Les angines réfractaires

Options pour les sans options

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Conflits of Interests

Conseiller scientifique	Neovasc	2010-4
	Eli Lilly	2011-3
	Baxter Healthcare	2013-4
	AstraZeneca	2009-13
	Tasly	2014
Conférencier	Baxter Healthcare	2013
	Astrazeneca	2013
	Eli Lilly	2013
Recherche	Gilead Inc	2012-4
	Servier	2013-4
	Boston Scientific	2013-6
	AstraZeneca	2013-6

FIDE SPLENDET ET SCIENTIA

Fonds de la recherche en santé Québec

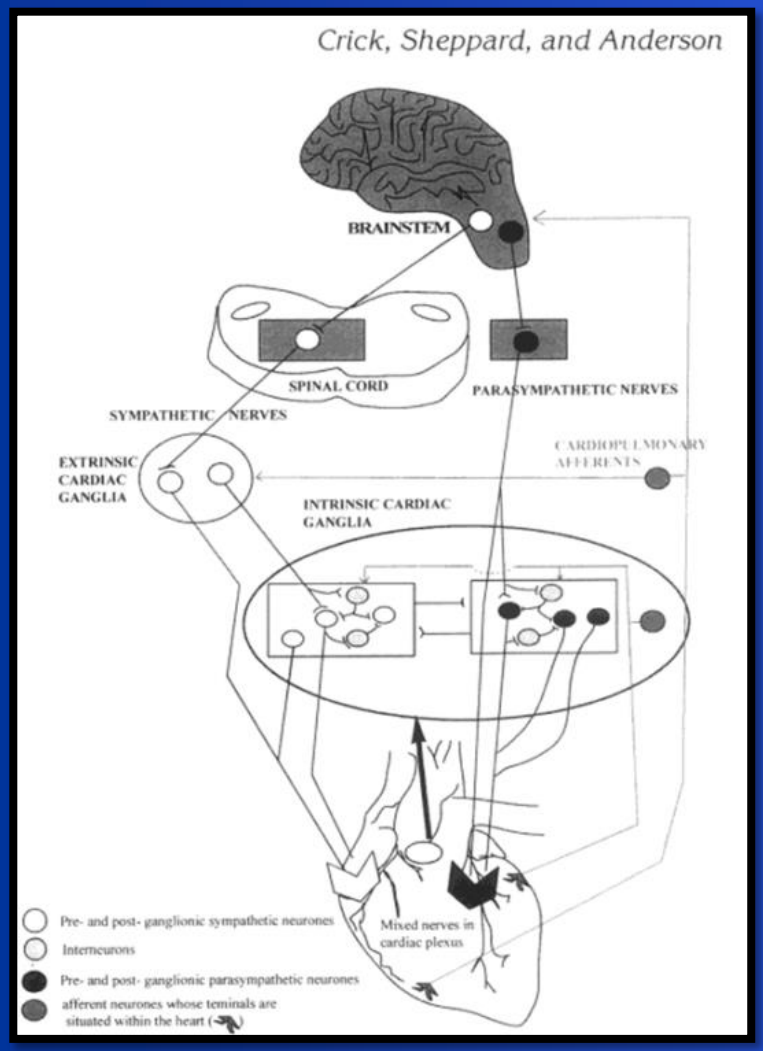
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Objectifs

- Distinguer les différentes pathologies pouvant mener aux douleurs cardiaques chroniques;
- Comprendre la pyramide du traitement de l'angine réfractaire chez le patient avec MCAS avancée;
- Intégrer les éléments de prise en charge multidisciplinaire des patients avec angine réfractaire.

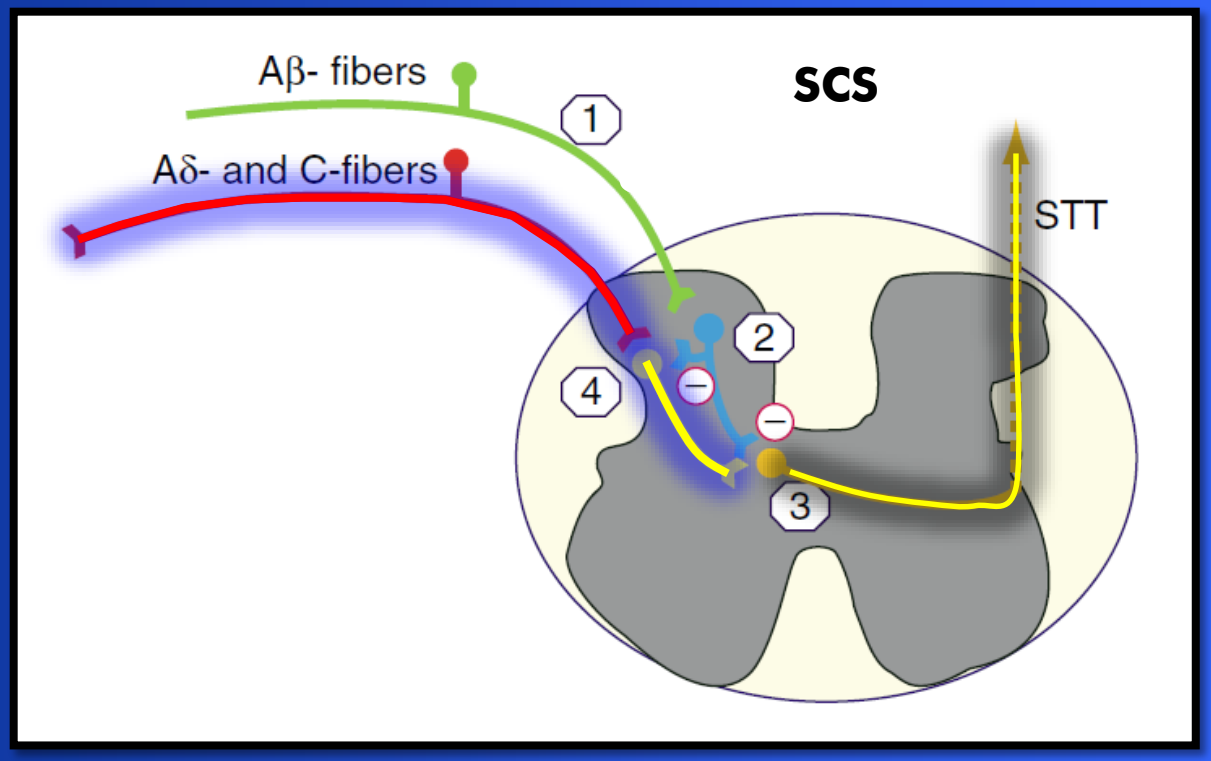
Qu'est-ce que l'angine au juste?

Neuro-anatomie du coeur



- Il n'existe pas de nocicepteur connu dans le myocarde
- Les nerfs sympathiques permettent la principale efférence nociceptive du myocarde
- Le signal nociceptif converge vers les ganglions stellaires et cervicaux, jusqu'à la colonne intermédiolatérale (T2 to T6)
- Ultimement, le signal converge vers le SNC via les voies spinothalamiques

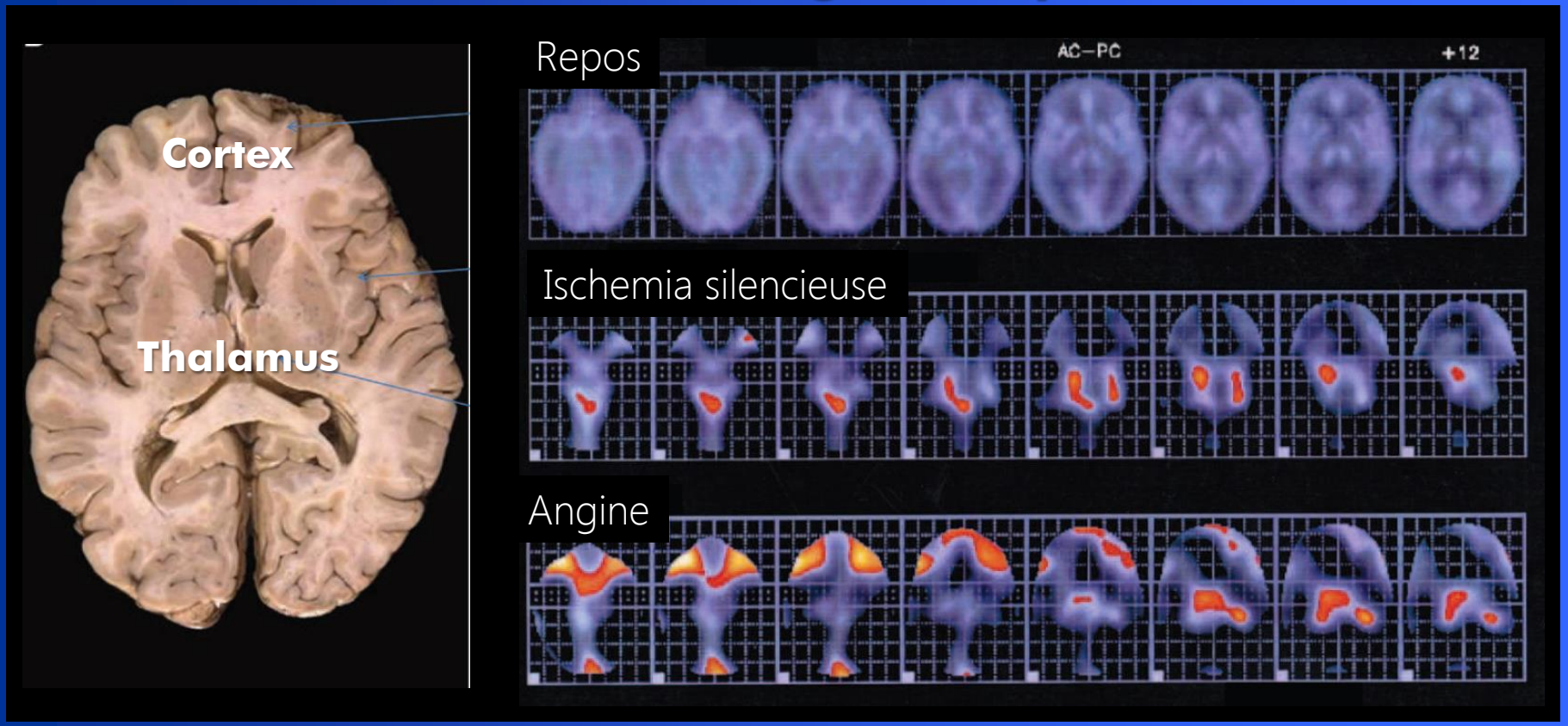
Adapted from Gert J. Ter Horst, The Nervous System and the Heart,. 2000
Rosen and Camici, Functional Pain Syndromes: Presentation and Pathophysiology 2009



The contemporary view of the gate control theory assumes that the stimulation of the large afferent non-nociceptive A-alpha and A-beta fibers by spinal cord stimulation can stop the transmission of the nociceptive impulse in the small afferent A-delta and C fibers to the central nervous system.

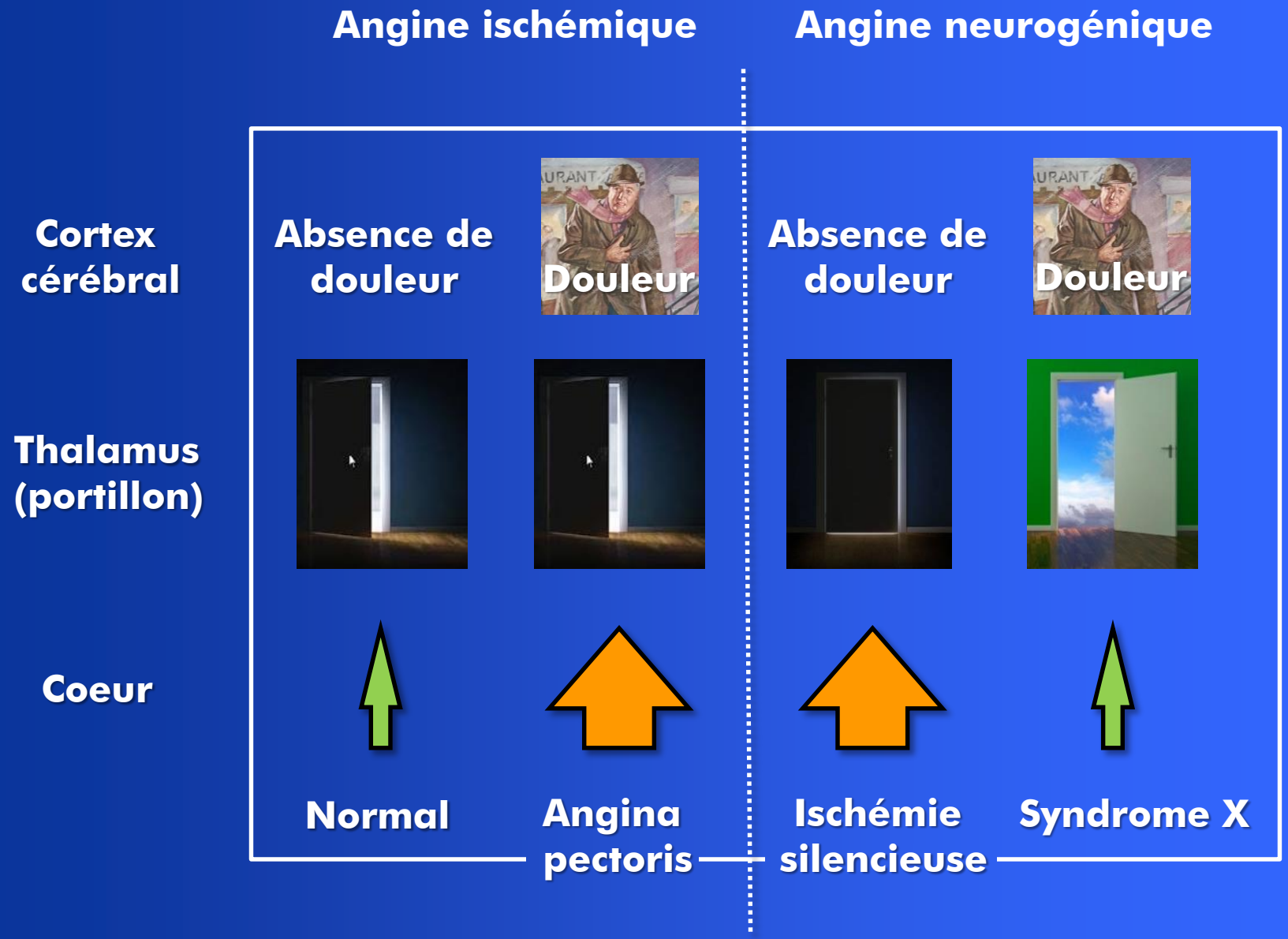
Jolicoeur et al., Invasive and Device Management of Refractory Angina

Variation de la perfusion cérébrale régionale durant l'ischémie silencieuse et l'angine de poitrine



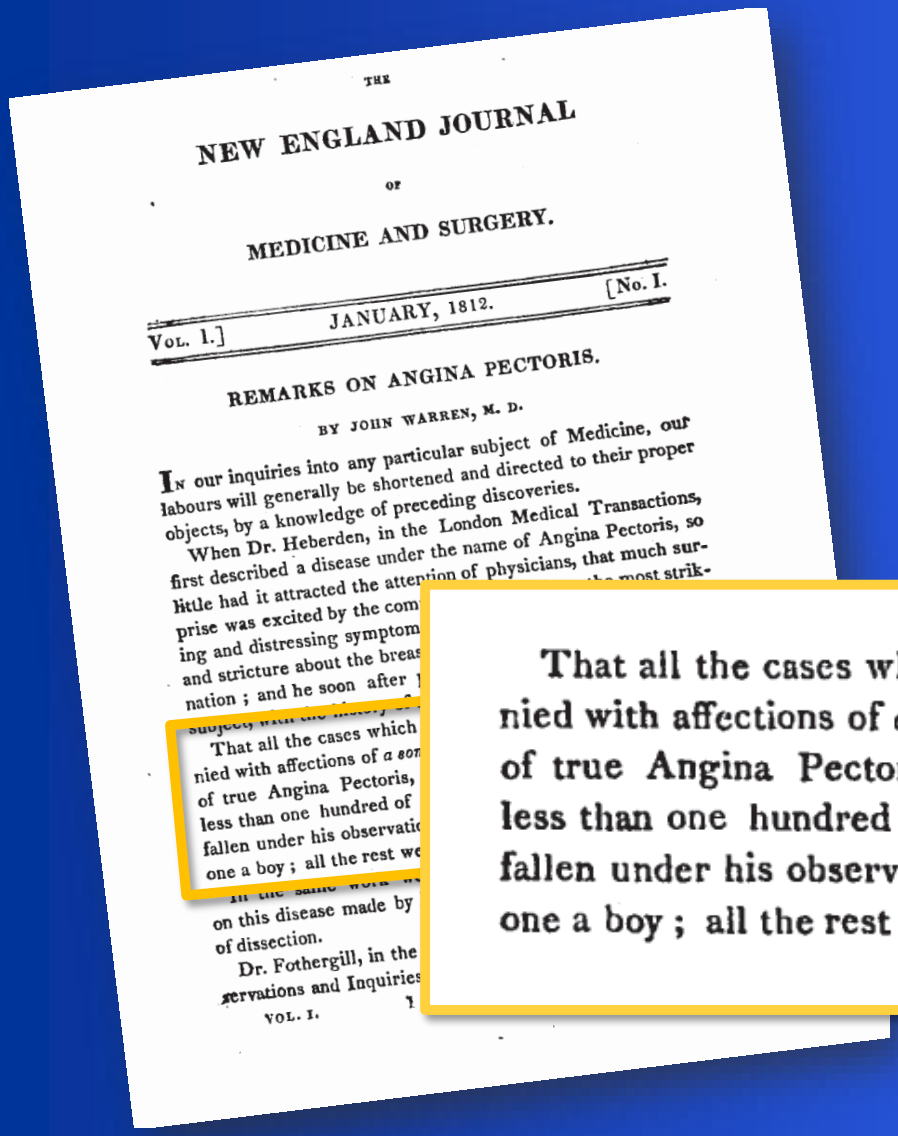
TEP H_20 marqué avec oxygen-15

Adapté de Rosen SD, CJC 2012:28 Supp; S7



Adapted from Rosen SD, CJC 2012:28 Supp; S7

La prophétie de Warren -1812



THE

NEW ENGLAND JOURNAL

OF

MEDICINE AND SURGERY.

VOL. I.] JANUARY, 1812. [No. I.

REMARKS ON ANGINA PECTORIS.

BY JOHN WARREN, M. D.

IN our inquiries into any particular subject of Medicine, our labours will generally be shortened and directed to their proper objects, by a knowledge of preceding discoveries.

When Dr. Heberden, in the London Medical Transactions, first described a disease under the name of Angina Pectoris, so little had it attracted the attention of physicians, that much surprise was excited by the com... ing and distressing symptom... and stricture about the breas... nation; and he soon after ...

That all the cases which ... nied with affections of *a som...* of true Angina Pectoris, ... less than one hundred of ... fallen under his observatio... one a boy; all the rest we...

on this disease made by ... of dissection.

Dr. Fothergill, in the ... servations and Inquiries ...

VOL. I. 1

La sévérité des symptômes corrèle mal avec l'étendue de la MCAS

That all the cases which this author had noticed as accompanied with affections of *a somewhat similar nature*, were instances of true Angina Pectoris, is by no means probable; for not less than one hundred of those were supposed by him to have fallen under his observation. Of those, three only were women, one a boy; all the rest were men, and about the age of fifty.

Innovations récentes dans le traitement de l'angine réfractaire

Laser (TMR)

Ad-VEGF

rFGF

phVEGF-A^{165}

L-arginine

rhVEGF

Ad5FGF-4

Chelation

Combien de nouvel agent approuvés par Santé Canada pour le traitement de l'angor chronique depuis 25 ans?

Zérooo

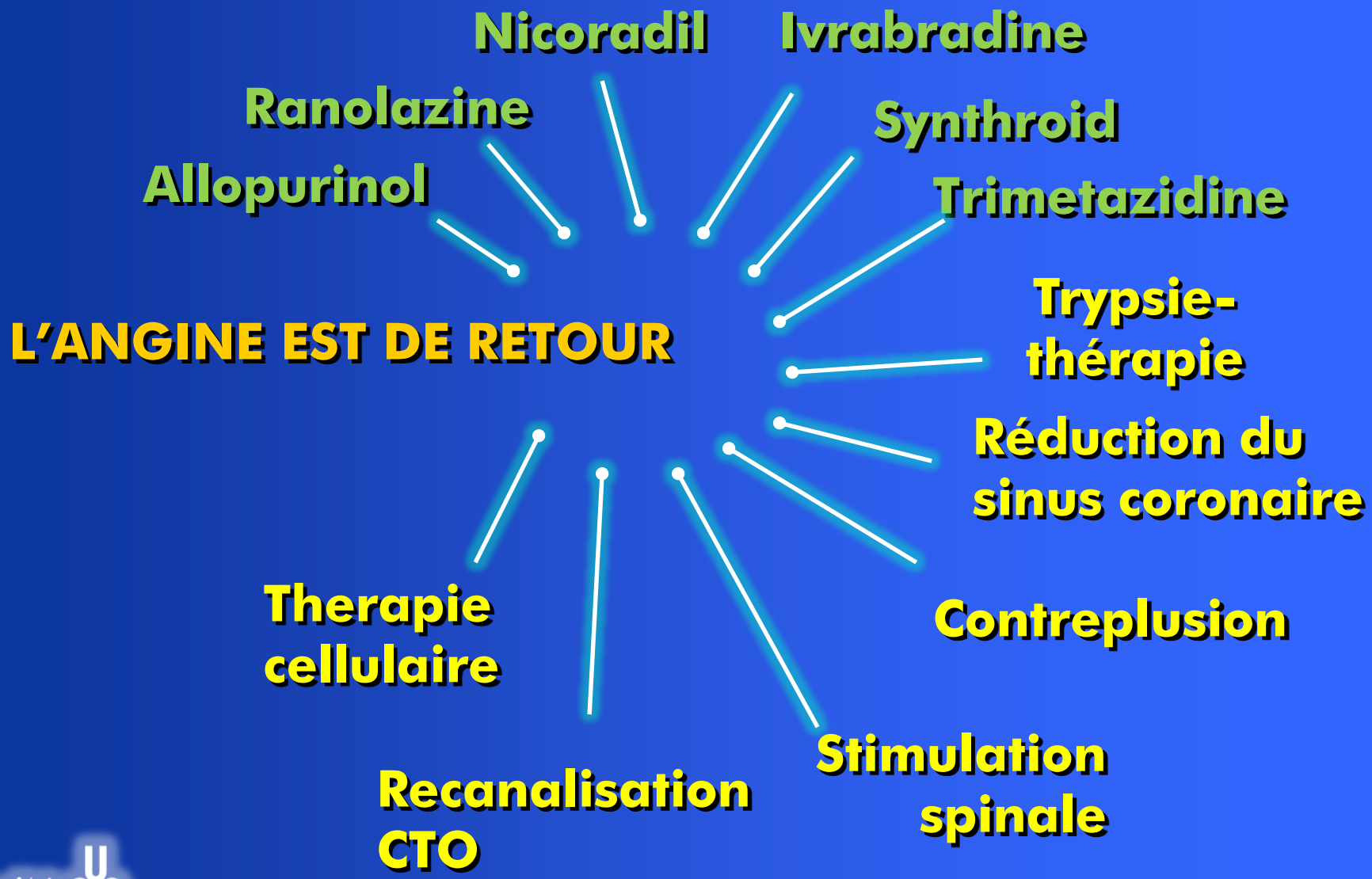
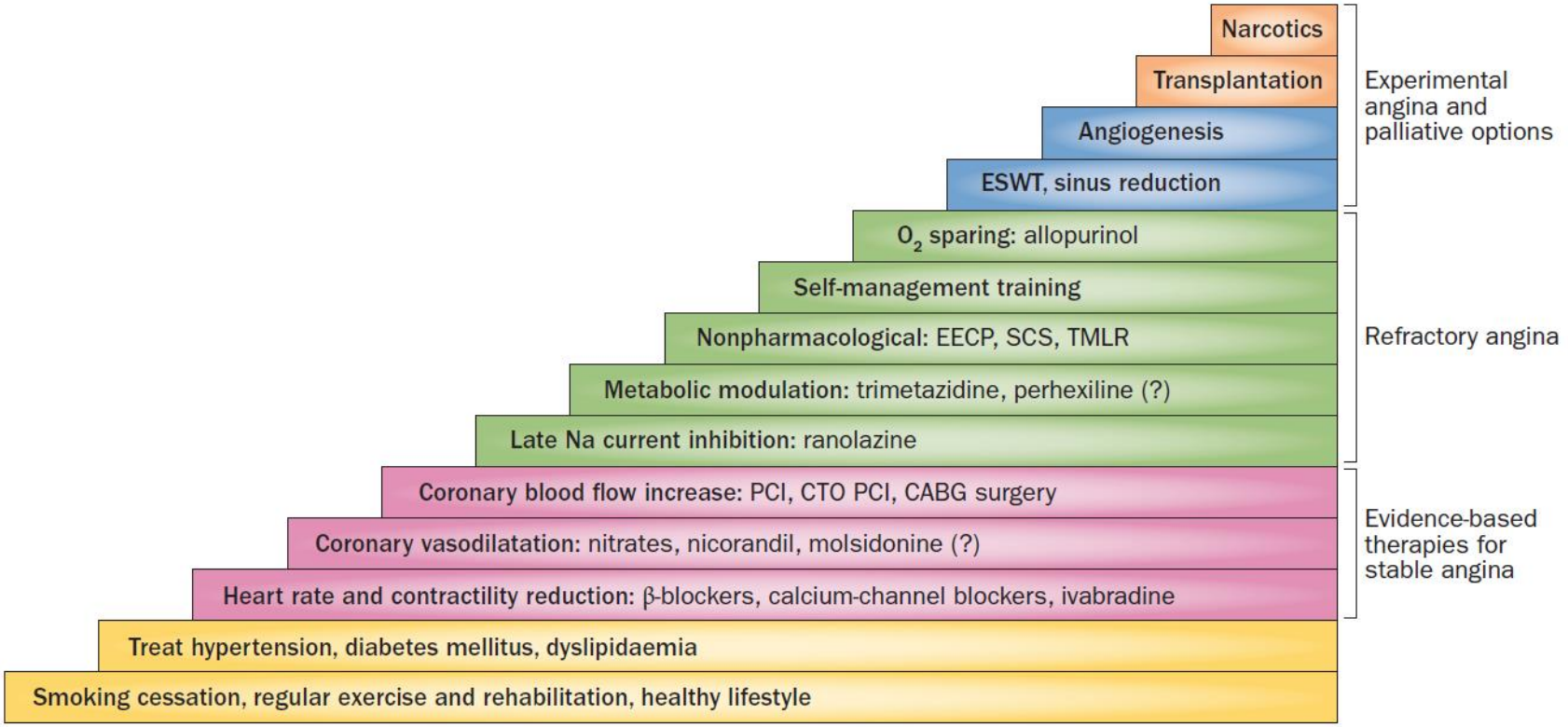
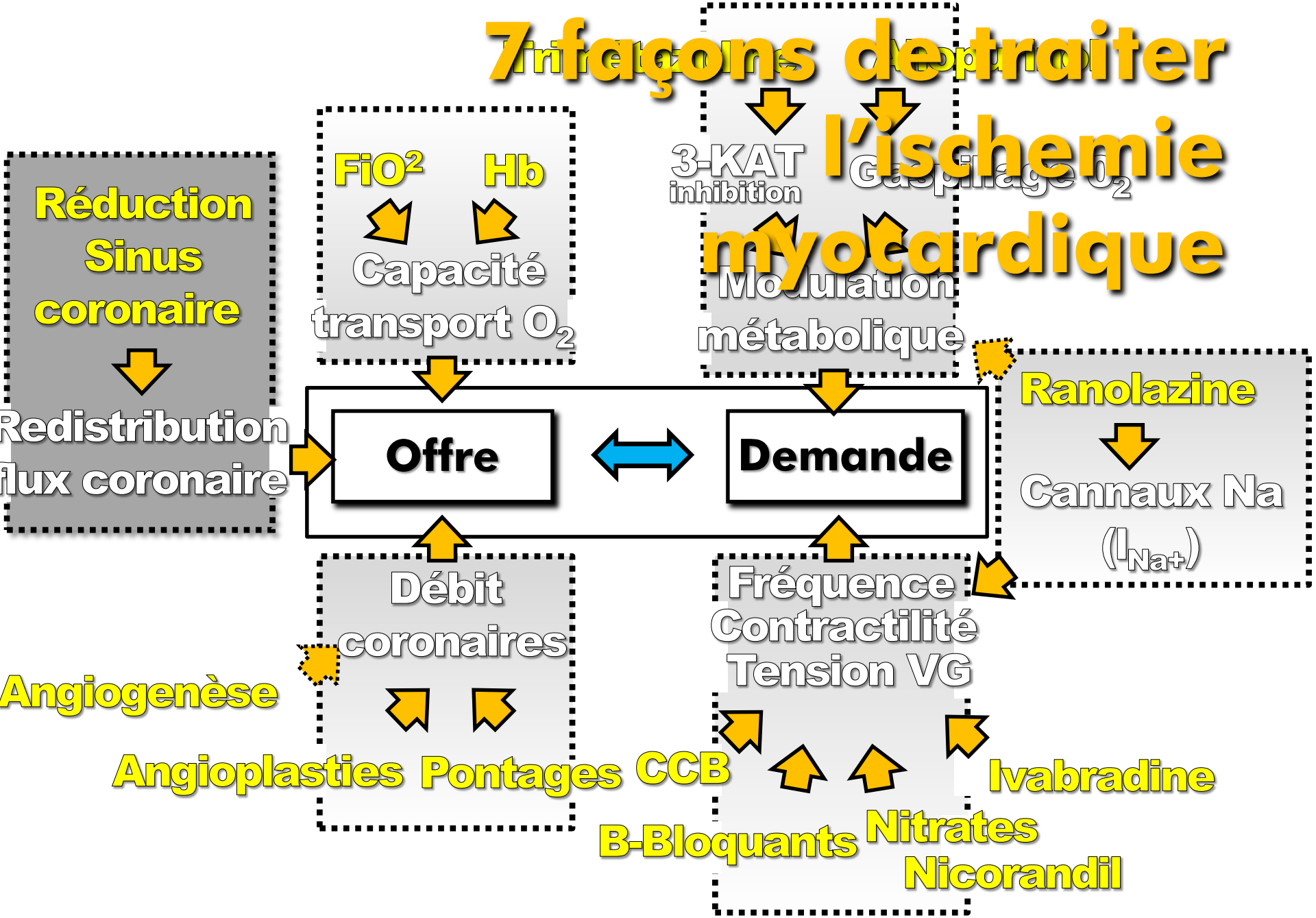


Figure 2



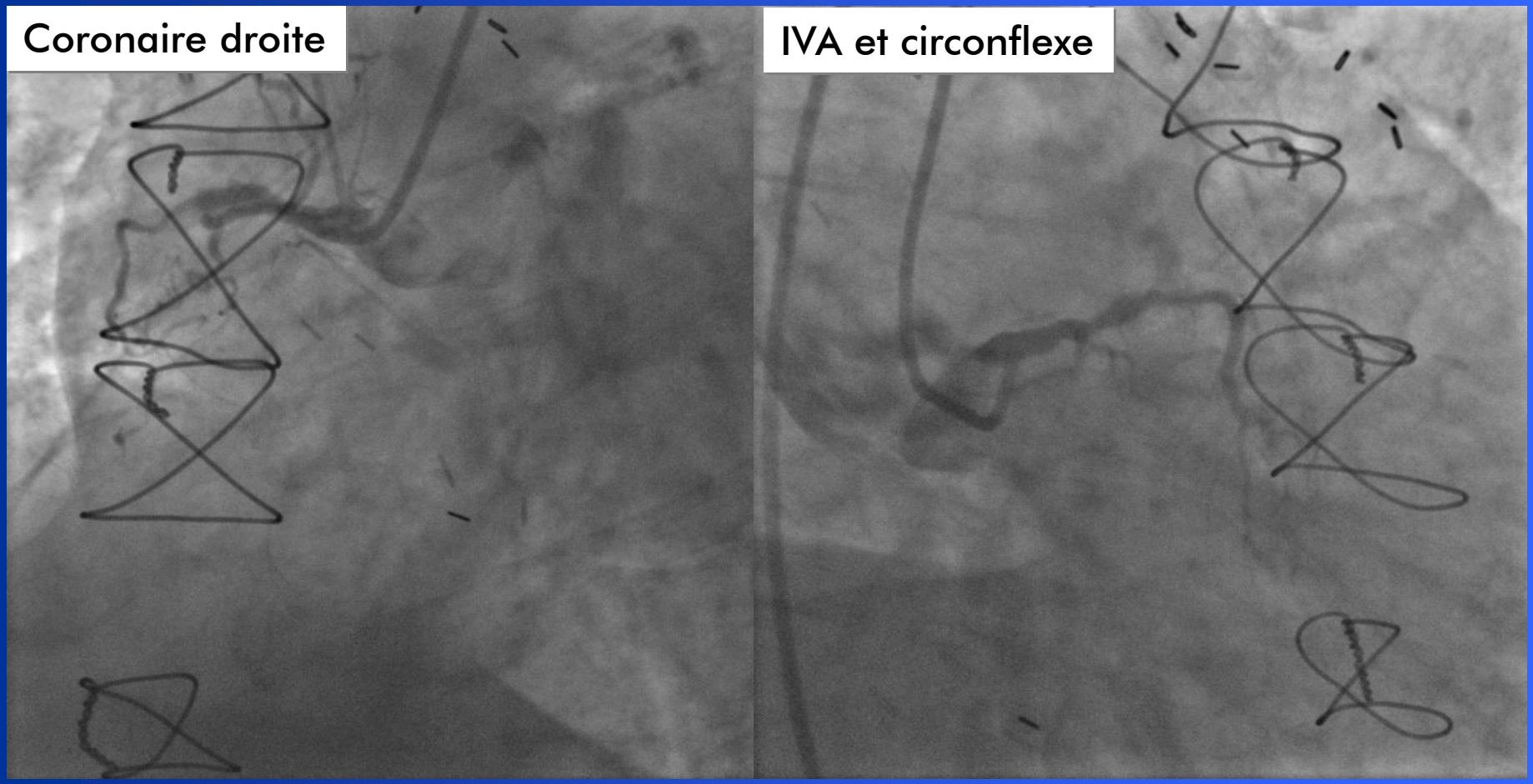
Henry and Jolicoeur, Nature Reviews Cardiology 2014;11:78

7 façons de traiter l'ischemie myocardique



THE ISCHEMIC ANGINA

Une image vaut milles mots



Coronaropénie = manque grossier d'artère coronaire

Université de Montréal

Contrepulsation externe diastolique
Enhanced External Counterpulsation

EECP®

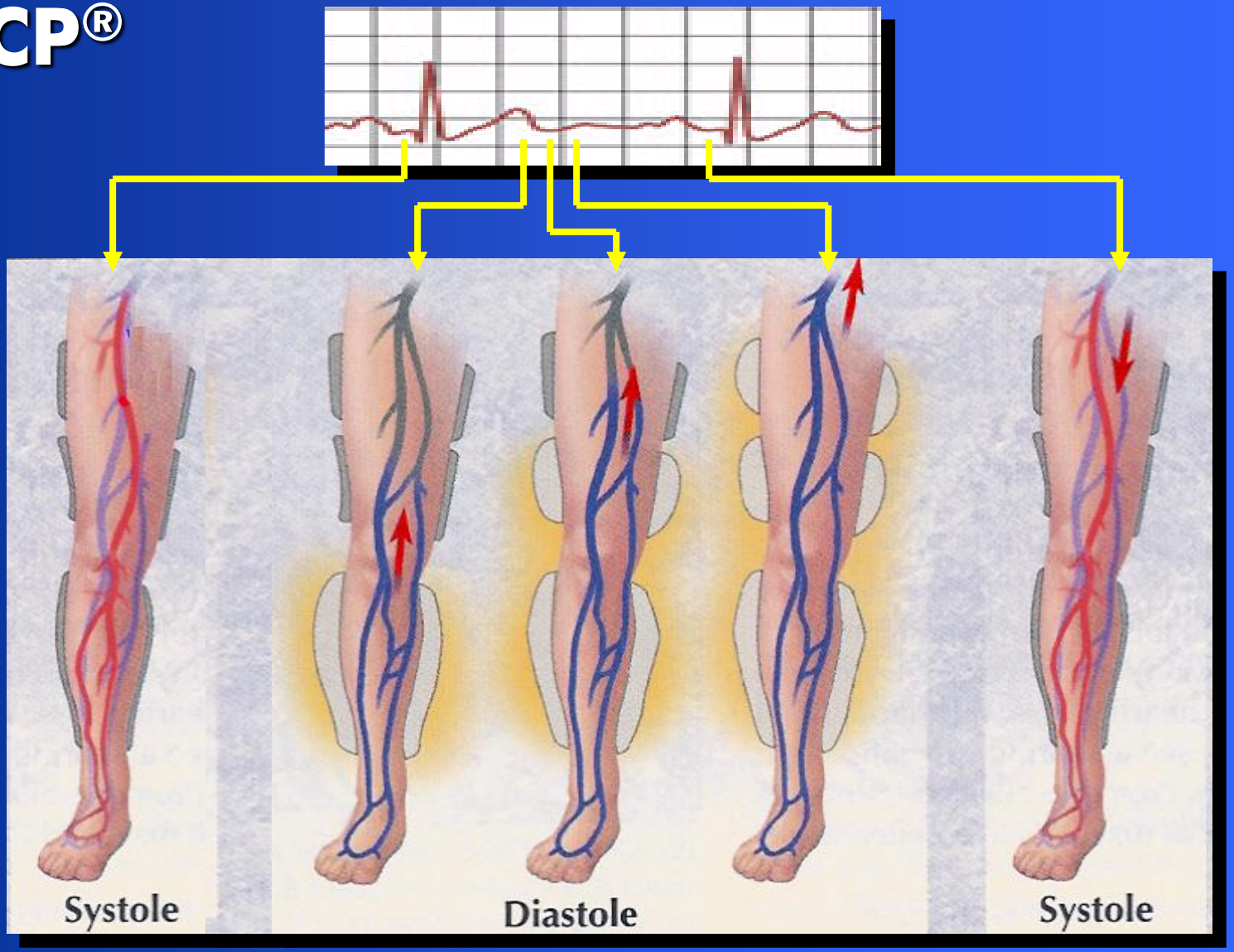


Table 35 Treatment options in refractory angina

Recommendations	Class [a]	Level [b]	Ref. [c]
EECP should be considered for symptom relief in patients with invalidating angina refractory to optimal medical and revascularization strategies.	IIa	B	509, 510
TENS may be considered to ameliorate symptoms of invalidating angina refractory to optimal medical and revascularization strategies.	IIb		
SCS may be considered to ameliorate symptoms and quality of life in patients with invalidating angina refractory to optimal medical and revascularization strategies.	IIb	B	511, 512, 513
TMR is not indicated in patients with invalidating angina refractory to optimal medical and revascularization strategies.	III	A	514

EECP = enhanced external counterpulsation; TENS = transcutaneous electrical nerve stimulation; TMR = transmyocardial revascularization; SC = spinal cord stimulation.

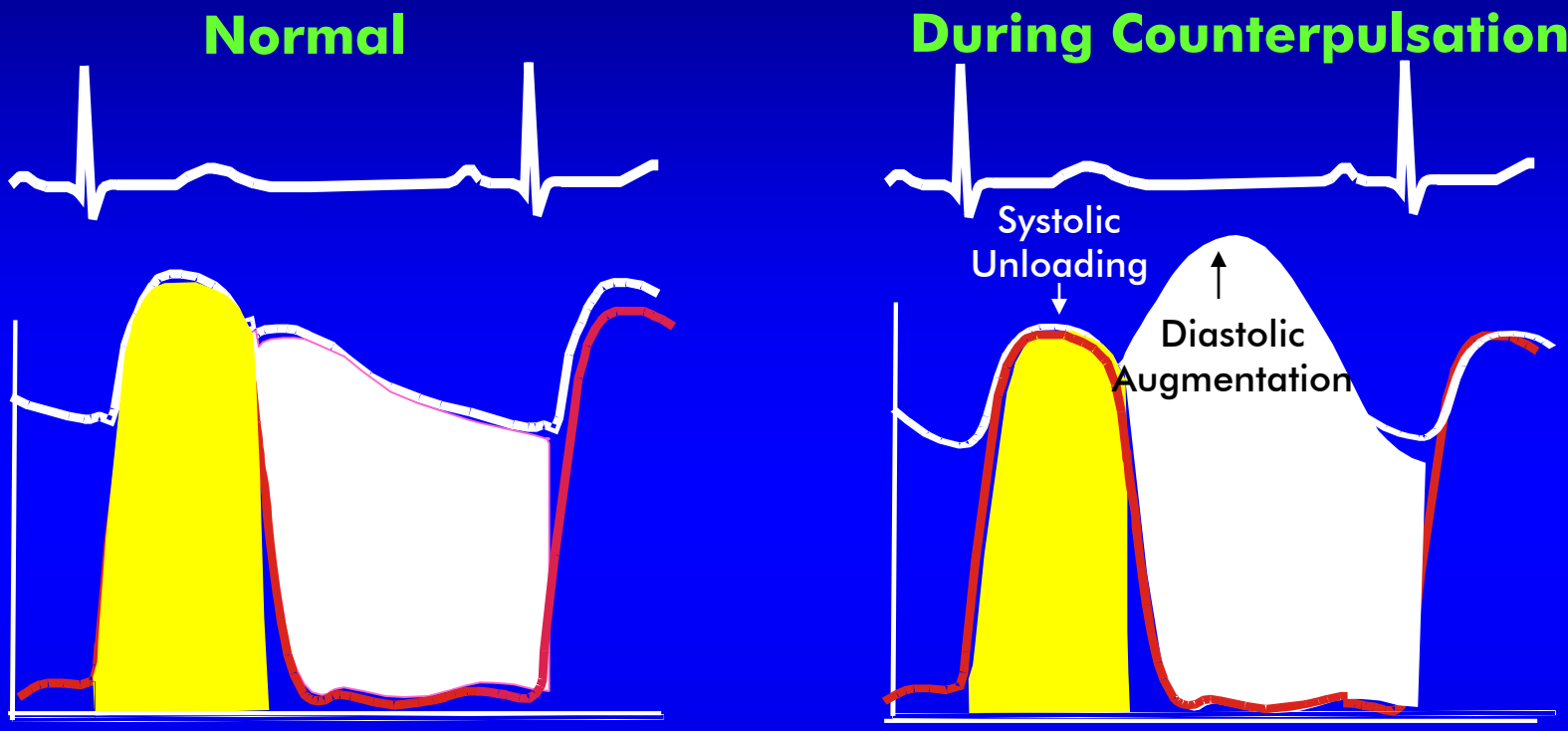
[a] Class of recommendation.

[b] Level of evidence.

[c] Reference(s) supporting levels of evidence.

Eur Heart J. 2013 Oct;34(38):2949-3003

Myocardial Energy Demand and Supply



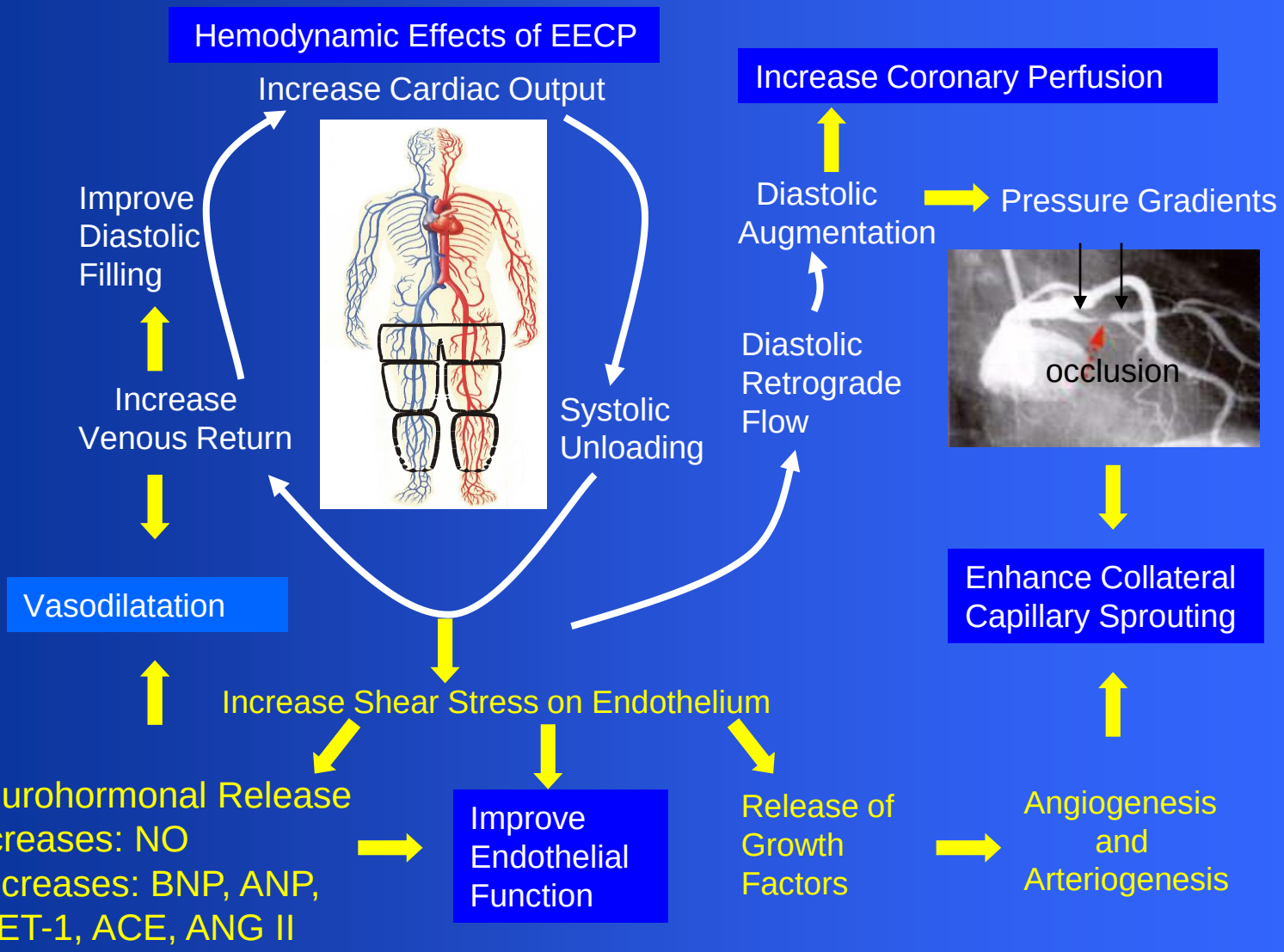
Time Tension Index
Workload of the heart is related to myocardial oxygen consumption

Diastolic Pressure Time Index
Energy supply to the myocardium in proportion to coronary perfusion pressure

Contrepulsation externe diastolique

- Un traitement complet requiert
  - 30-35 sessions quotidiennes
  - 1-2 heures chacune
  - Reparties sur 3 à 7 semaines
- Approuvé par la FDA
  - Angina stable CCS I à III
  - Infarctus du myocarde
  - Choc cardiogenic
  - Défaillance cardiaque
- Traitement de Class IIa

EECP Mechanisms of Action



Enhanced external counterpulsation (EECP)

Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 33, No. 7, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00140-0

CLINICAL STUDIES **Myocardial Ischemia**

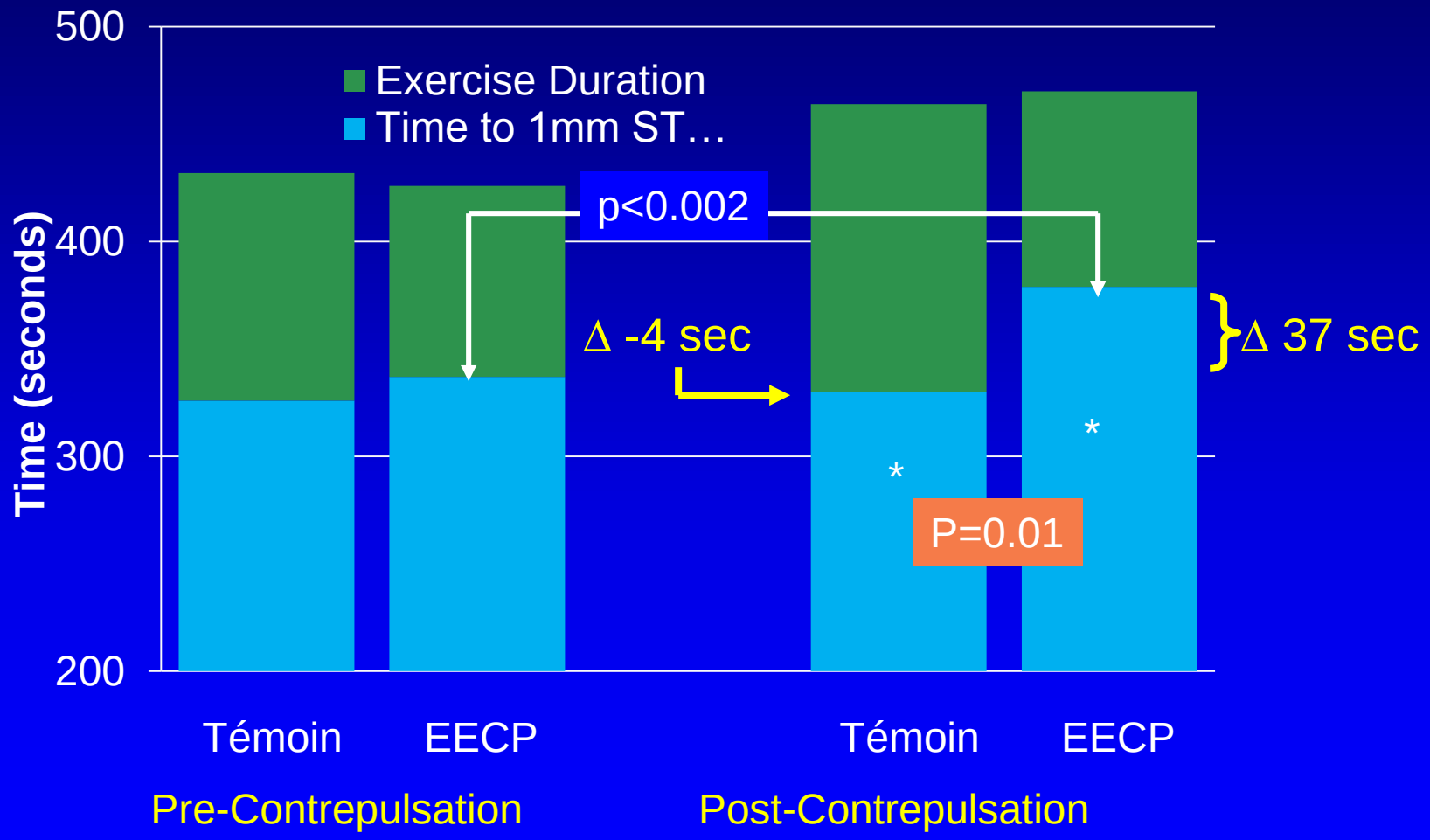
The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): Effect of EECP on Exercise-Induced Myocardial Ischemia and Anginal Episodes

Patients were given 35 h of active or inactive counterpulsation over a 4 – 7 weeks period

CONCLUSIONS: EECP reduces angina and extends time to exercise-induced ischemia in patients with symptomatic CAD. Treatment was relatively well tolerated and free of limiting side effects in most patients

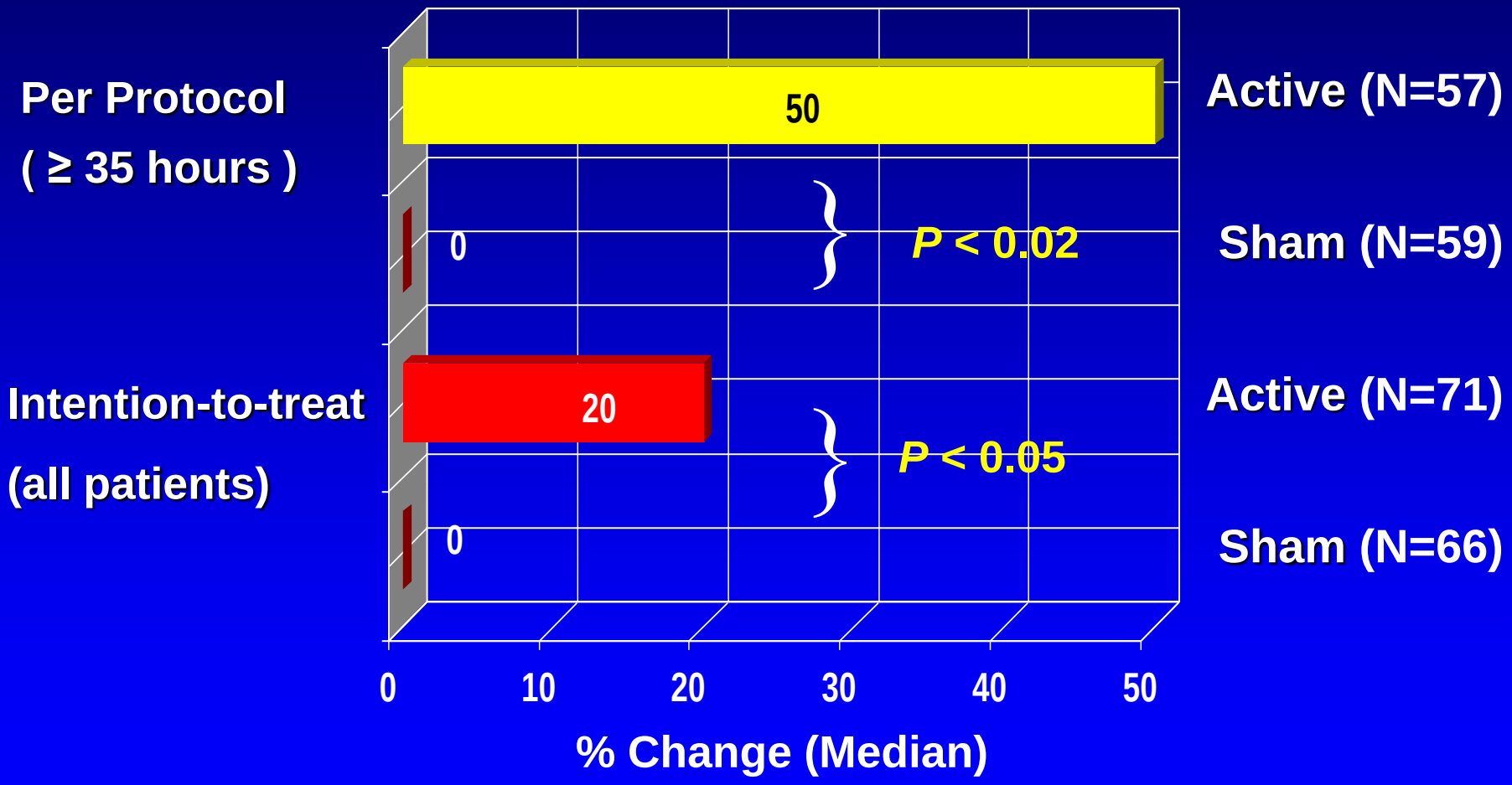
Rohit R Arora, et al: *J Am Coll Cardiol*. 1999;33(7):1833-1840

MUST-EECP (n=139, CCS I-III)



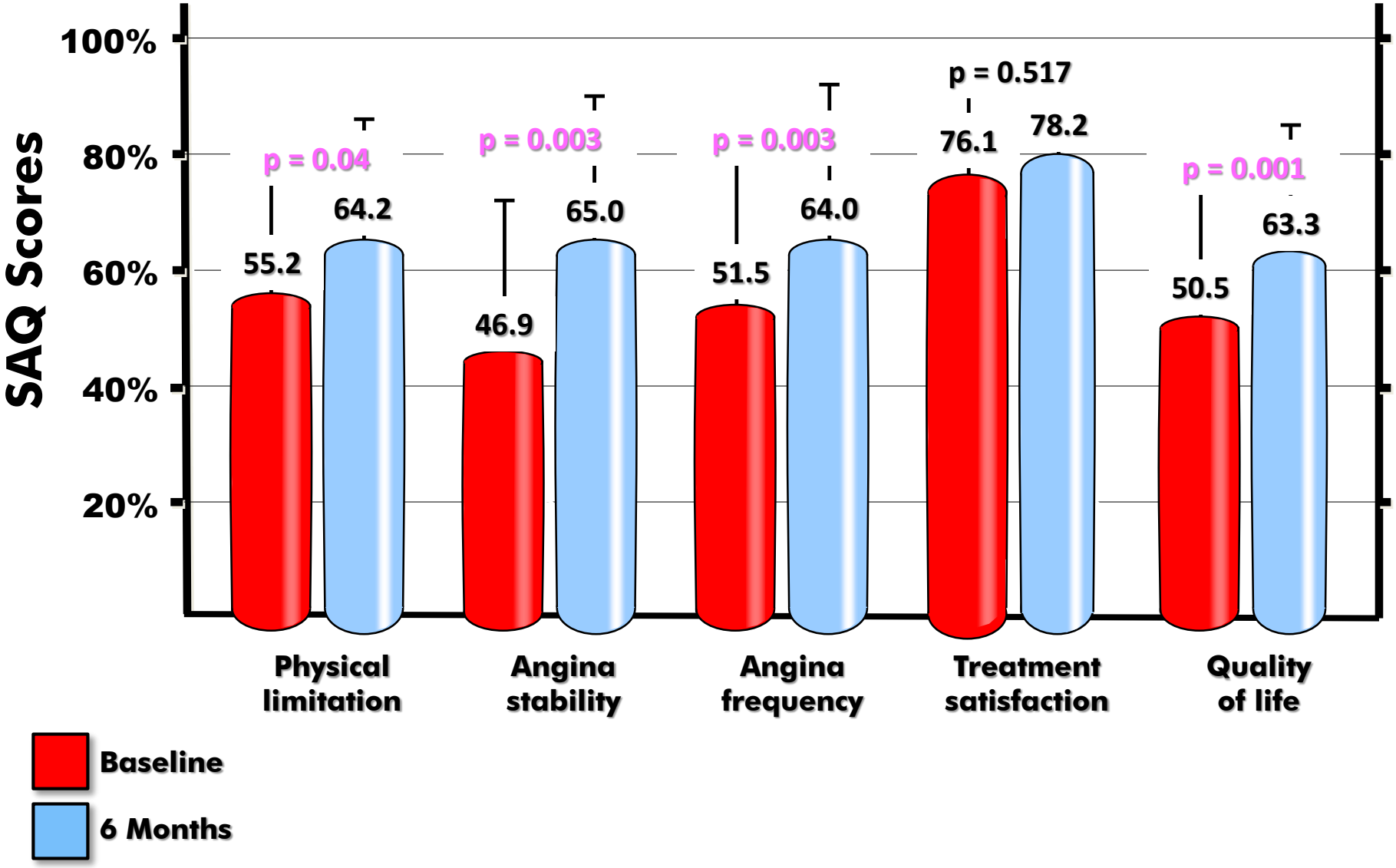
MUST-EECP

Daily Angina Counts



Arora RR, et al. *J Am Coll Card* 1999;33:1833-40

EECP-Quebec - Seattle Angina Questionnaire



Unpublished data; performed in Collaboration with Dr Eric Sabbah et al., Hôpital Pierre Boucher

EECP-Quebec SF-36v2® Health Survey

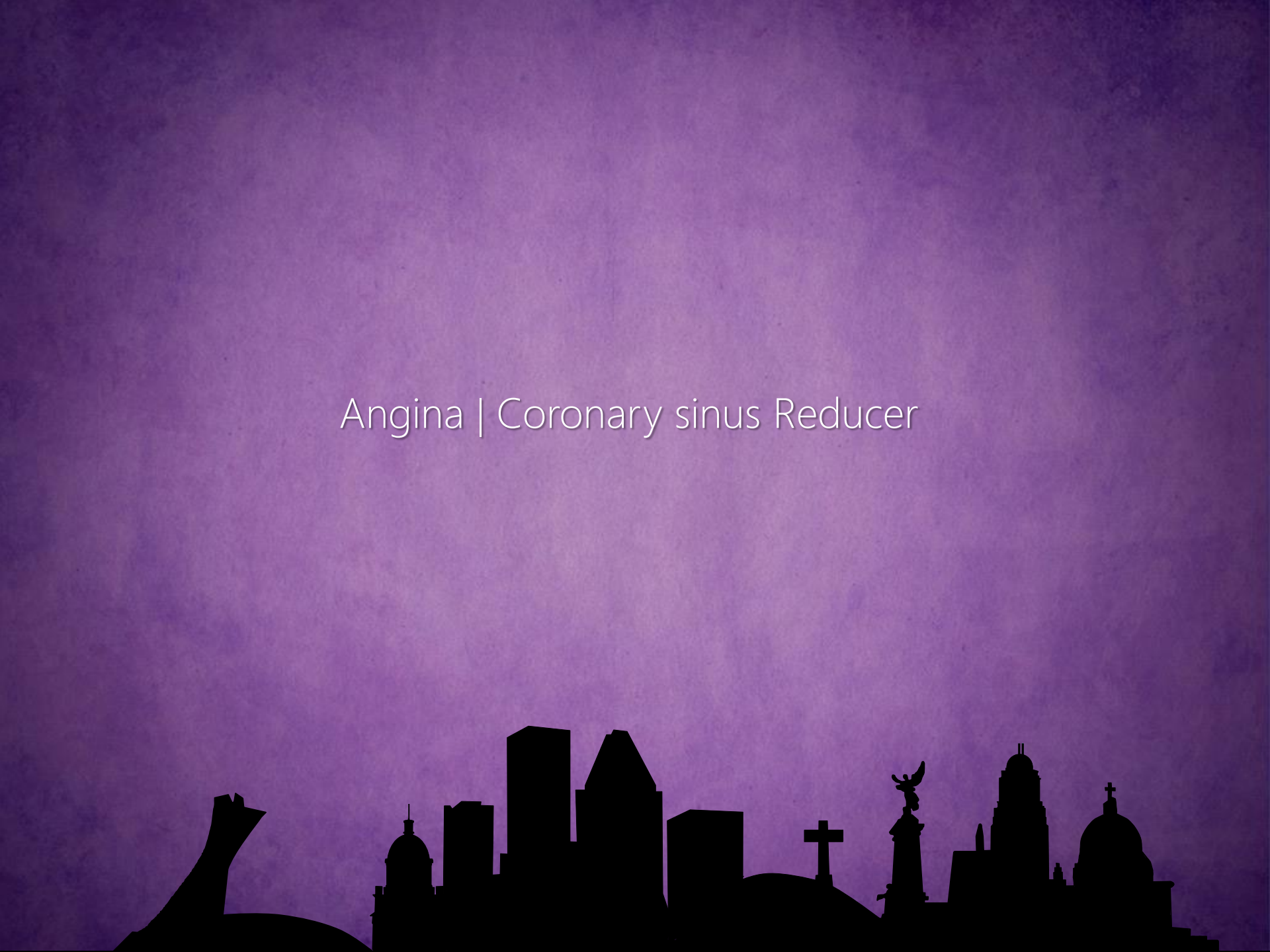
Measurements (n = 58)

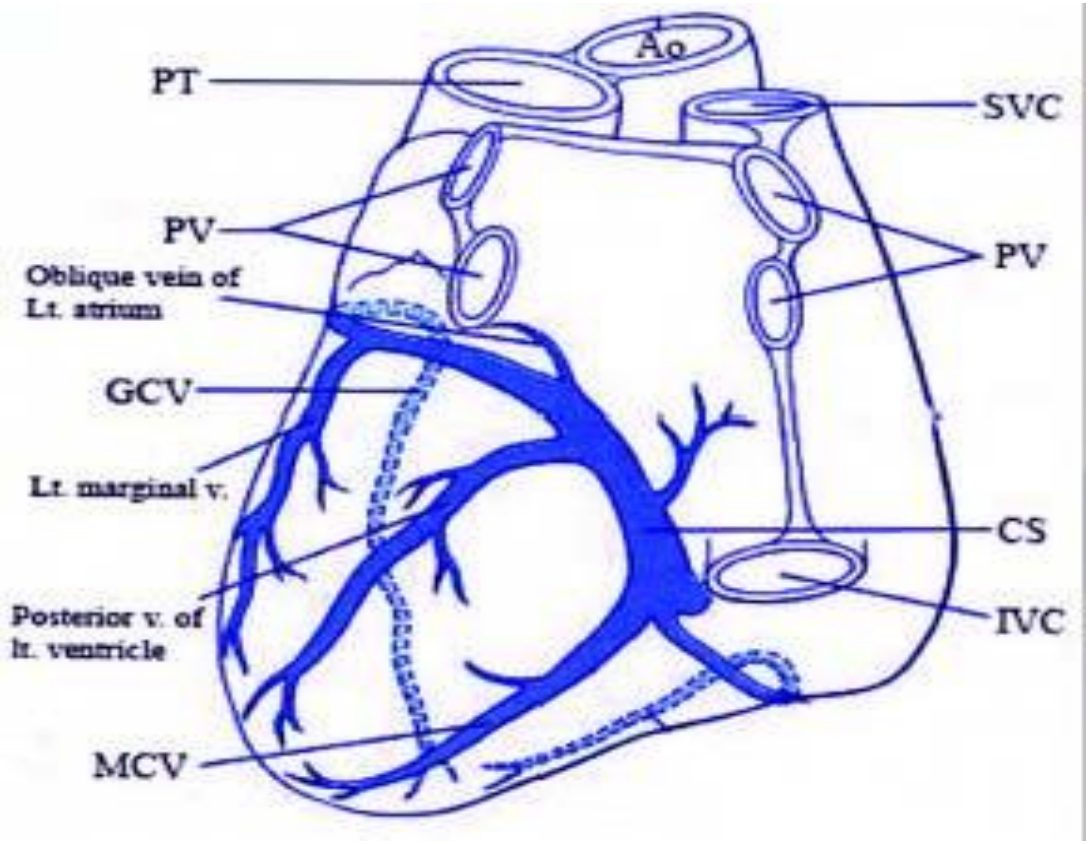
Physical health	Baseline	6 months	Δ	IC 95%	*p value*
Physical Functioning	32.1±8.8	36.4±11.1	4.4	1.3 to 7.5	0.007
Role Physical	33.4±11.1	38.0±11.6	4.6	1.1 to 8.0	0.01
Bodily Pain	37.6±8.0	42.6±11.2	5.0	2.2 to 7.8	0.001
General Health	36.0±9.8	38.4±10.8	2.4	0.1 to 4.8	0.04
Mental Health					
Vitality	42.6±10.9	45.6±9.8	3.0	-0.2 to 6.2	0.07
Social functioning	38.7±10.9	41.8±11.1	3.2	-0.7 to 7.0	0.11
Role emotional	36.0±13.7	38.7±14.9	2.6	-2.1 to 7.3	0.27
Mental Health	43.2±11.5	45.8±11.1	2.5	-0.4 to 5.5	0.09

Data presented as norm-based scoring (NBS) where normal = 50±10

Unpublished data; performed in Collaboration with Dr Eric Sabbah et al, Hôpital Pierre Boucher

Angina | Coronary sinus Reducer




Ao
PT
SVC
PV
PV
Oblique vein of
Lt. atrium
GCV
Lt. marginal v.
CS
Posterior v. of
lt. ventricle
IVC
MCV

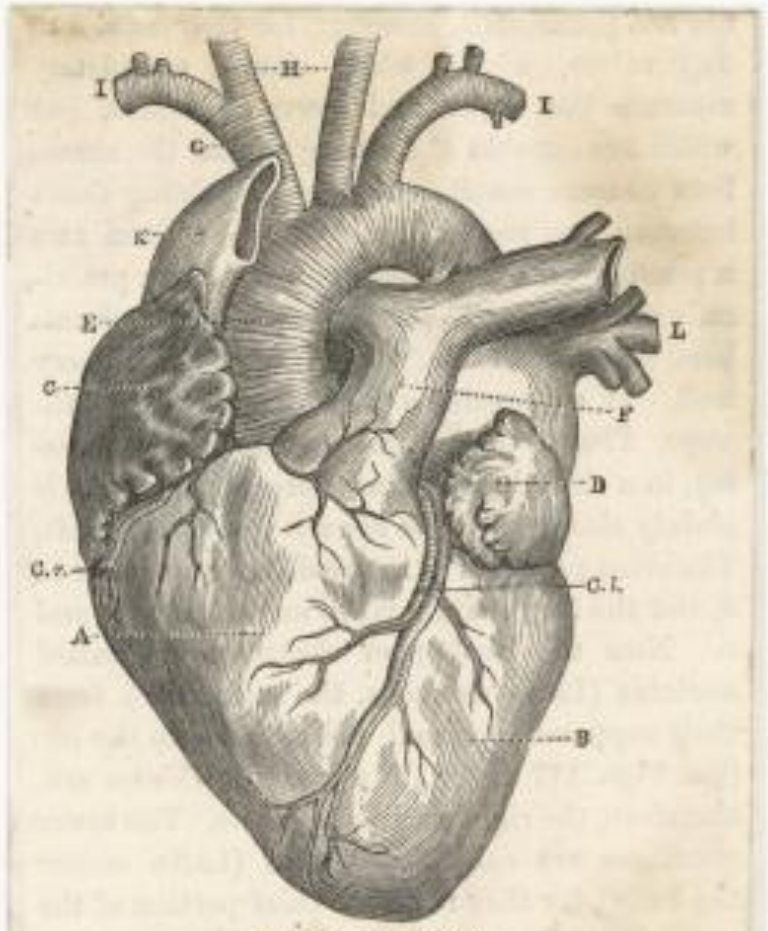


Fig. 117.—The Heart.

A and B, Right and Left Ventricles. C and D, Right and Left Auricles. E, Aorta. F, Pulmonary Artery. G, Innominate Artery, branch of Aorta. H, Right and Left Carotid Branches (to head and neck). I, I, Subclavian Branches (to upper limbs). K, Superior Vena Cava. L, Pulmonary Veins. C. r, Right Coronary Vessels. C. l, Left Coronary Vessels. Arteries are marked by cross shading in the figure; Veins are shaded lengthways.

J.A.M.A., Nov. 26, 1955

SCIENTIFIC BASIS FOR THE SURGICAL TREATMENT OF CORONARY ARTERY DISEASE

Claude S. Beck, M.D.
and
David S. Leighninger, M.D., Cleveland

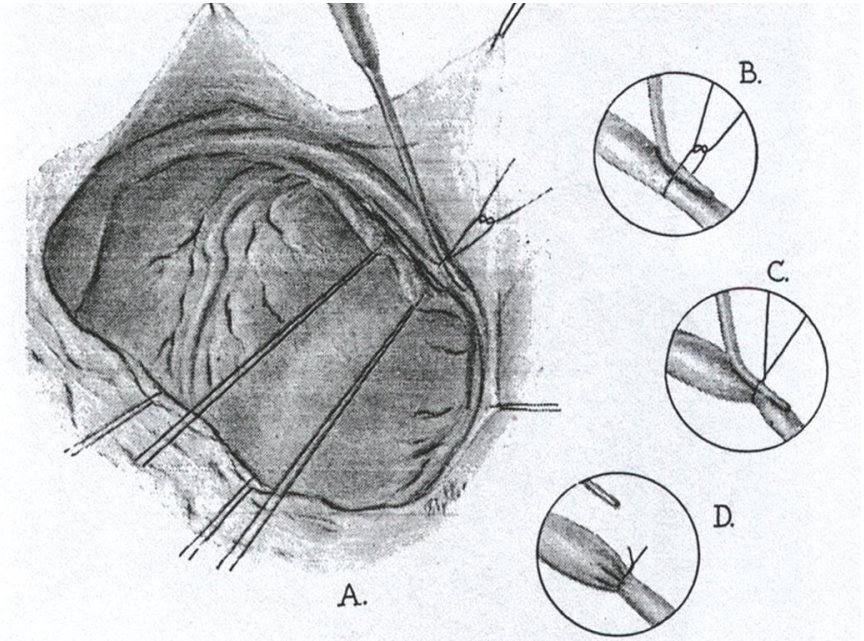


Fig. 10.—Partial ligation of the coronary sinus. The ligature is tied on a stilet 3 mm. in diameter, as in *A*, *B*, and *C*, and the stilet is removed after the ligature is tied, as in *D*.

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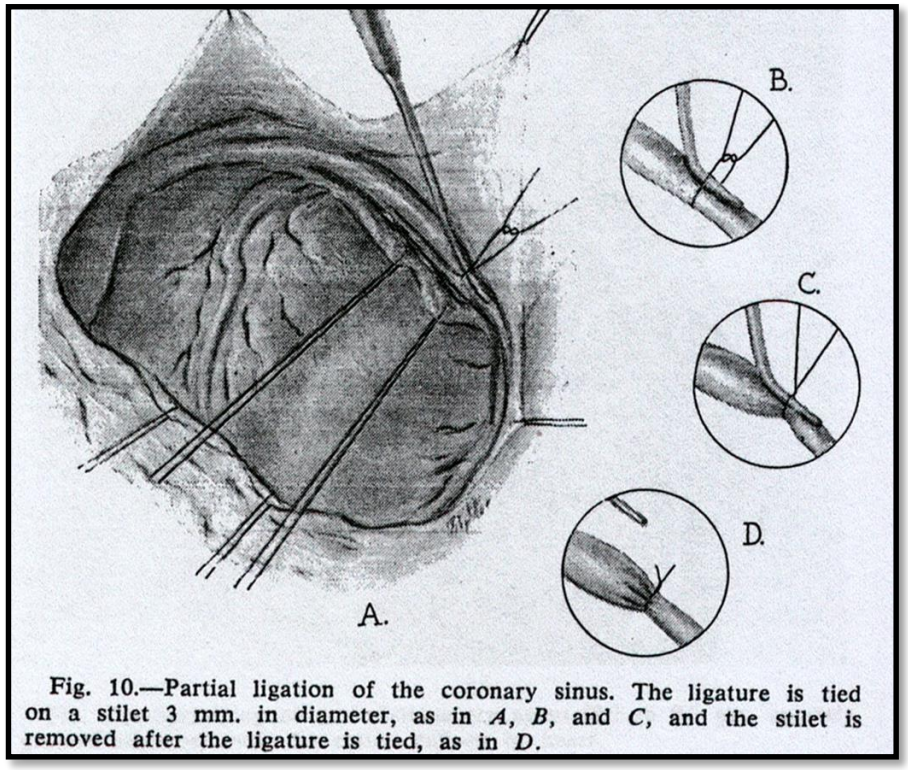
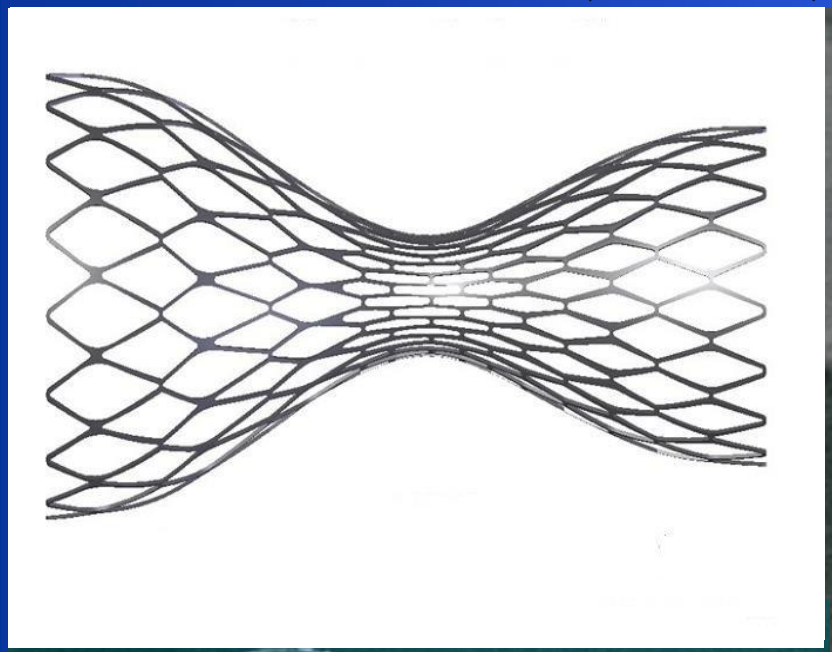


Fig. 10.—Partial ligation of the coronary sinus. The ligature is tied on a stilet 3 mm. in diameter, as in *A*, *B*, and *C*, and the stilet is removed after the ligature is tied, as in *D*.

Chirurgie Beck I :
Mount Sinai Hospital,
Cleveland, Ohio

- **Réduction de mortalité de 43%**
- **Réduction taille infarctus de 60%**

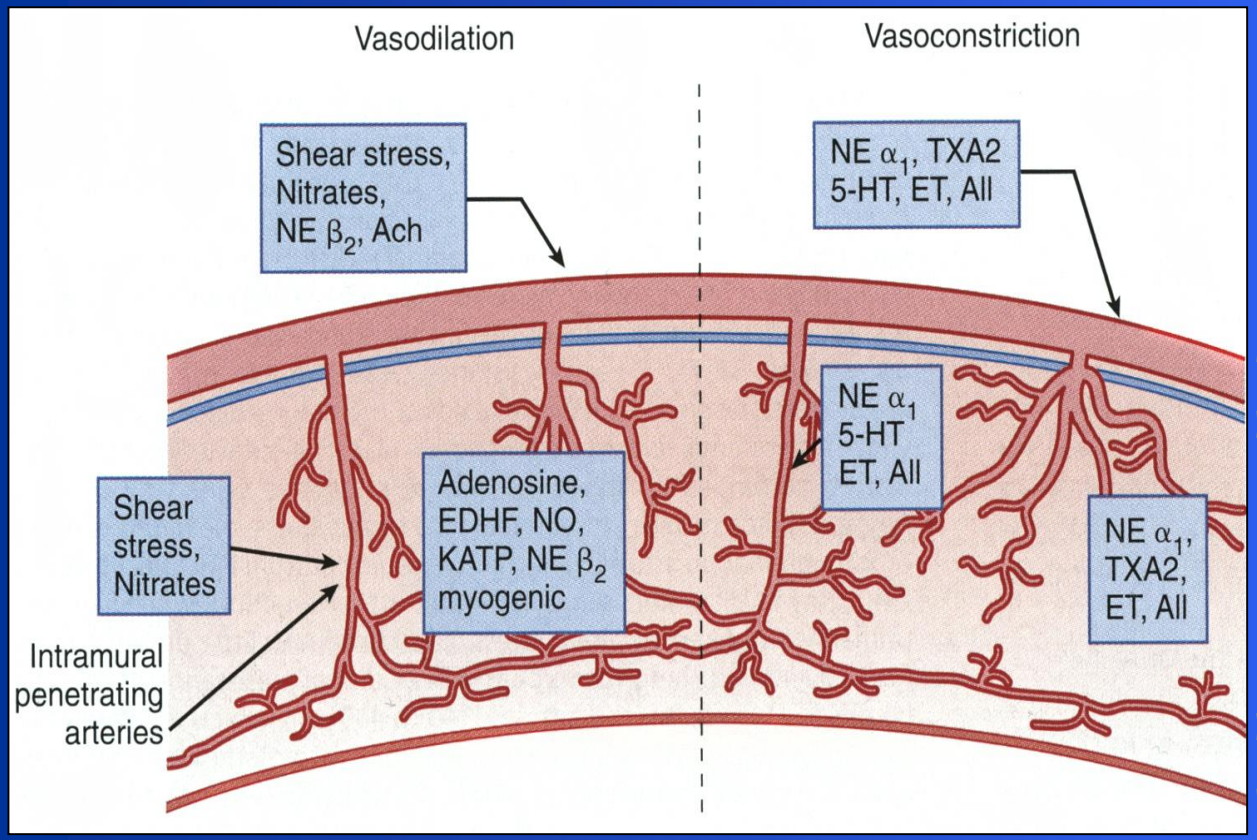
Reducer (TM) - Neoavasc



JACC 2007;49:1783

- Prothèse implantée dans le sinus coronaire
- Engendre une réduction de la lumière du sinus coronaire pour moduler le flux et la pression sinusale
- L'élévation de la pression sinusale augmente la perfusion sous-endocardique pour amoindrir l'ischémie et l'angine

Perfusion coronarienne

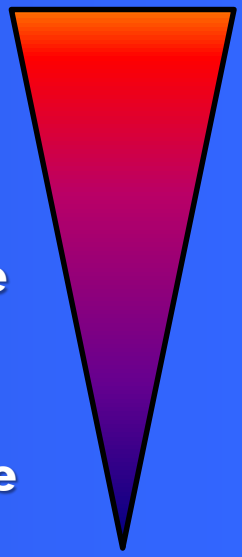


épicarde

myocarde

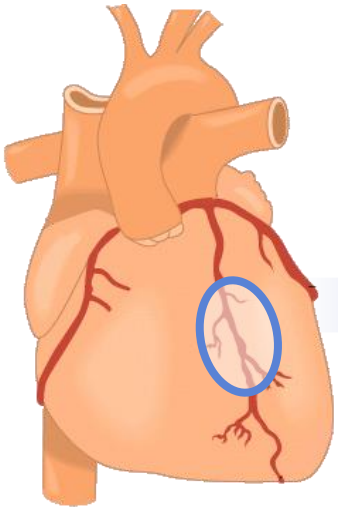
Endocarde

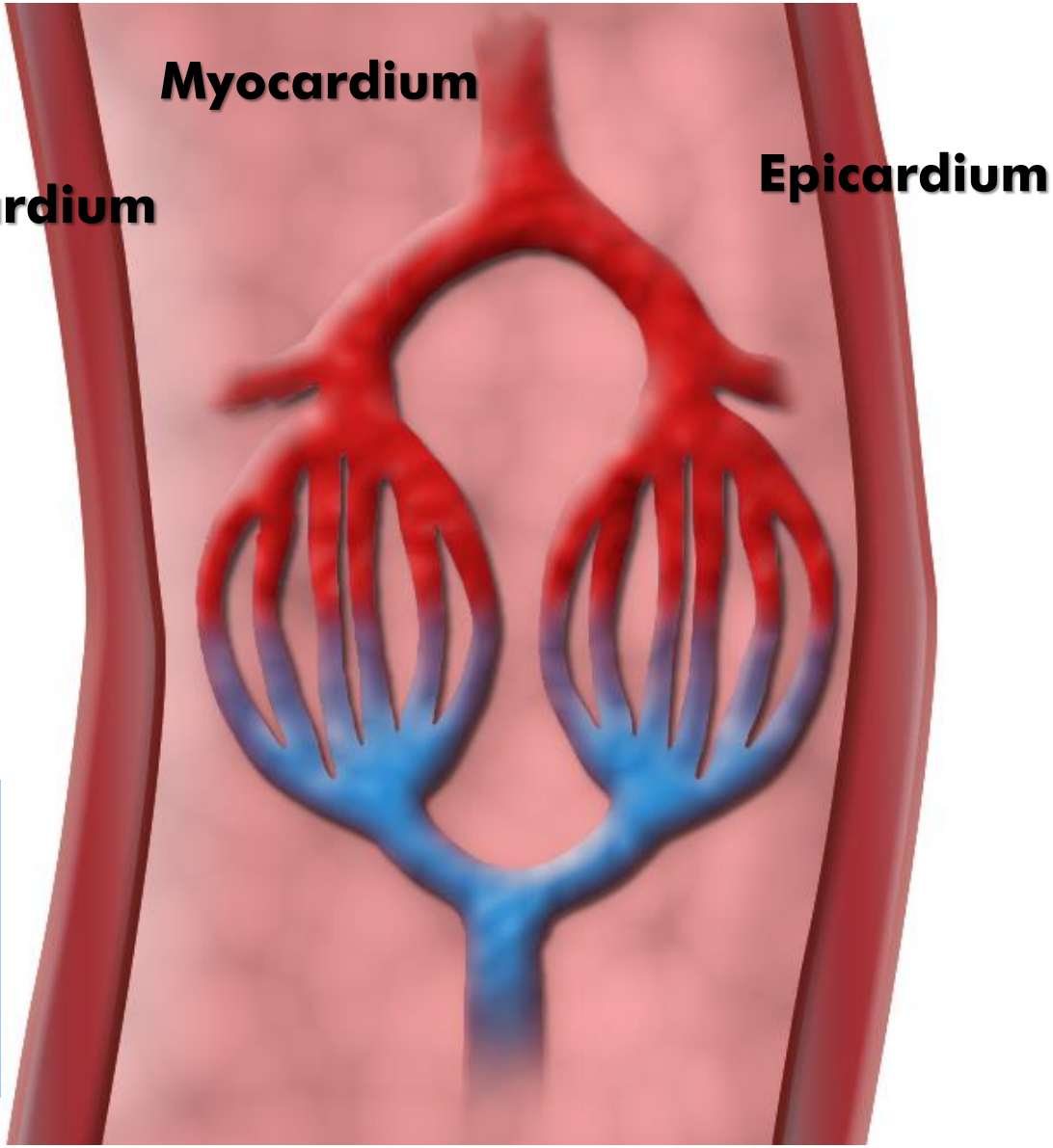
Tension O2 ↑



Tension O2 ↓

Normal Perfusion of the Myocardium

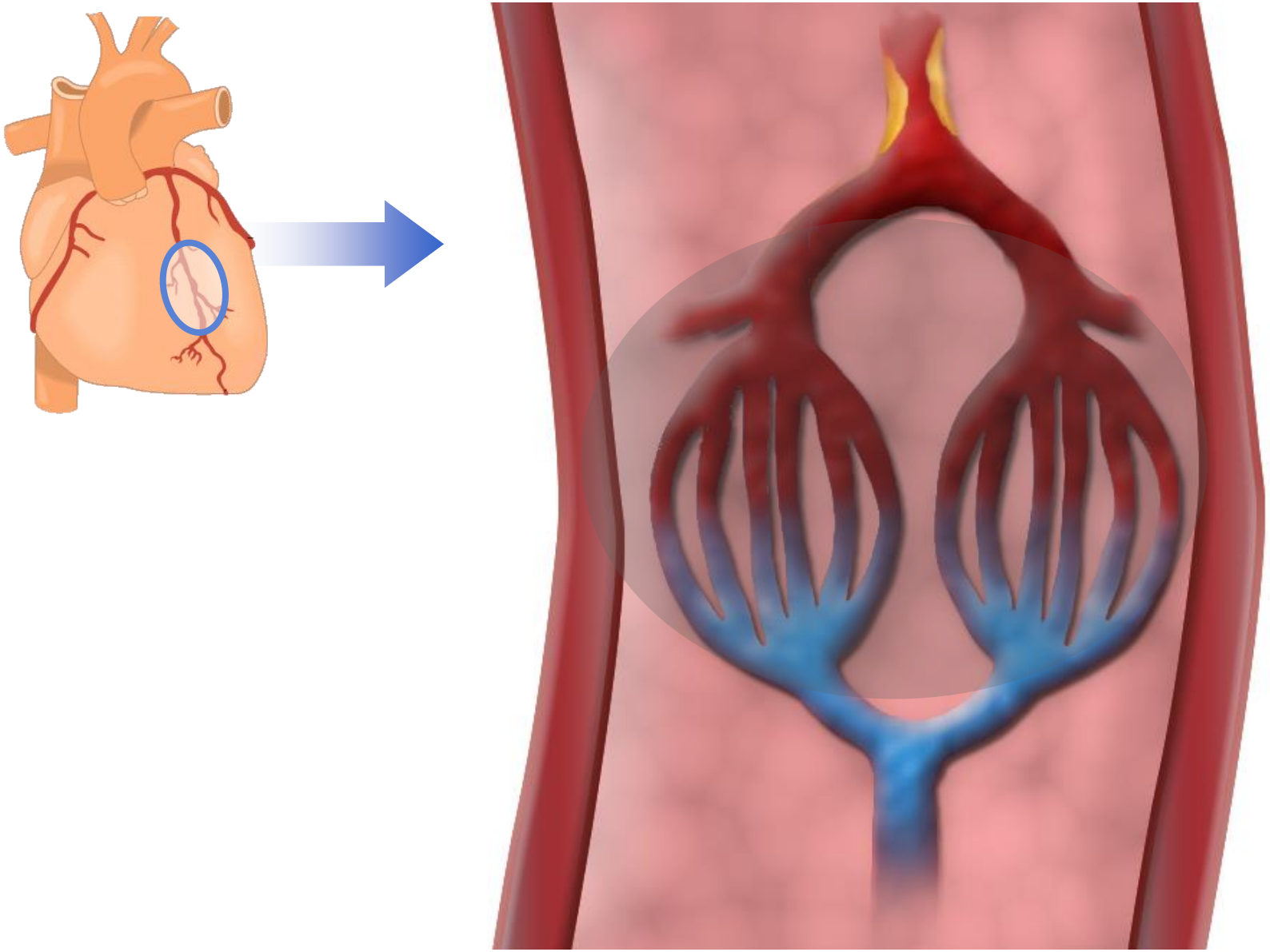




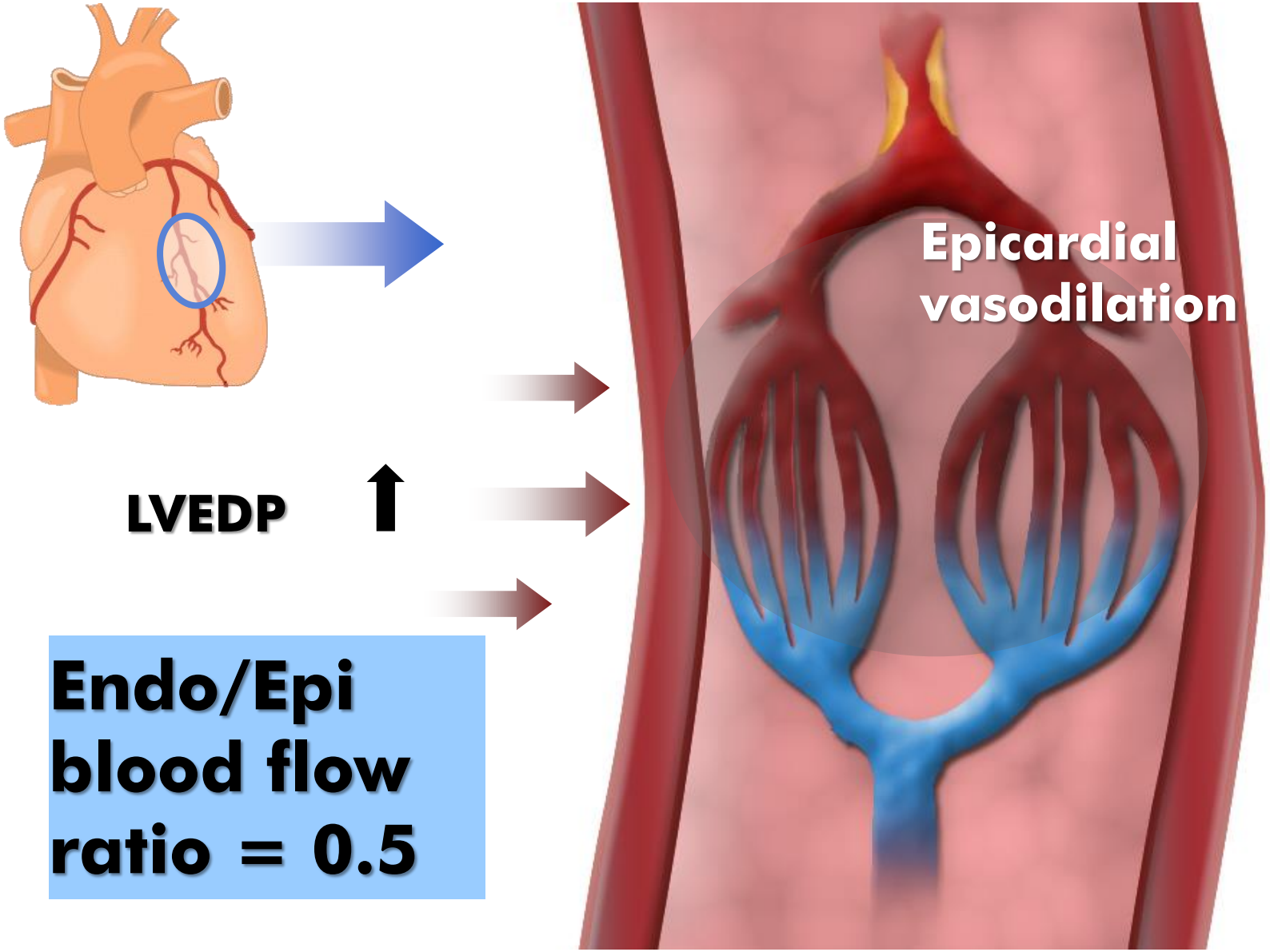
Left Ventricular Cavity

Endo/Epi blood flow ratio = 1.2

Ischemic Myocardium



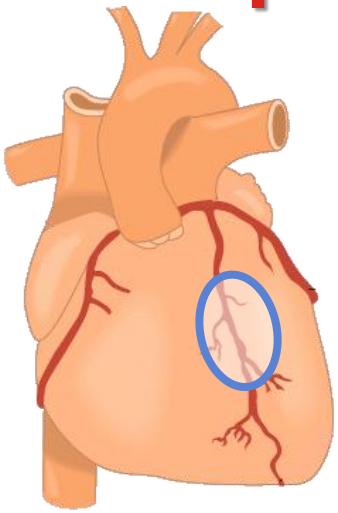
Ischemic Myocardium



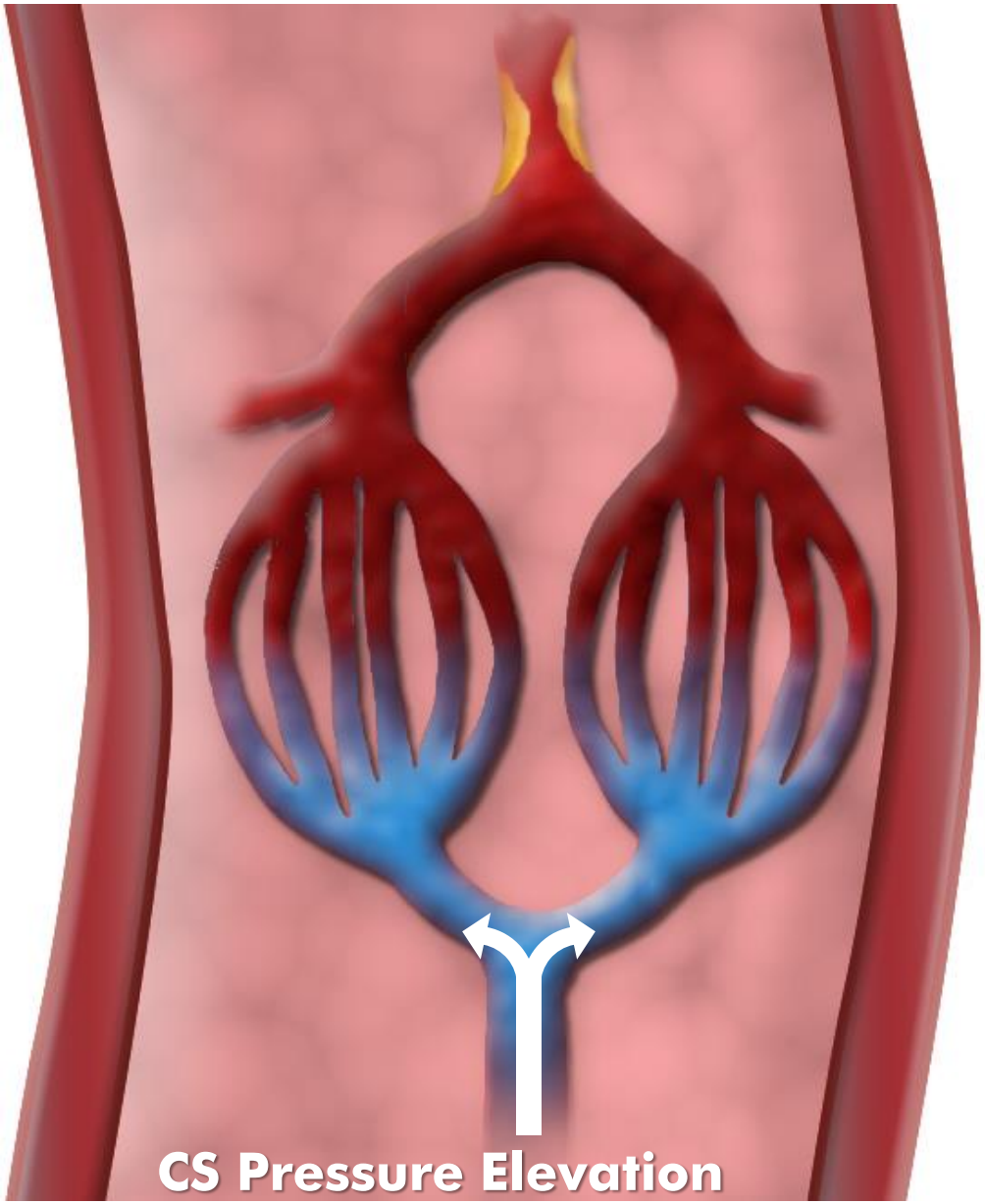
LVEDP ⬆

Endo/Epi blood flow ratio = 0.5

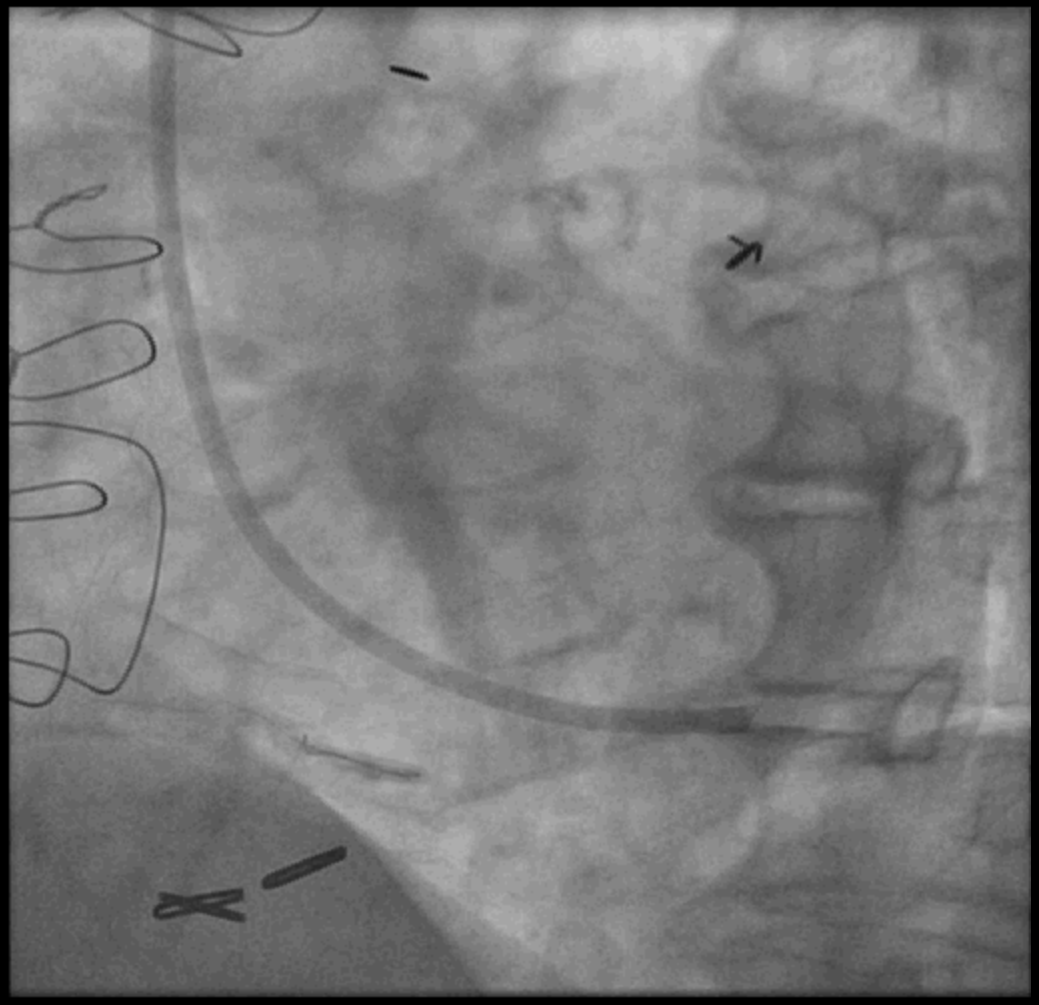
Ischemic Myocardium with elevated CS pressure

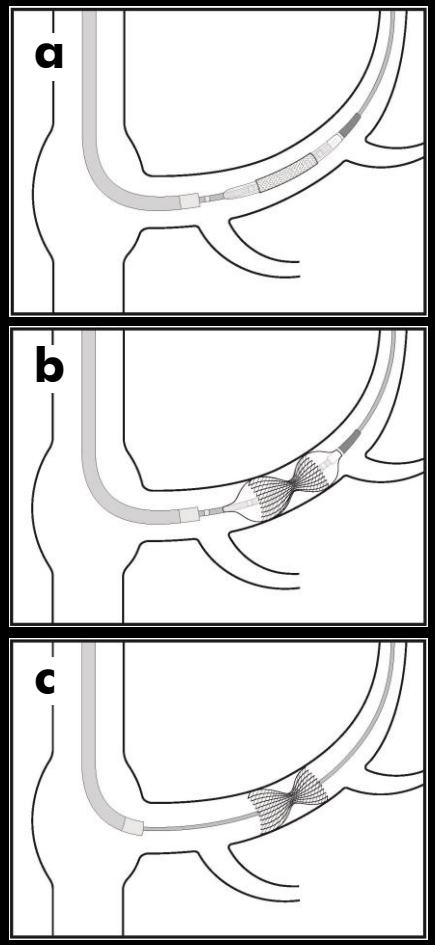


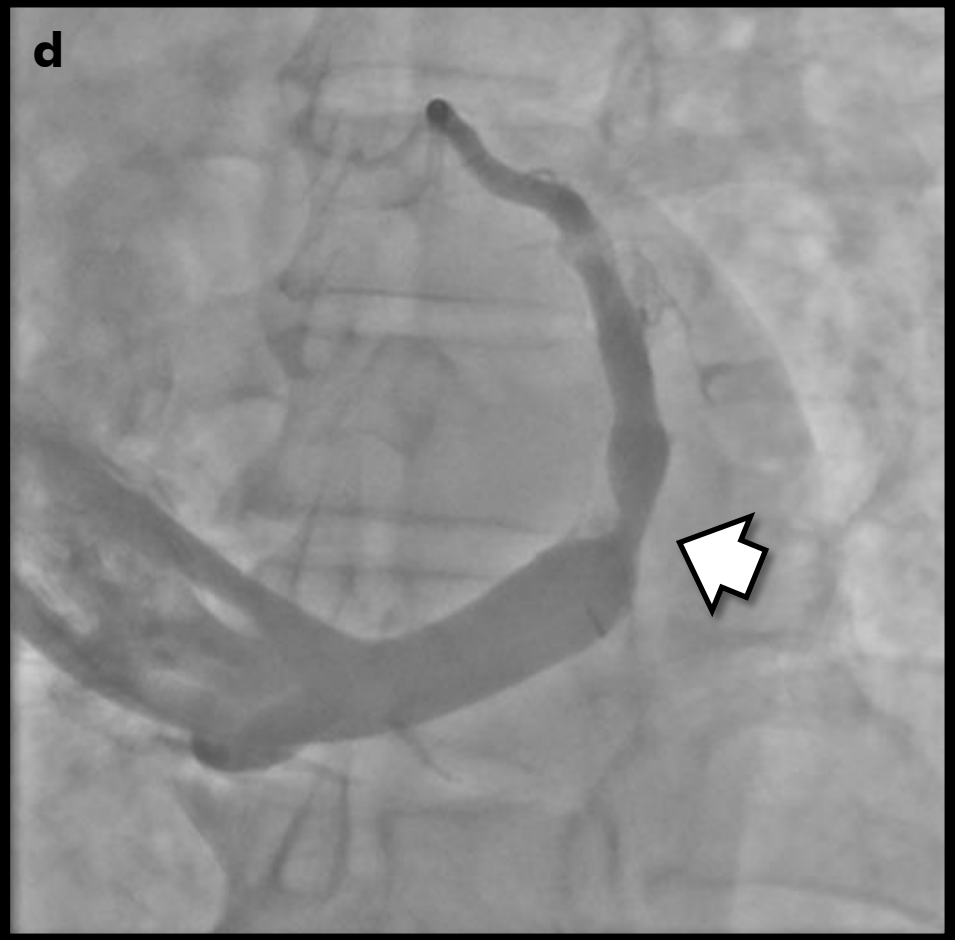
Endo/Epi blood flow ratio = 1.2



Neovasc Reducer: final result




a
b
c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Jolicœur *et al. Trials* 2013, **14**:46
http://www.trialsjournal.com/content/14/1/46

TRIALS

STUDY PROTOCOL Open Access

A phase II, sham-controlled, double-blinded study testing the safety and efficacy of the coronary sinus reducer in patients with refractory angina: study protocol for a randomized controlled trial

E Marc Jolicœur[1*], Shmuel Banai[2], Timothy D Henry[3], Marc Schwartz[4], Serge Doucet[1], Christopher J White[5], Elazer Edelman[6,7] and Stefan Verheye[8]

COronary SInus Reducer for Treatment of Refractory Angina

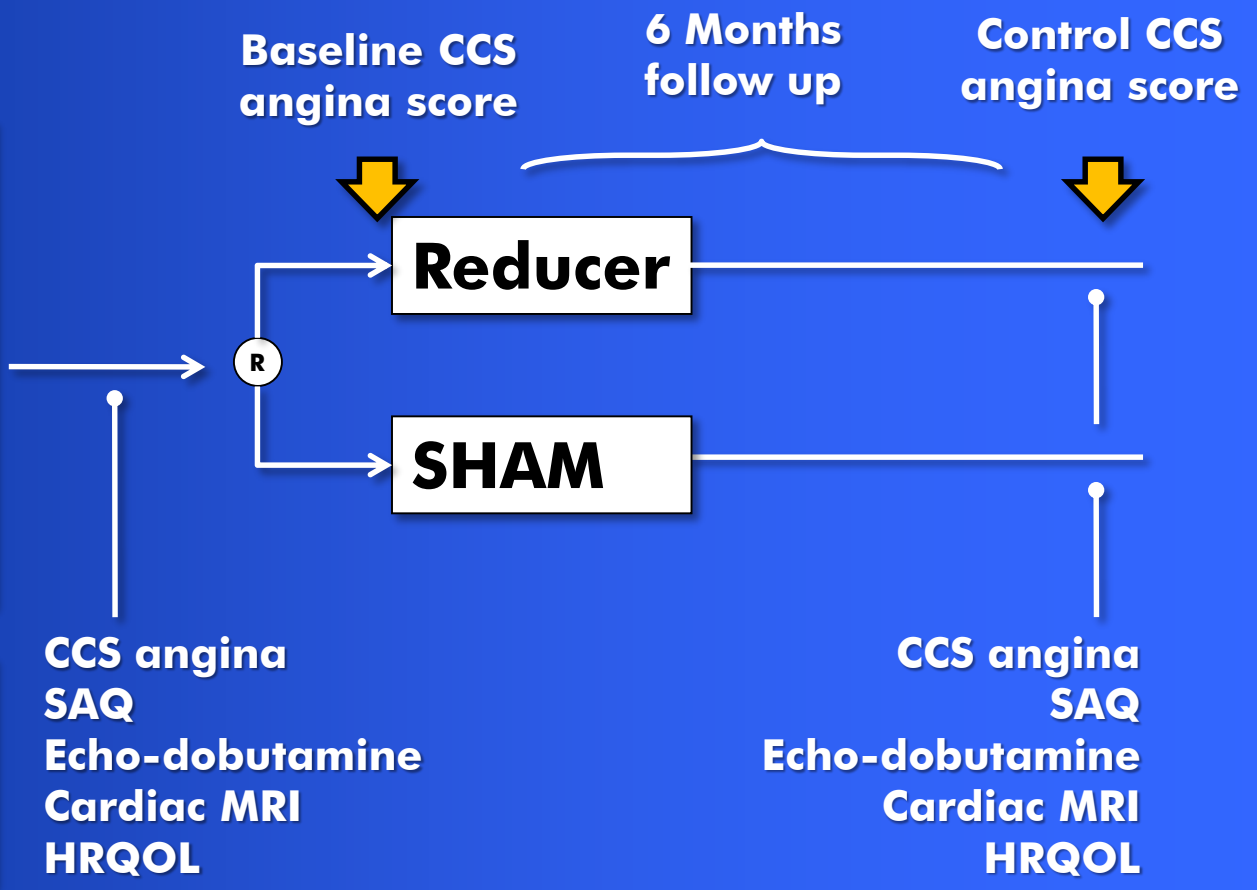
NCT: NCT01205893

COSIRA trial design

Key Inclusion criteria:

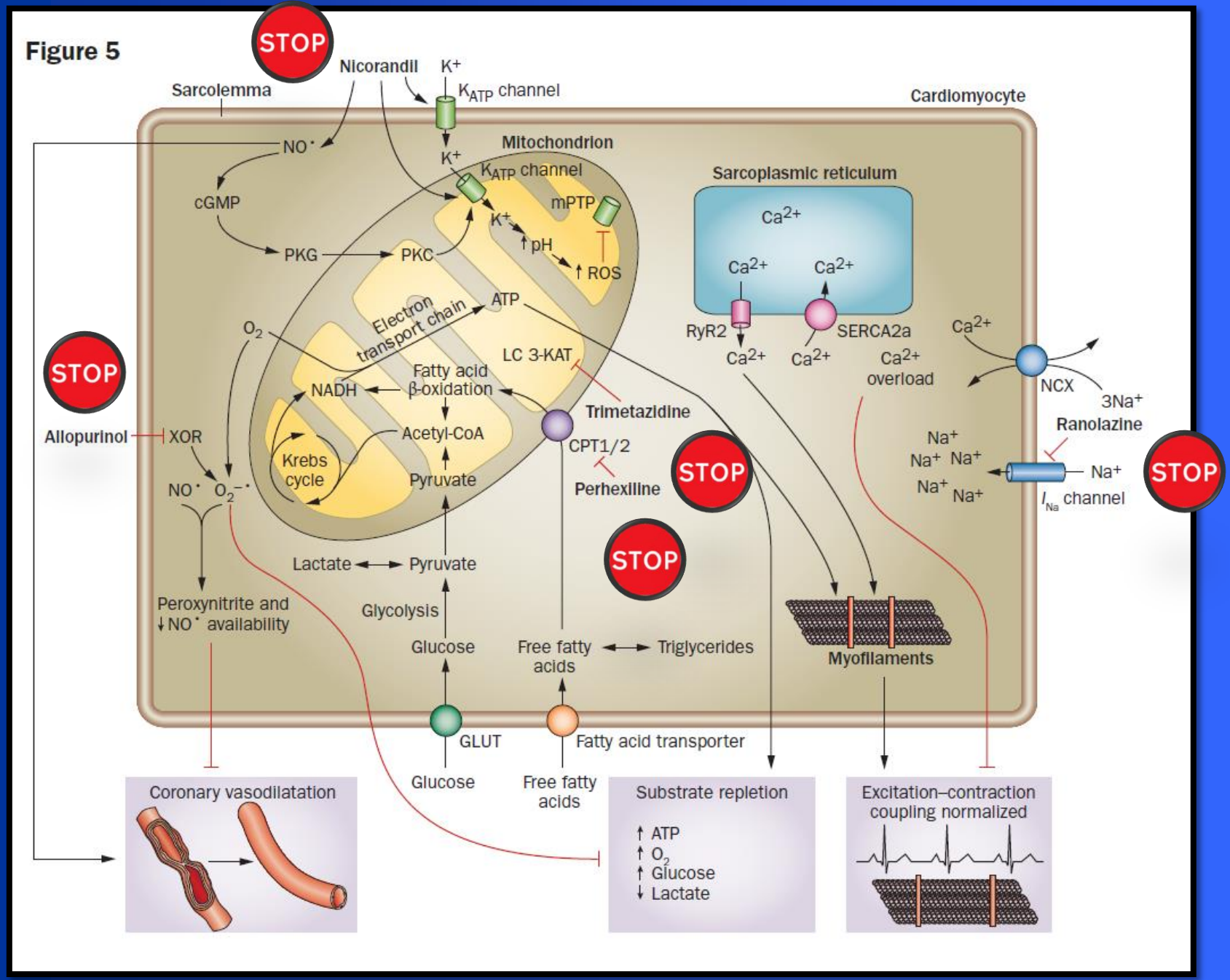
- Stable CCS III-IV angina
- Myocardial ischemia in the left circulation
- Limited revasc. option
- Optimal medical tx
- > 1 mm ↓ on stress test
- LVEF > 25%

Phase II trials with two Canadian centers:
- MHI
- Ottawa



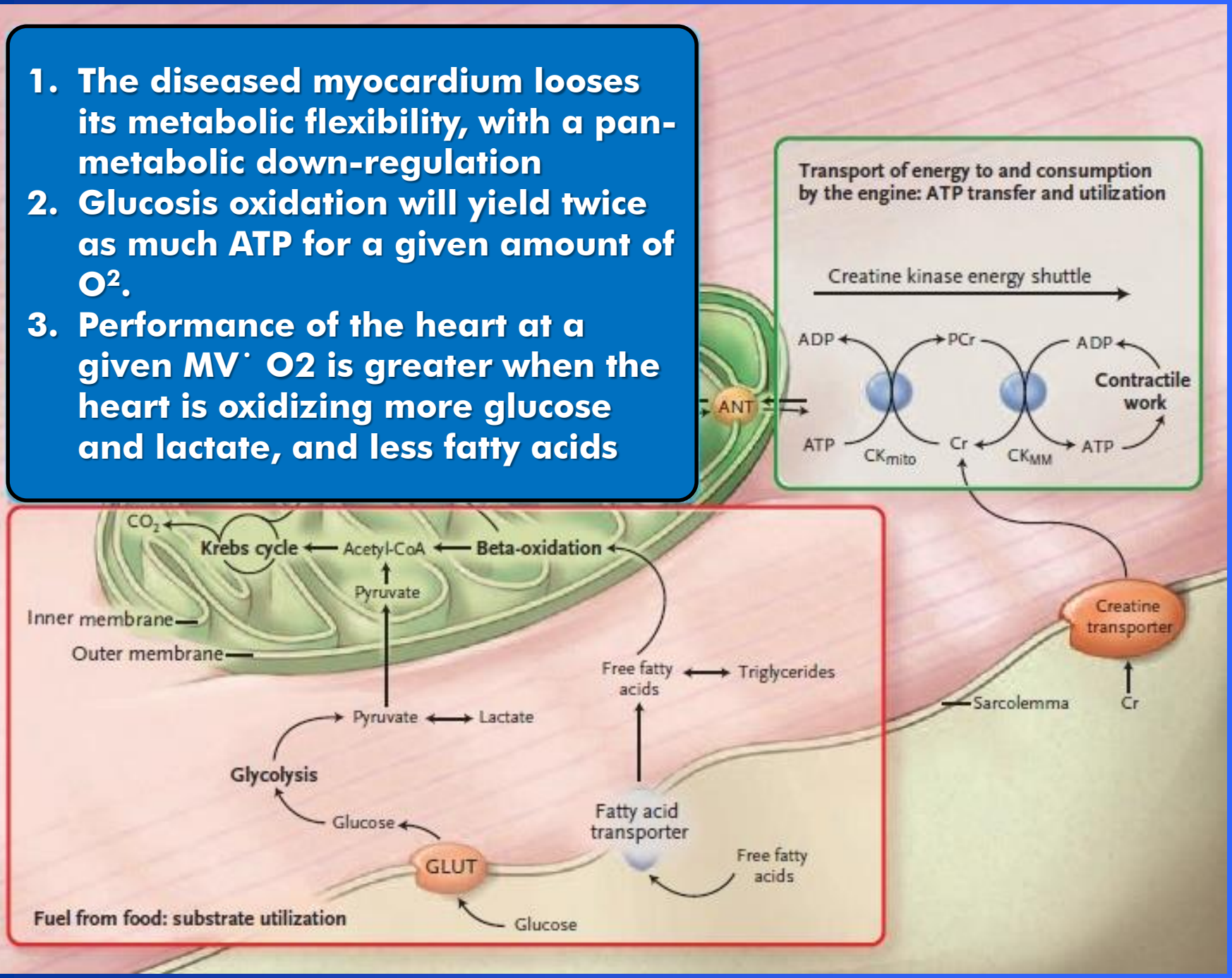
Essai parallèle, prospectif, multicentrique, randomisé (1:1), double-insu, contrôlé avec groupe témoin à procédure fictive

THE MITOCHONDRIAL ANGINA

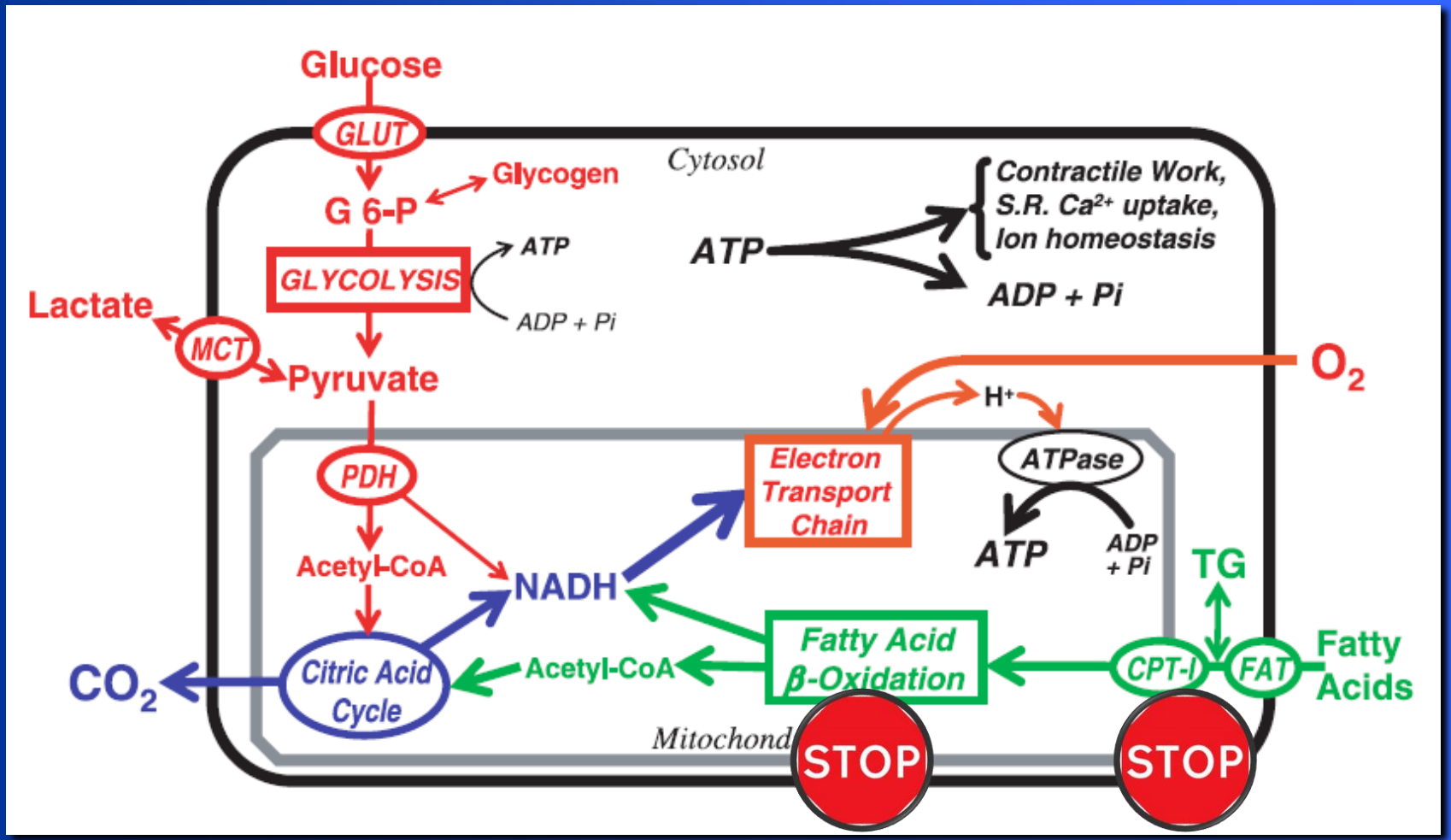


Henry and Jolicoeur, Nature Reviews Cardiology 2014;11:78

1. The diseased myocardium looses its metabolic flexibility, with a pan-metabolic down-regulation
2. Glucosis oxidation will yield twice as much ATP for a given amount of O^2.
3. Performance of the heart at a given MV˙ O2 is greater when the heart is oxidizing more glucose and lactate, and less fatty acids



Cardiac metabolism



Trimetazidine (LC 3-KAT)

Perhexiline
2 (carnitine-palmitoyl-transferase

Physiol Rev 85:1093-1129, 2005

Université de Montréal

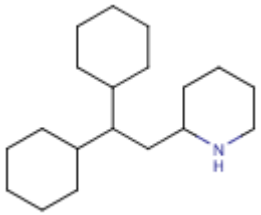
Mitochondrial agents

Metabolic modulators

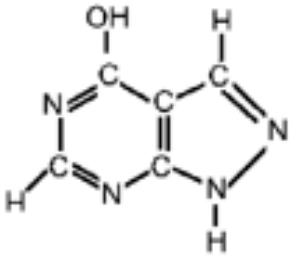
Ranexa®
ranolazine extended-release tablets

Ranolazine

Trimetazidine

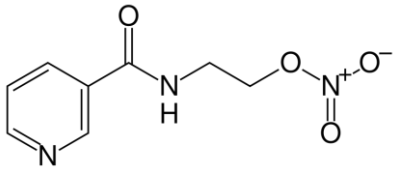


Perhexiline



Allopurinol

Conditionners



Niconrandil

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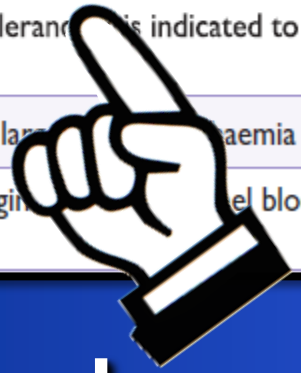
Angina/ischaemia[d] relief		
Short-acting nitrates are recommended.	I	B
First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.	I	A
For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.	IIa	B
For second-line treatment, trimetazidine may be considered.	IIb	B
According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients.	I	C
In asymptomatic patients with large ischaemia (>10%) ß-blockers should be considered.	IIa	C
In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B



Great drugs because can be added on top of optimal doses of negative chronotropic agents

European Heart Journal Advance Access published August 30, 2013

Santé Canada Health Canada

PROTÉGÉ UNE FOIS COMPLÉTÉ

PROGRAMME D'ACCÈS SPÉCIAL

FORMULAIRE A – DEMANDE AXÉE SUR LE PATIENT

SECTION A : INFORMATION SUR LE PRATICIEN

Nom du praticien :

Nom de l'hôpital ou clinique : (si applicable)

Adresse : (adresse d'expédition seulement)

Ville : | Province : | Code postal :

Médicament envoyé a/s de :
Pharmacie d'hôpital ☐
Bureau du praticien ☐
Médecine nucléaire ☐
Banque de sang ☐

Personne-ressource : (si autre que le praticien)

Téléphone :

Télécopieur :

Adresse électronique : (optionnel) | Adresse électronique du praticien : (optionnel)

SECTION B : INFORMATION SUR LE MÉDICAMENT ET LE FABRICANT

Appellation commerciale : | Autre nom :

Nom du fabricant : | N° de commande :

Voie d'administration : ORALE ☐ I.V. ☐ I.M. ☐ TOPIQUE ☐ S.C. ☐ AUTRE :

Forme posologique : COMPRIMÉ ☐ CAPSULE ☐ LIQUIDE ☐ POUDRE ☐ CRÈME ☐ ONGUENT ☐ TIMBRE ☐ AUTRE :

SECTION C : INFORMATION SUR LE PATIENT

Si vous disposez d'approvisionnement en médicament et souhaiteriez le transférer à un autre patient, veuillez demander une **autorisation seulement**. Veuillez cocher la case suivante ☐ et compléter le tableau ci-après. Précisez la quantité de médicament transférée dans la section à cet effet.

Initiales du patient (p. ex. A.B.C.)	Date de naissance (JJ/MM/AAAA)	Sexe	Indications thérapeutiques du médicament	Première demande?	Posologie et durée du traitement (p. ex. mg bid x nombre de jours)	Concentration (p. ex. en mg)	Quantité (p. ex. nombre de comprimés)
		H ☐ F ☐		O ☐ N ☐			
		H ☐ F ☐		O ☐ N ☐			
		H ☐ F ☐		O ☐ N ☐			
		H ☐ F ☐		O ☐ N ☐			**Total :**

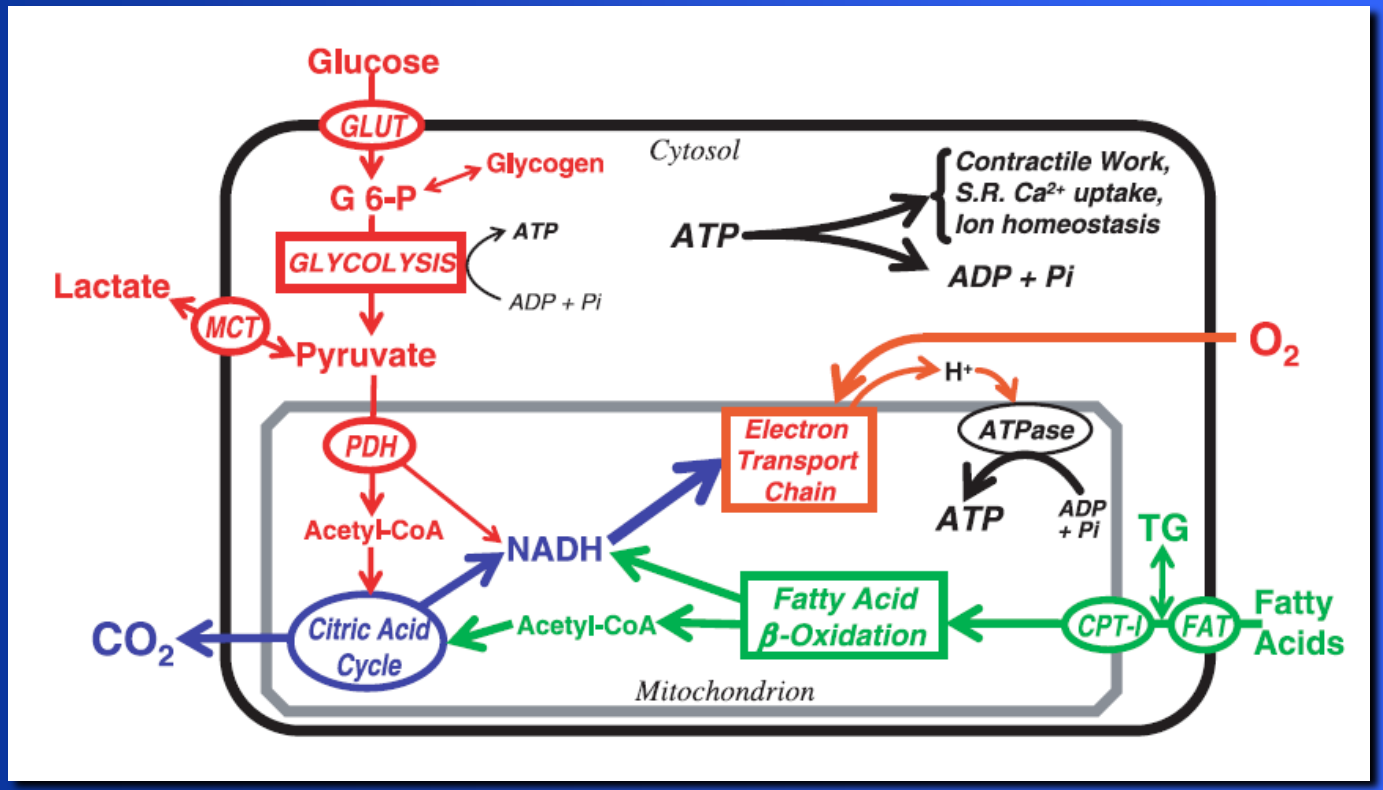
Veuillez préciser la **QUANTITÉ EXACTE** de produit requise (p. ex. nombre de comprimés, de flacons, d'unités, etc.). Le PAS ne calculera pas la quantité.

Veuillez préciser le moment où le médicament sera administré (c.-à-d. une date) :

Révisé janvier 2008

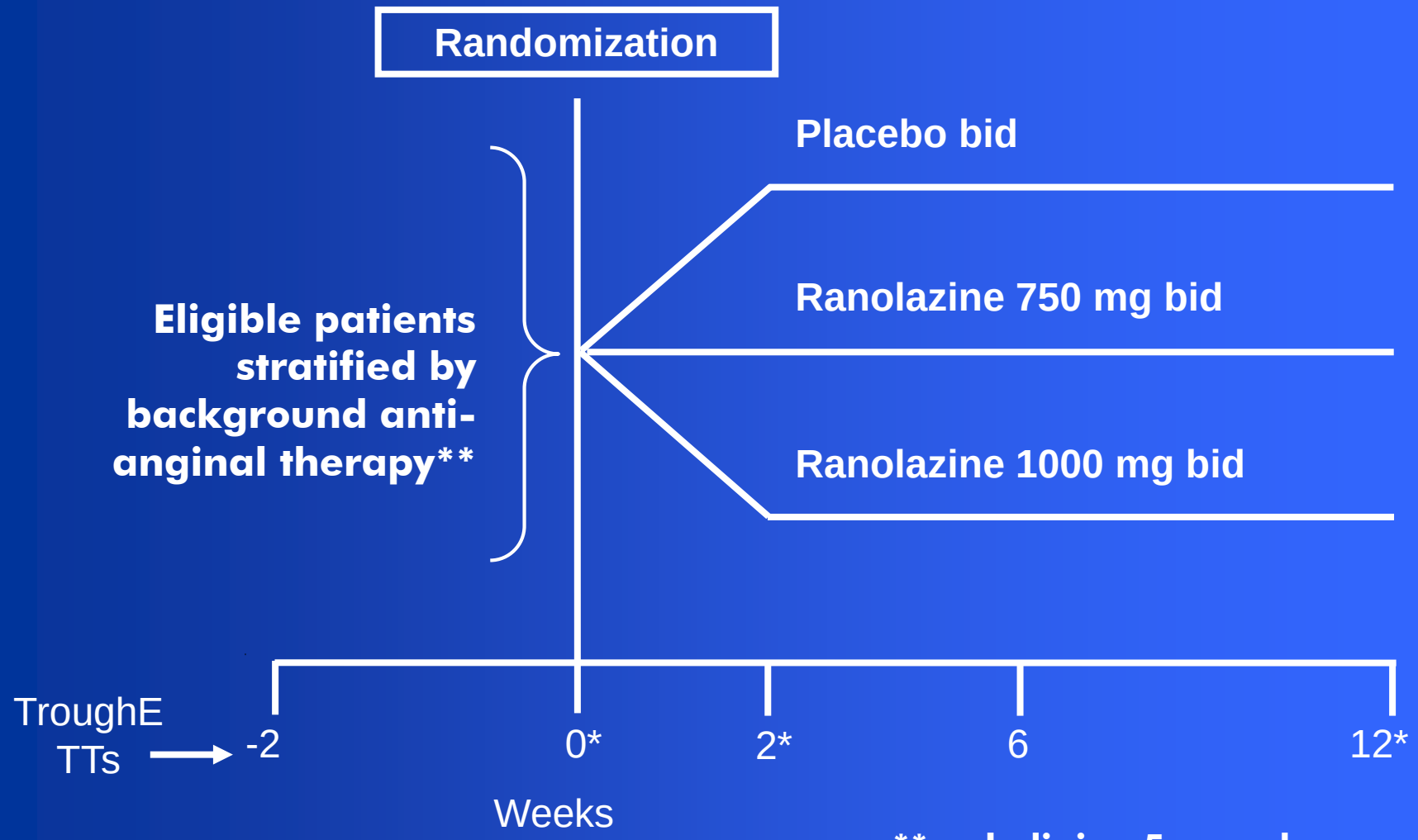
Ranolazine (ranexa™)

- Inhibitor of Late I_{na+} channels
- Inhibitor of the fatty acid β-oxidation



Physiol Rev 85:1093-1129, 2005

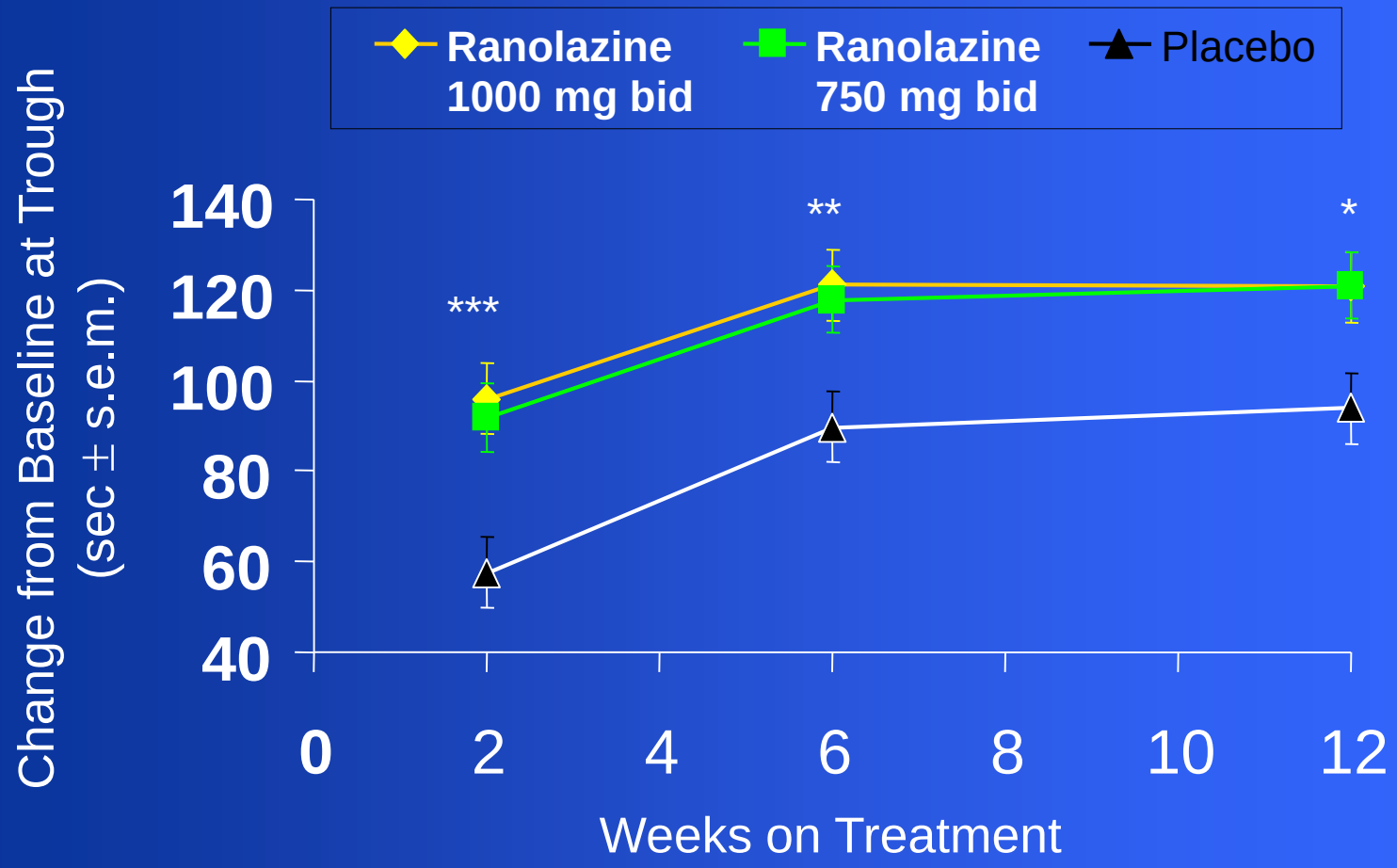
CARISA



*Additional Peak ETTs

**amlodipine 5 mg qd, or atenolol 50 mg qd, or diltiazem CD 180 mg qd

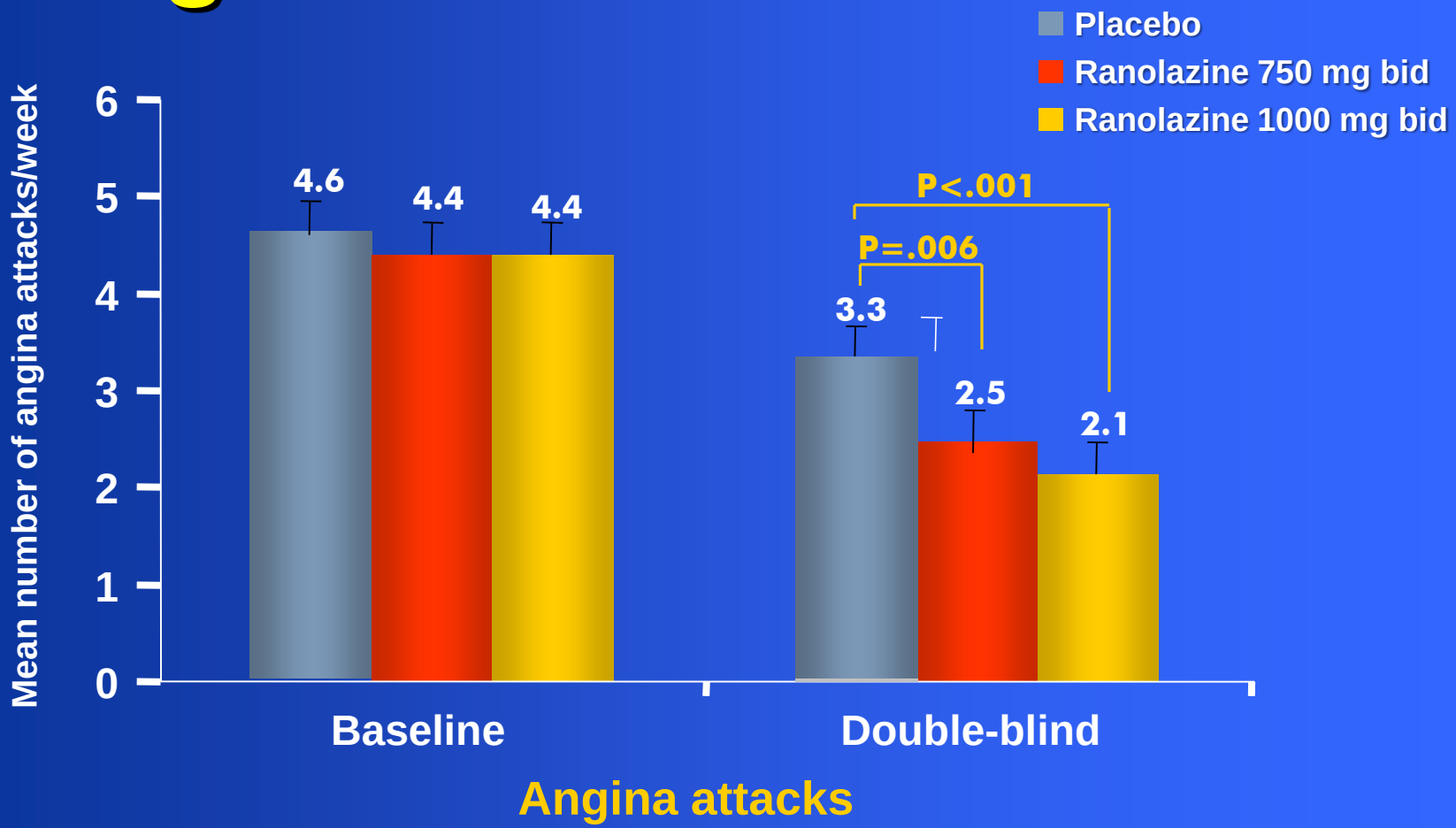
Total exercise time at 12 weeks



For both ranolazine doses vs. placebo:
*p ≤ 0.02, **p < 0.01 and ***p < 0.001.

Chaitman et al JAMA 2004; 291:309-16

Ranolazine: effet sur l'angine hebdomadaire



n=791, ITT/LOCF; LS mean ± SE.

Chaitman BR, et al. *JAMA*. 2004.

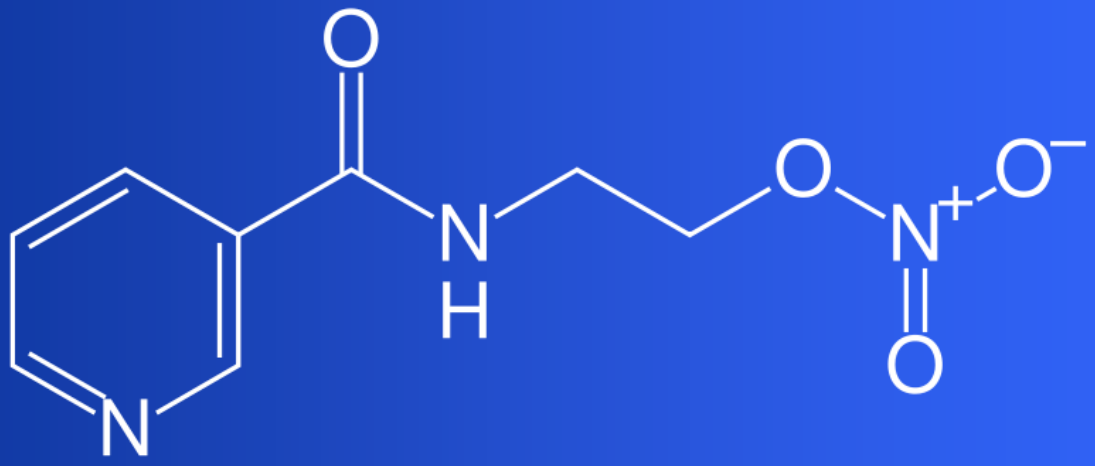
Chaitman et al JAMA 2004; 291:309-16

Ranolazine (ranexa™)

- Nouveau mécanisme d'action
- Pas d'effet sur fréquence cardiaque et tension artérielle
- Peu de donnée chez le patient avec MCAS avancée
- Pas encore disponible au Canada

K-ATP Channel Openers

- Nicorandil has both an anti-anginal and a disease-modifying effect



IONA

Primary Hypothesis :

Treatment with nicorandil will reduce
the incidence of the primary endpoint by 25%

Primary End Point :

Coronary Heart Disease Death

+

Non fatal Myocardial Infarction

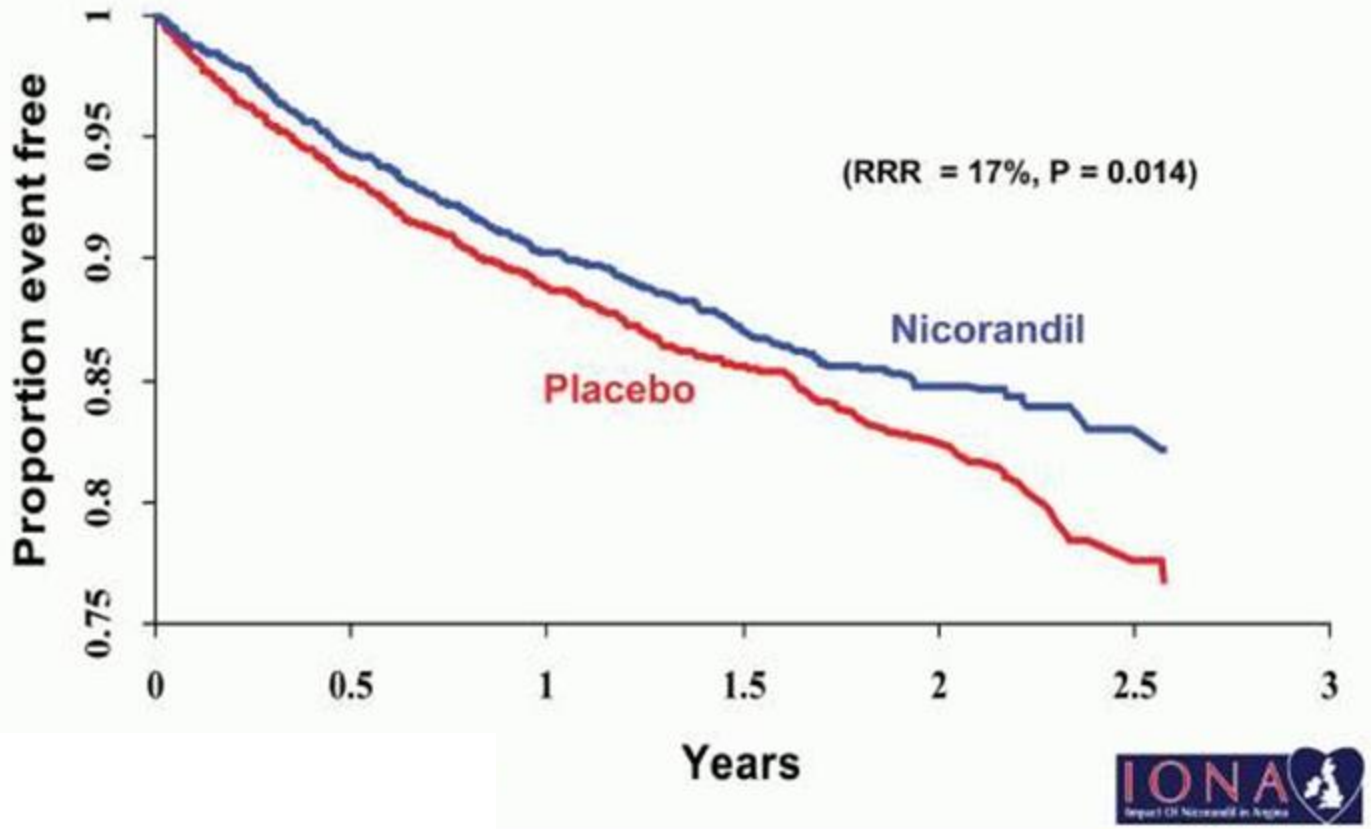
+

Unplanned Hospitalisation for Cardiac Chest Pain

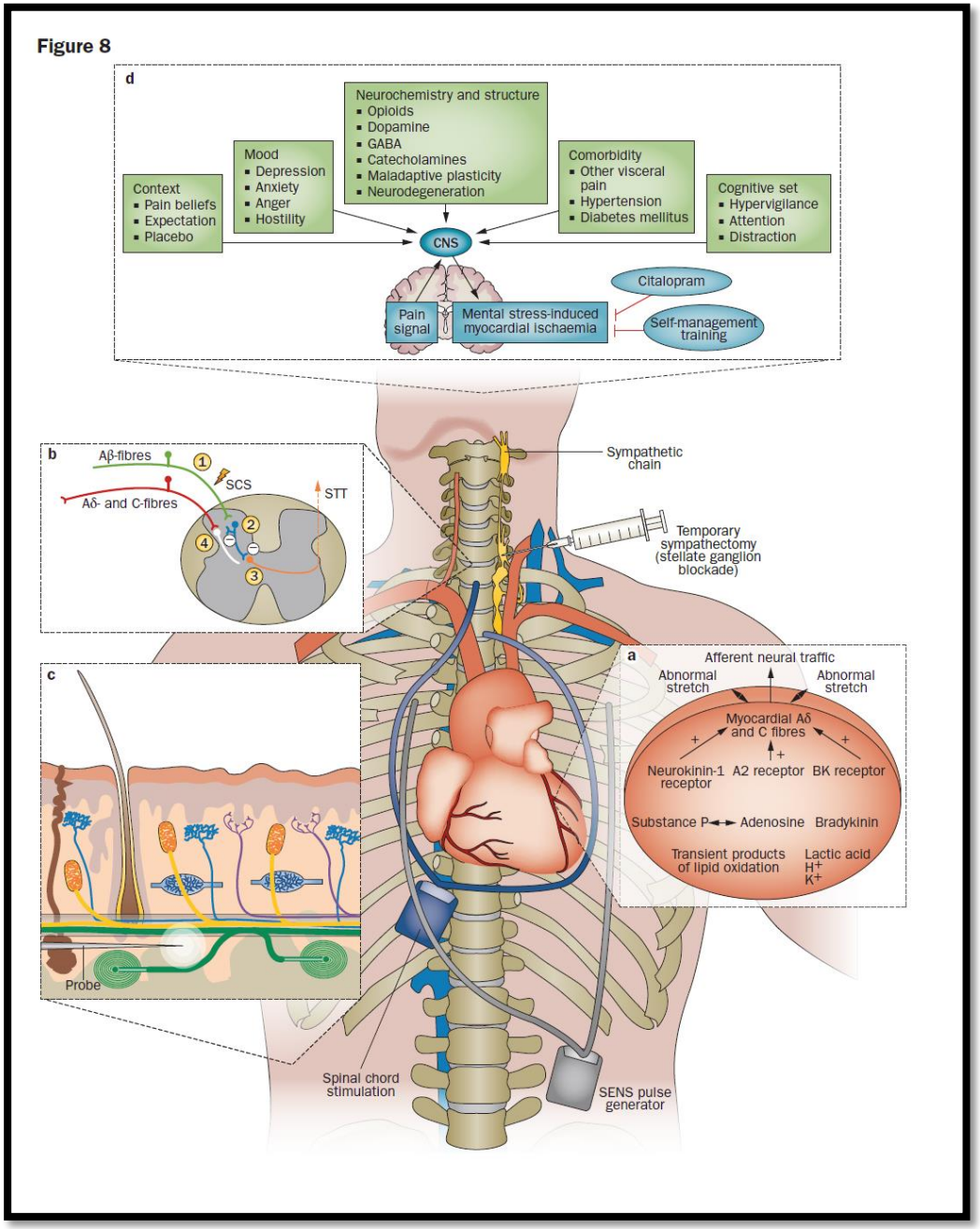
Preliminary results AHA 2001

Lancet 2002;359:1269

CHD death, non-fatal MI or unplanned hospitalisation for cardiac chest pain

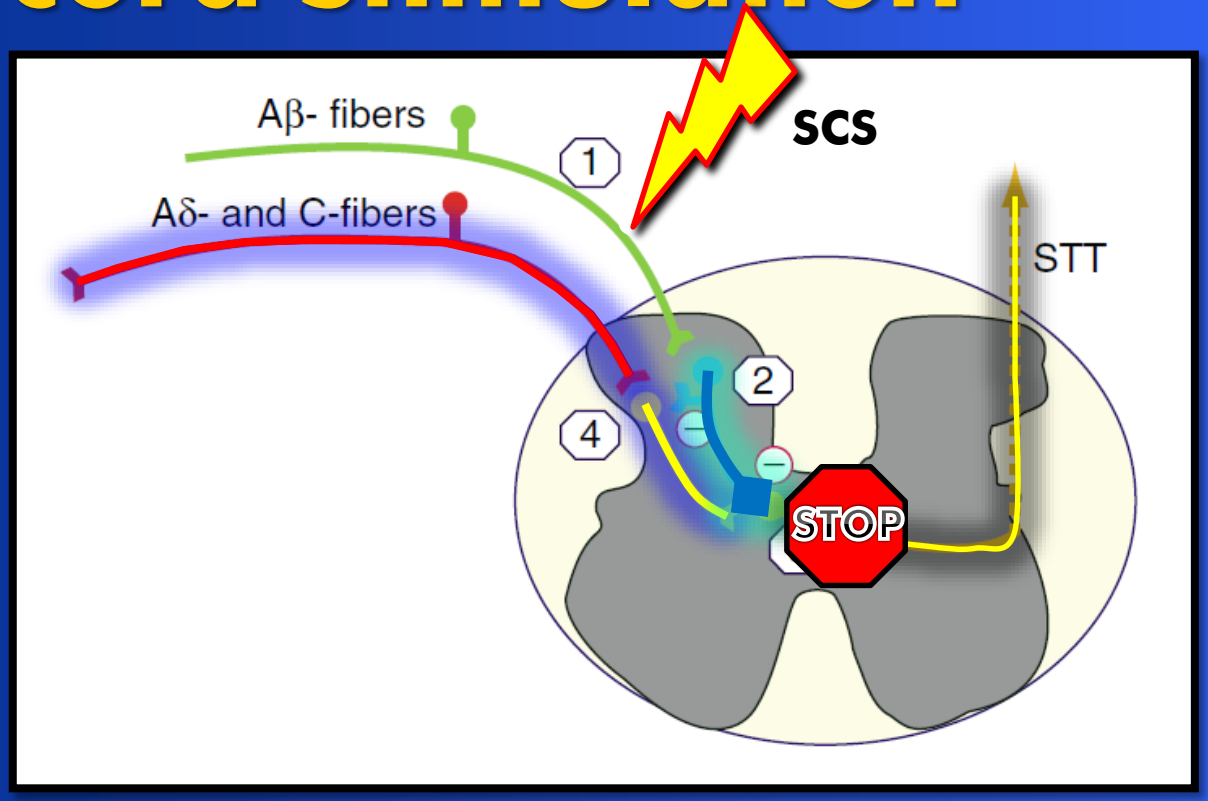


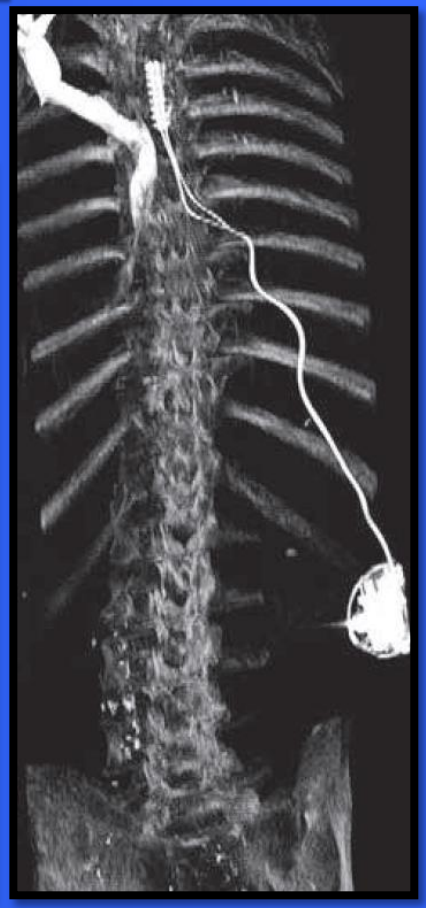
THE NEUROGENIC AND PSYCHOGENIC ANGINA



Henry and Jolicoeur, Nature Reviews Cardiology 2014;11:78

Neuromodulation: spinal cord stimulation





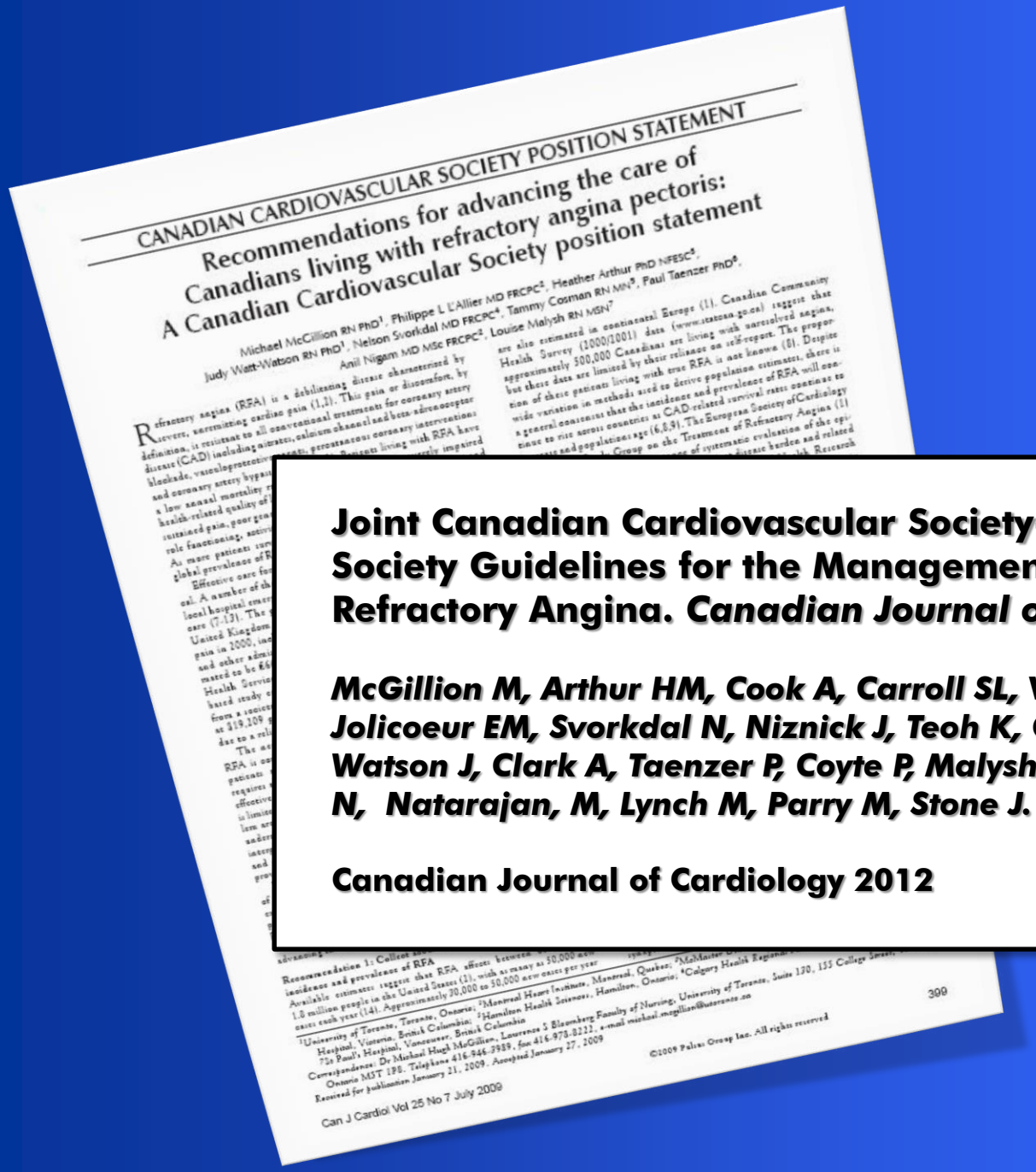
The contemporary view of the gate control theory assumes that the stimulation of the large afferent non-nociceptive A-alpha and A-beta fibers by spinal cord stimulation can stop the transmission of the nociceptive impulse in the small afferent A-delta and C fibers to the central nervous system.

Jolicoeur et al., Invasive and Device Management of Refractory Angina

How Does Neurostimulation reduce angina?

SCS may alleviate angina by two ways:

- Direct pain-inhibiting effect
- Affecting underlying ischemia, as shown by:
  - reduced ST segment depression[2]
  - increased time to ST segment depression[2]
  - reduced total ischaemic burden during Holter monitoring[2]


CANADIAN CARDIOVASCULAR SOCIETY POSITION STATEMENT

Recommendations for advancing the care of Canadians living with refractory angina pectoris: A Canadian Cardiovascular Society position statement

Joint Canadian Cardiovascular Society-Canadian Pain Society Guidelines for the Management of Patients with Refractory Angina. *Canadian Journal of Cardiology*

McGillion M, Arthur HM, Cook A, Carroll SL, Victor JC, L'Allier PL, Jolicoeur EM, Svorkdal N, Niznick J, Teoh K, Cosman T, Sessle B, Watt-Watson J, Clark A, Taenzer P, Coyte P, Malysh L, Galte C, Suskin N, Natarajan, M, Lynch M, Parry M, Stone J.

Canadian Journal of Cardiology 2012

Can J Cardiol, 2012;28(2 Suppl):S20-41