochrane 2016

Indications

- **Frost bite (Helsinki protocol)**
- **Synd de Raynaud (Ilre, Sclerodermie)**
 - Activité sur la production de cytokine (Th17)
- **Mal. De Buerger**
- **Insuffisance artérielle critique?**
 - Non revascularisable

Survival



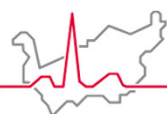


Table II. Characteristics and outcomes of patients treated or not treated with iloprost.

	Iloprost (n=84)	Non-Iloprost (n=97)	p-value
Age (years) \pm SD	74 \pm 6	71 \pm 7	NS
Diabetes mellitus	52% (n=44)	39% (n=38)	NS
Hypertension	64% (n=54)	69% (n=67)	NS
Fontaine stage III	30% (n=25)	26% (n=25)	NS
Fontaine stage IV	70% (n=59)	74% (n=72)	NS
Previous procedures			
Vascular surgery	30% (n=25)	33% (n=32)	NS
Sympathicolysis	1% (n=1)	11% (n=11)	NS
SCS	12% (n=10)	0% (n=0)	<0.05
Contralateral amputation	1% (n=1)	3% (n=3)	NS
Subsequent procedures			
Major amputations	6% (n=5)	21% (n=20)	<0.00001
Minor amputations	7% (n=6)	12% (n=12)	NS
Vascular surgery	4% (n=3)	32% (n=31)	<0.00001
Sympathicolysis	0% (n=0)	5% (n=5)	NS
SCS	1% (n=1)	7% (n=7)	<0.05
Survival:			
1 year	86% (n=72)	84% (n=81)	NS
2 years	80% (n=67)	73% (n=71)	NS
5 years	69% (n=58)	47% (n=46)	<0.0001



Ischémie critique

Prostanoids compared with placebo for critical limb ischaemia

Patient or population: people with critical limb ischaemia

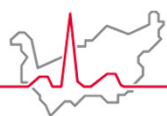
Setting: hospital

Intervention: prostanoids

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with prostanoids				
Cardiovascular mortality Follow-up: range 2 months to 7 months	Study population 32 per 1000	26 per 1000 (13 to 51)	RR 0.81 (0.41 to 1.58)	1170 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	
Total amputations Follow-up: range 1 month to 12 months	Study population 269 per 1000	261 per 1000 (231 to 293)	RR 0.97 (0.86 to 1.09)	2825 (12 RCTs)	⊕⊕⊕⊕ HIGH ^c	
Quality of life	See comments.		-	-	-	None of the included trials reported this outcome.
Adverse events (participants) Follow-up: range 3 weeks to 7 months	Study population 319 per 1000	674 per 1000 (572 to 798)	RR 2.11 (1.79 to 2.50)	655 (8 RCTs)	⊕⊕⊕○ MODERATE ^a	
Rest-pain relief (dichotomous) Follow-up: range 1 month to 12 months	Study population		RR 1.30 (1.06 to 1.59)	1179 (10 RCTs)	⊕⊕⊕○ MODERATE ^a	

Vietto et al Cochrane 2018



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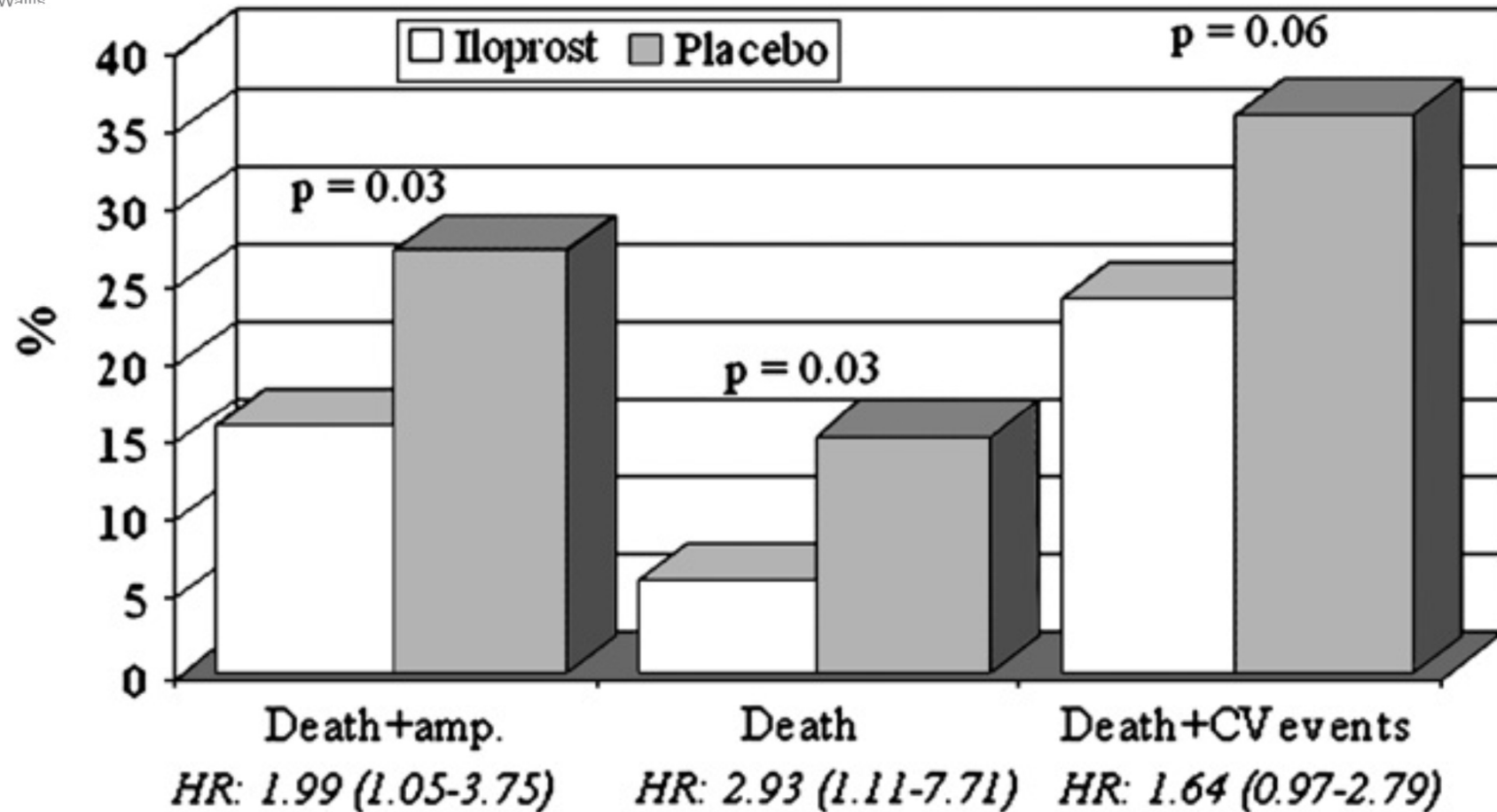
Plaies

		228 per 1000	296 per 1000 (241 to 362)		
Ulcer healing Follow-up: range 3 weeks to 6 months	Study population			RR 1.24 (1.04 to 1.48)	1719 (11 RCTs)
		358 per 1000	444 per 1000 (373 to 530)		⊕⊕⊕○ MODERATE ^a

Indications

- **Frost bite (Helsinki protocol)**
- **Synd de Raynaud (Ilre, Sclerodermie)**
 - Activité sur la production de cytokine (Th17)
- **Mal. De Buerger**
- **Insuffisance artérielle critique?**
 - Non revascularisable
- **Experimental**
 - TT adjuvant en chirurgie vasculaire

Ischémie aigue TT adjuvant >70ans

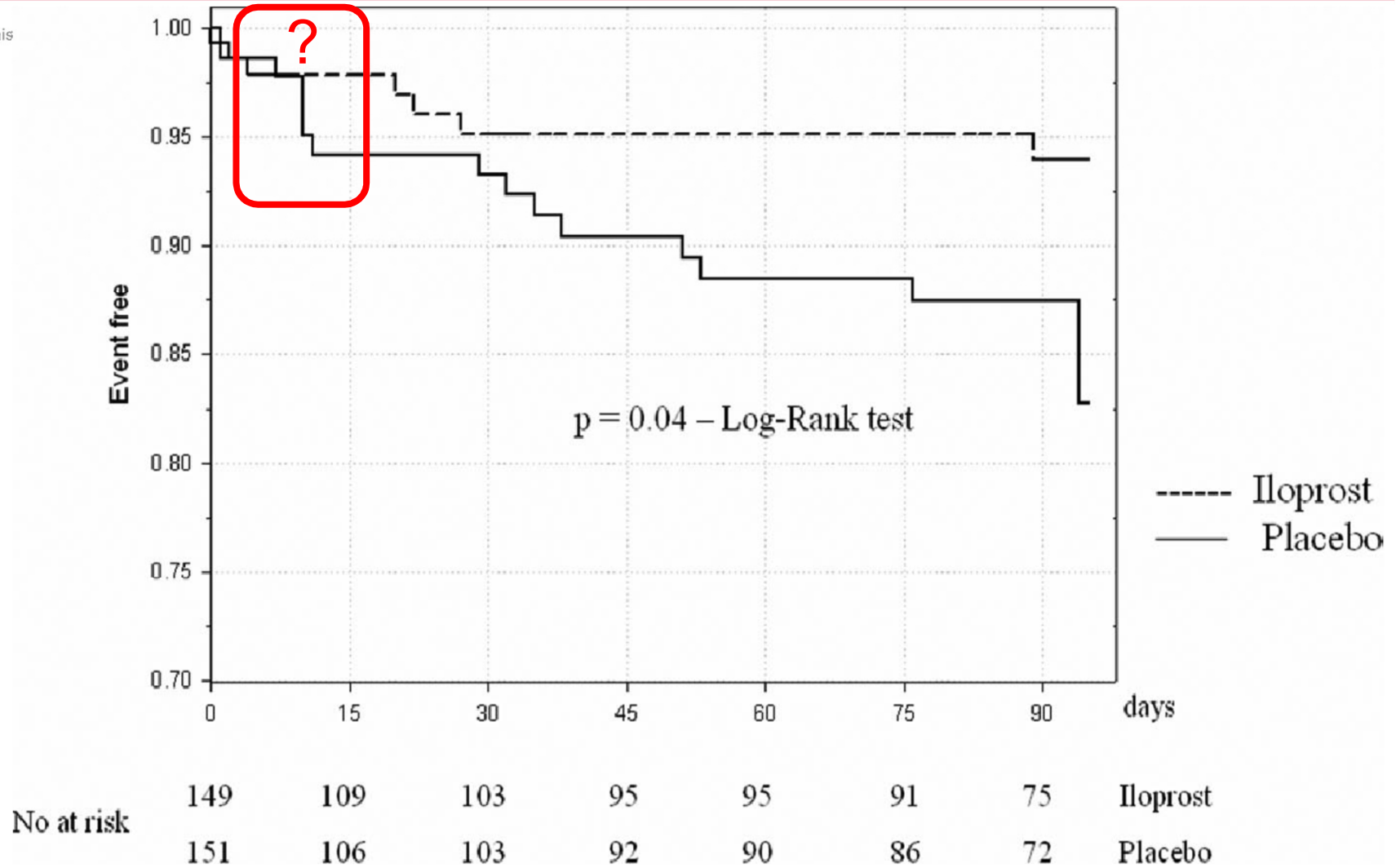


ILAILL Study Eur J Vasc Endovasc Surg 2007

Table 3. Details of major clinical events in patients treated with placebo or iloprost

Characteristic	Placebo (N = 92) N.of cases (%)	Iloprost (N = 100) N.of cases (%)	p value
Death	14 (15.2%)	6 (6%)	0.03
Reported causes			
Stroke	2	2	
Acute myocardial infarction	1		
Cardiac failure	2	3	
Arrhythmia	1		
Other thrombotic events	2		
Acute renal failure	1		
Bleeding	1		
Pneumonia	1		
Tumoral progression		1	
Unknown (death at home)	3		
Amputation	11 (11.9%)	10 (10%)	ns
Other major cardiovascular events	8 (8.7%)	8 (8.0%)	ns
Stroke		2	
Acute myocardial infarction		1	
Cardiac failure	1		
Arrhythmia	1		
Additional revascularization	3	4	
Recurrent ALLI	3	1	

Ischémie aiguë adjuvant?



De Donato et al Ann Vasc 2006

Effet réel ou puissance insuffisante

TABLE 2. Occurrence of Major Clinical Events in the 2 Study Groups

Event	Placebo (n = 151)	Iloprost (n = 149)	<i>P</i> *
Death + amputation primary (endpoint)	30 (19.9)	21 (14.1)	0.18
Death	16 (10.6)	7 (4.7)	0.05
Amputation	14 (9.3)	14 (9.4)	0.97
Other major events	20	13	0.21
Additional revascularization	9 (6.0)	7 (4.7)	0.62
Recurrent acute ischemia	4 (2.6)	2 (1.3)	0.41
Acute myocardial infarction	2 (1.3)	1 (0.7)	0.57
Cardiac failure	2 (1.3)	0	0.16
Arrhythmia	2 (1.3)	1 (0.7)	0.57
Stroke	0	2 (1.3)	0.15
Pulmonary embolism	1	0 (0.7)	0.32
Death + other major events (total)	50 (33.1)	34 (22.8)	0.04

Values are no. (%) of cases.

*Comparison between treatment groups (χ^2 test).

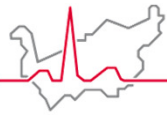


Indications

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- **Mal. De Buerger**
- **Insuffisance artérielle critique?**
 - Non revascularisable
- **Experimental**
 - TT adjuvant en chirurgie vasculaire
 - Insuff art intestinale (Nuzzo et al, Ann Vasc Surg 2017)
 - Application topique pour plaie chronique
- **Autre indication**
 - HTAP (sildenafil,...)
 - TT adjuvant en chirurgie digestive majeure (protection endotheliale) (Johansson et al, Eur J Gastroenterol Hepatol 2017)



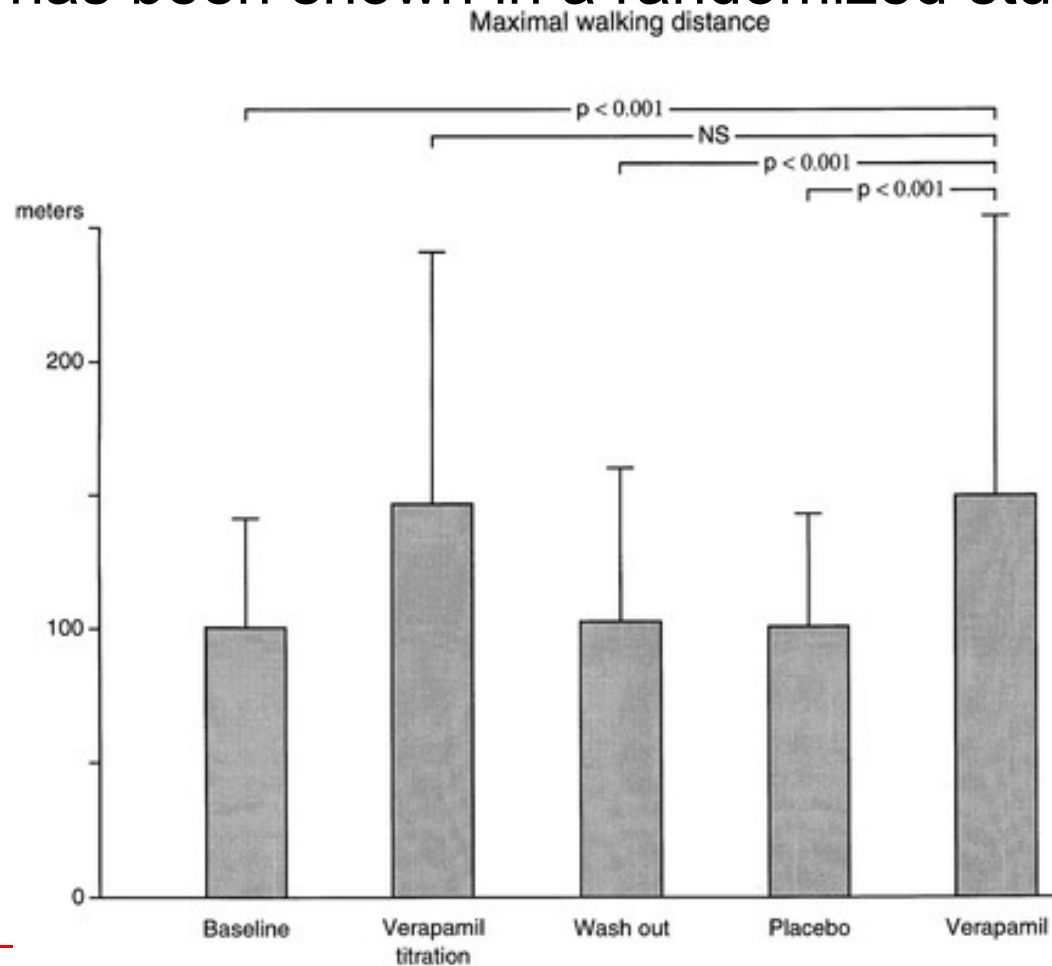
Autres médocs?



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Anticalcique

- The benefit of verapamil in improving WD in LEAD has been shown in a randomized study



Bagger et al Circ 2018

Recommendations on the management of chronic limb-threatening ischaemia

Recommendations	Class ^a	Level ^b
Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage. ³¹⁷	I	C
In patients with CLTI, assessment of the risk of amputation is indicated. ³¹⁷	I	C
In patients with CLTI and diabetes, optimal glycaemic control is recommended. ^{318,319}	I	C
For limb salvage, revascularization is indicated whenever feasible. ³¹⁴	I	B
In CLTI patients with below-the-knee lesions, angiography including foot runoff should be considered prior to revascularization.	IIa	C
In patients with CLTI, stem cell/gene therapy is not indicated. ³²⁸	III	B

CLTI = chronic limb threatening ischaemia.

^aClass of recommendation.

^bLevel of evidence.

ESVS/ESC Guidelines 2017

Médicaments de la «mauvaises circulation»

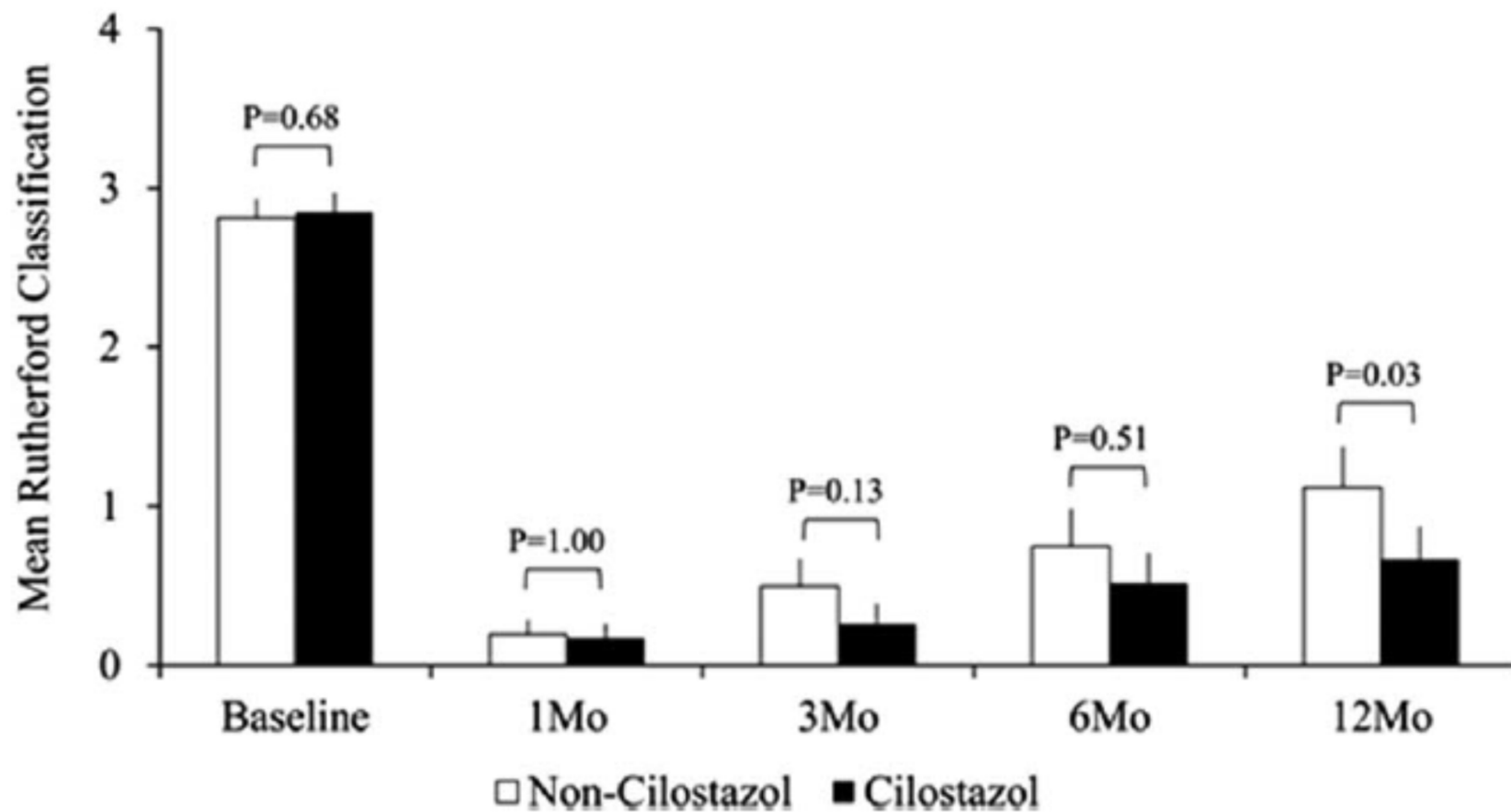
- Cilostazol
- Naftidrofuryl
- Pentoxifylline
- Buflomedil
- Carnitine and propionyl-L-carnitine.

Cilostazol

- Inhibiteur de la phosphodiesterase type III.
- Nb études favorable concernant la distance de marche comparé au placebo ou à la pentoxifylline (Pentoxi-Mepha®).
- Effet secondaires: similaires à l'Ilomedin y compris plaquettaire
- Pas autorisé en Suisse, retiré en France

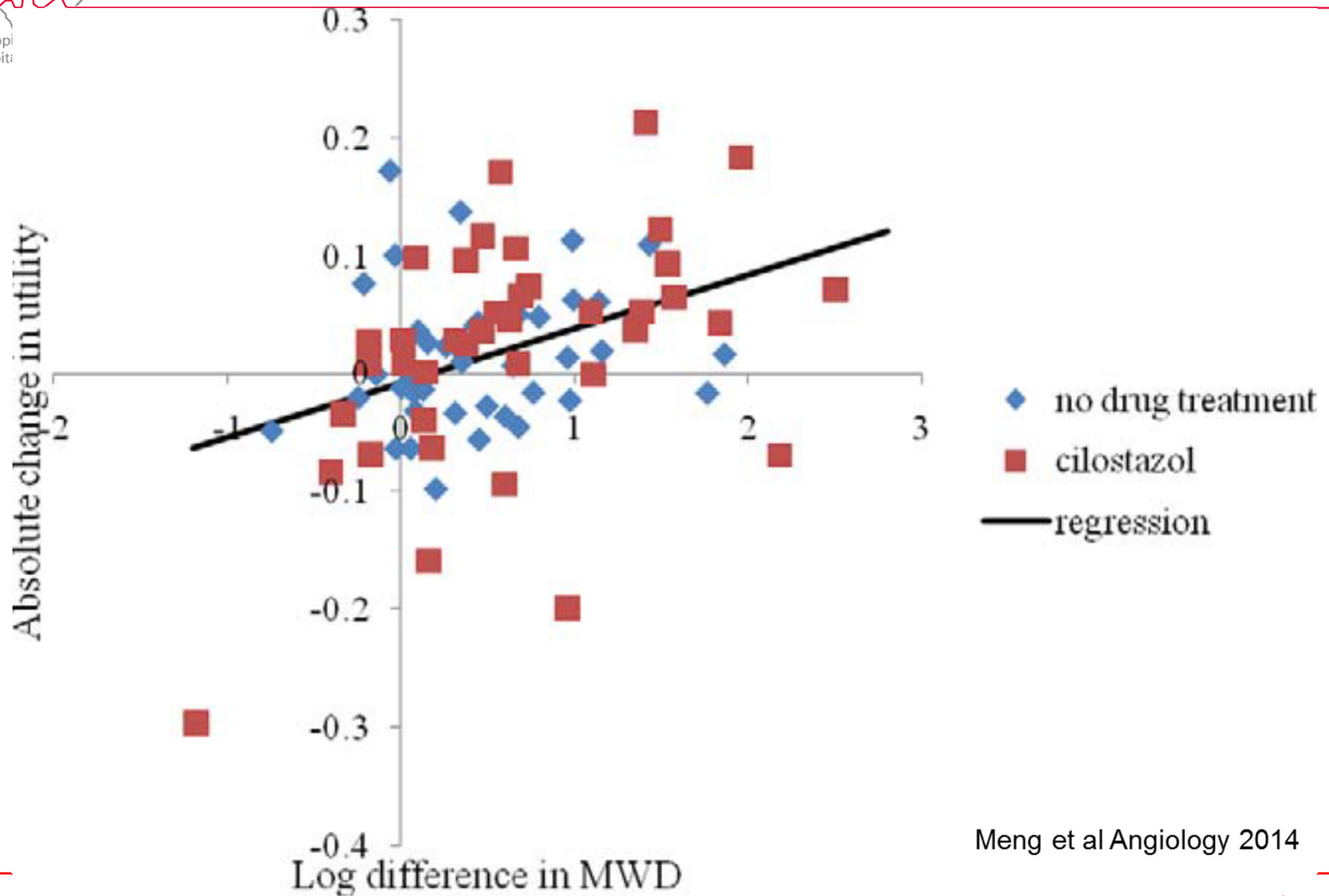


TT adjuvant après angioplastie



Iida et al Circ 2013

TT primaire



Meng et al Angiology 2014

Recommendations for Cilostazol, Pentoxifylline, and Chelation Therapy

COR	LOE	Recommendations
Cilostazol		
I	A	Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication (119, 163).
Pentoxifylline		
III: No Benefit	B-R	Pentoxifylline is not effective for treatment of claudication (119, 164).
Chelation Therapy		
III: No Benefit	B-R	Chelation therapy (eg, ethylenediaminetetraacetic acid) is not beneficial for treatment of claudication (165).

Gerhard-Herman MD, et al.

2016 AHA/ACC Lower Extremity PAD Guideline: Executive Summary

Naftidrofuryl oxalate (Praxilene®)

- Effets secondaires : Gastro intestinaux
- Plus “cost effective” que d’autres

Table 3. Incremental Discounted Cost-Effectiveness Results (Base Case).

Interventions and Comparator	Total Costs (Additional to No Vasoactive Drug Treatment; £)	Total QALYs	Incremental Cost-Effectiveness Ratio (£ per QALY Gained)	Dominance
No vasoactive drug (baseline technology)	£0	4.975	–	
Pentoxifylline	£493	4.984		Dominated by naftidrofuryl oxalate
Cilostazol	£964	4.994		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£298	5.024	£6070	

Abbreviation: QALY, quality-adjusted life year.

Compliance?

Table 1. Proportions of Patients Discontinue the Drugs Within 24 Weeks.

Reference	Year	Placebo	Cilostazol	Naftidrofuryl oxalate	Pentoxifylline
Beebe et al ¹³	1999	17.1% (n = 170)	21.1% (n = 175)		
O'Donnell et al ⁷	2009	12.7% (n = 55)	15.7% (n = 51)		
Otsuka (study 21-94-301) ¹⁹	2010	15.3% (n = 124)	27.6% (n = 123)		30.1% (n = 123)
Otsuka (study 21-98-213) ¹⁹	2010	26.9% (n = 262)	35.4% (n = 261)		31.5% (n = 262)
Kieffer et al ⁸	2001	16.3% (n = 98)		13.3% (n = 98)	
Adhoue et al ¹⁸	1986	9.3% (n = 54)		7.8% (n = 64)	
Dawson et al ¹⁷	2000	15.9% (n = 239)	27.0% (n = 227)		26.0% (n = 232)

Meng et al Angiology 2014

Buflomedil

- **Prescrit largo mano en France jusqu'en 2006 en cas d'insuffisance artérielle.**
- **Puis retiré du marché?**



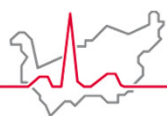
Conclusions européennes ESVS/ESC 2017

- «...prostanoids, pentoxifylline (Pentoxi-Mepha®), L-arginine, buflomedil or ginkgo biloba do not have enough consistent data from RCTs to be recommended in patients with Intermittent Claudicatio...»

En résumé sauf exception

- **Pour être efficace...**





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Ou alors...



Merci

