Diabète: de l'insuline aux nouvelles molécules

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Divulgations

- *Financement de recherche: CIHR, FRQS*
- *Consultant/présentations: Janssen, Novartis Pharmaceuticals Canada, NovoNordisk Canada, HLS Therapeutics, Eli Lilly*
- *Les appellations génériques seront employées pour les médicaments cités et les usages expérimentaux non couramment approuvés par Santé Canada seront mentionnées, le cas échéant.*

Objectifs

CENTRE DE RECHERCHE | CHUS

Rappel historique sur la découverte de l'insuline

Faire le point sur les avancées sur le plan du traitement du diabète

Offrir ma perspective quant aux avenues de recherche dans le domaine

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La découverte de l'insuline

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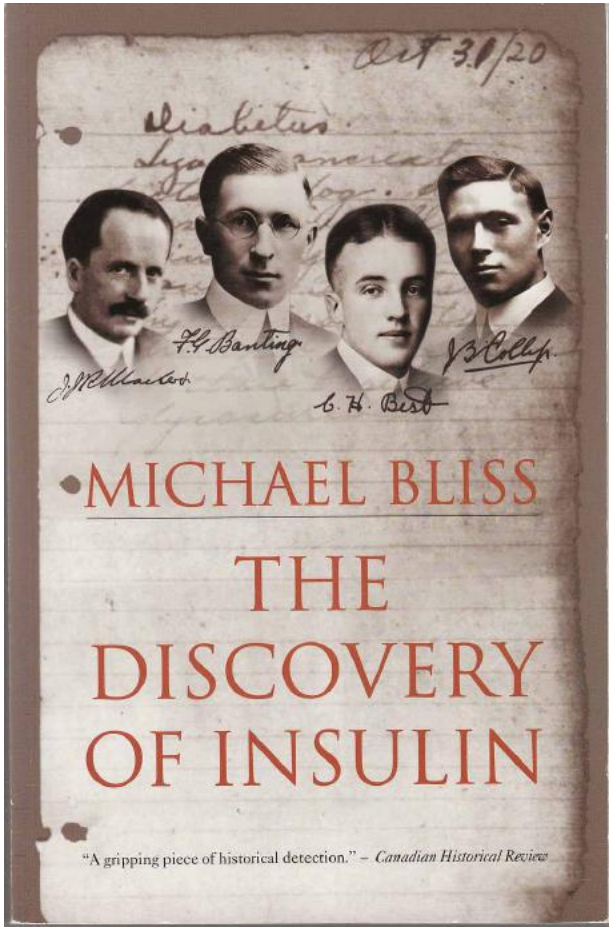
Le 2 décembre 1921, Leonard Thompson, 14 ans, 65 livres, est admis au Toronto General Hospital. Sous une diète hypocalorique de 450 cal/jour, il est en phase terminale de son diabète, diagnostiqué en 1919.

Le 11 janvier 1922, Leonard reçoit deux injections (2 x 7,5 ml) d'un extrait de pancréas de bœuf ('a thick brown muck') préparé par Best et Banting. La glucosurie de 24h a ensuite diminué de 91,5 à 84 g/24h.

Le 23 janvier 1922, Leonard a reçu 5 ml d'un nouvel extrait pancréatique préparé par Collip. Sa glycémie est passée de 0,520 le 23 à 0,120 g/dl (29 à 7 mmol/l) le 24 janvier.

La découverte de l'insuline



Patient JL, 15 pounds December 15, 1922

Patient JL, 29 pounds February 15, 1923

La découverte de l'insuline

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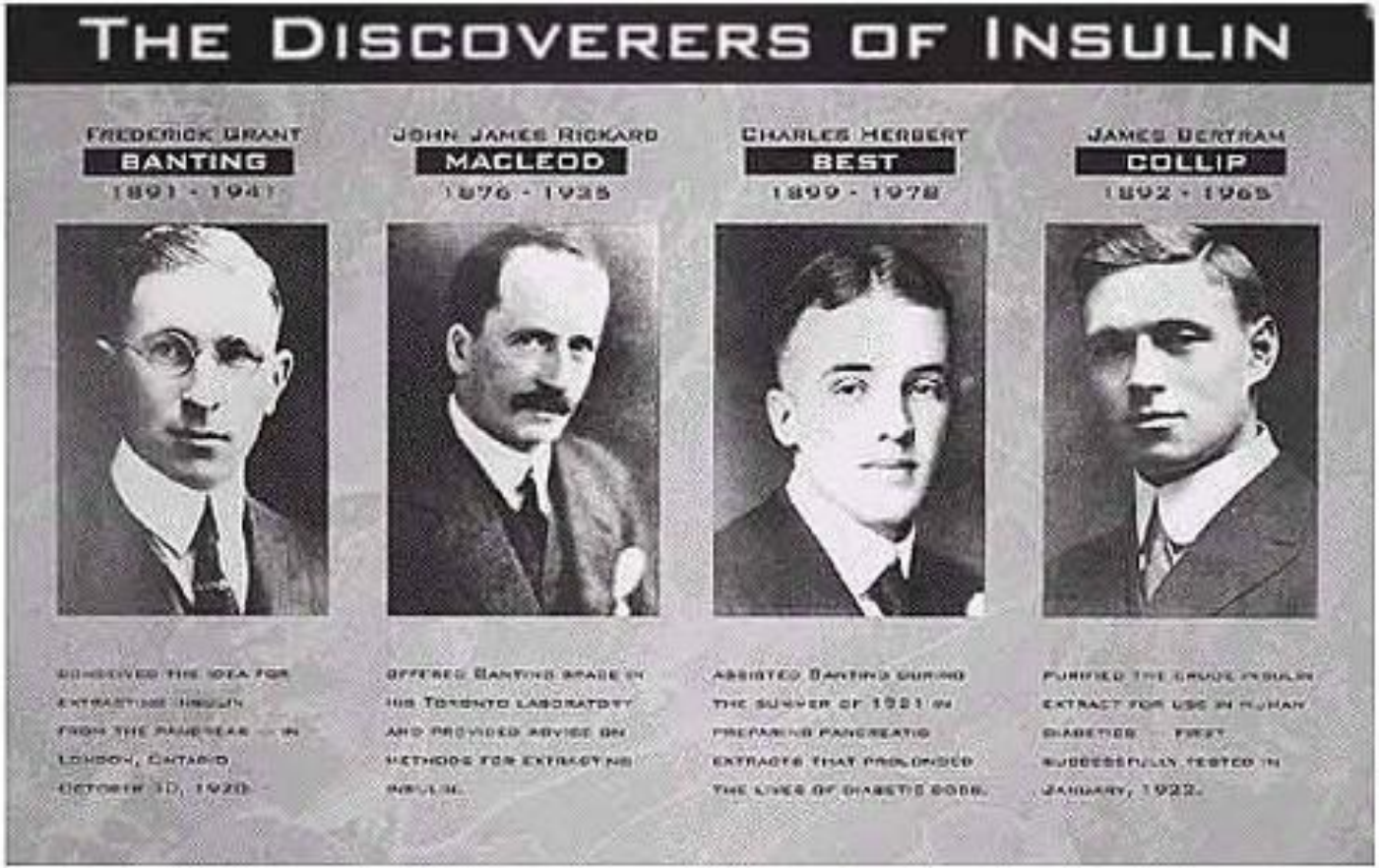
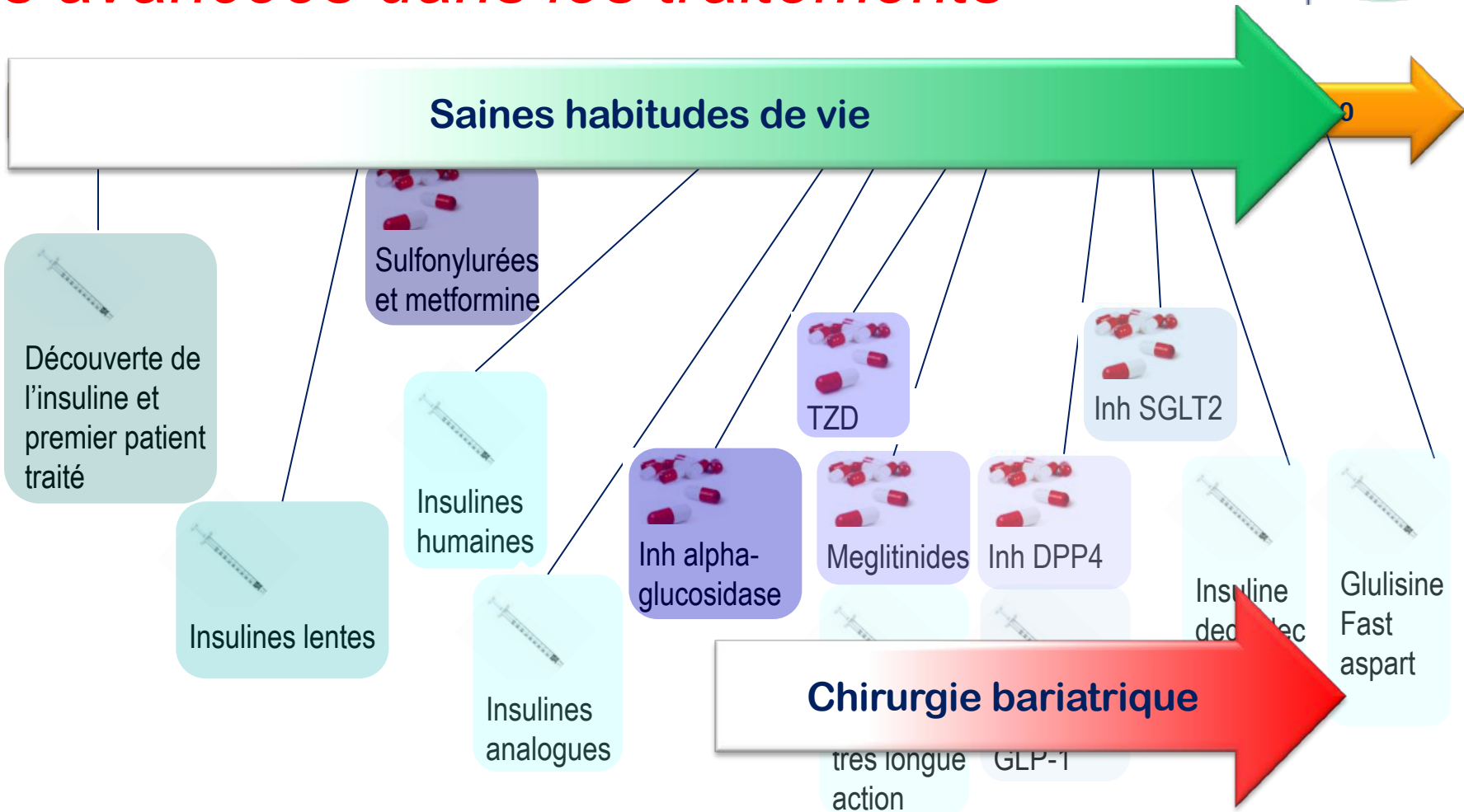
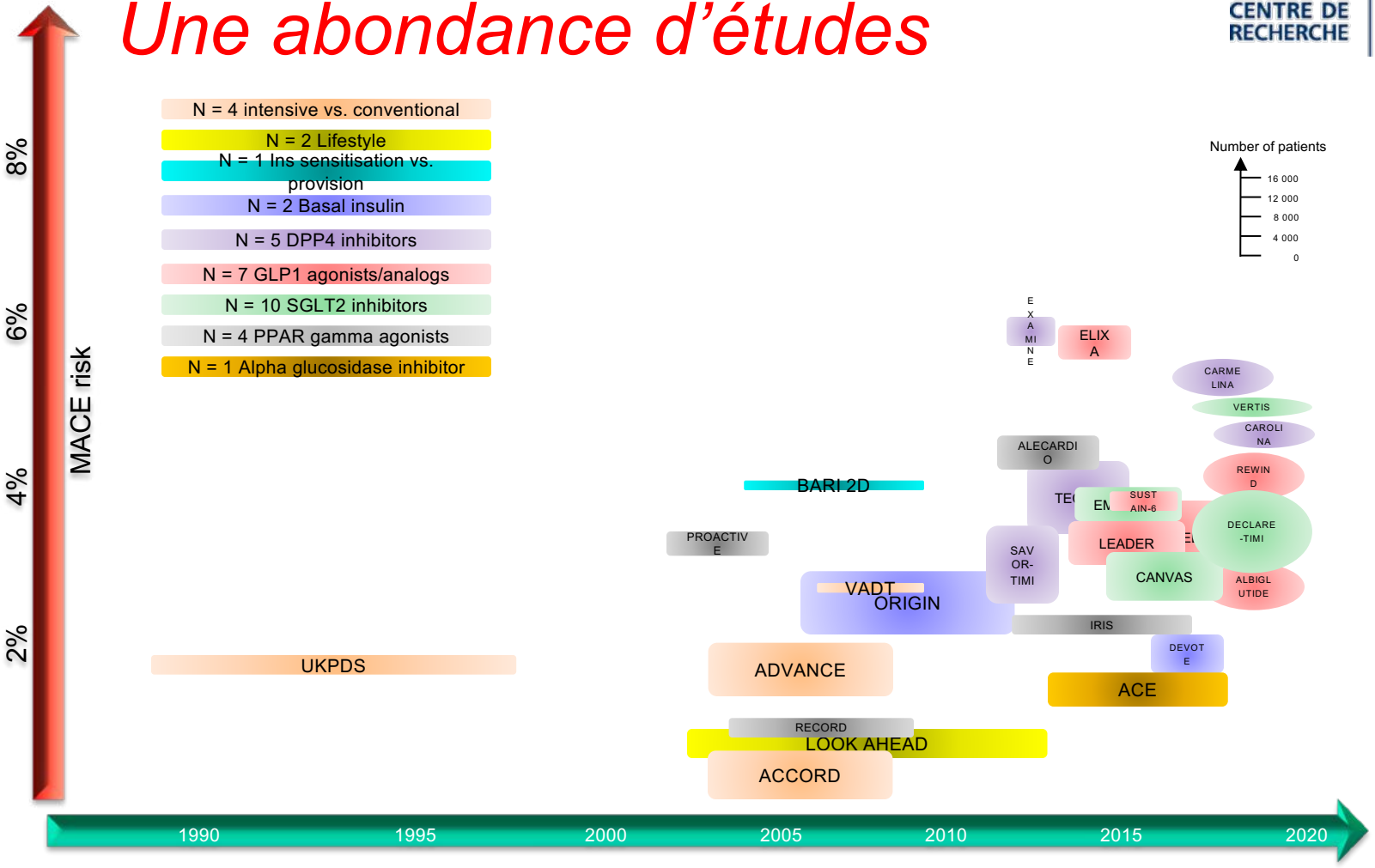


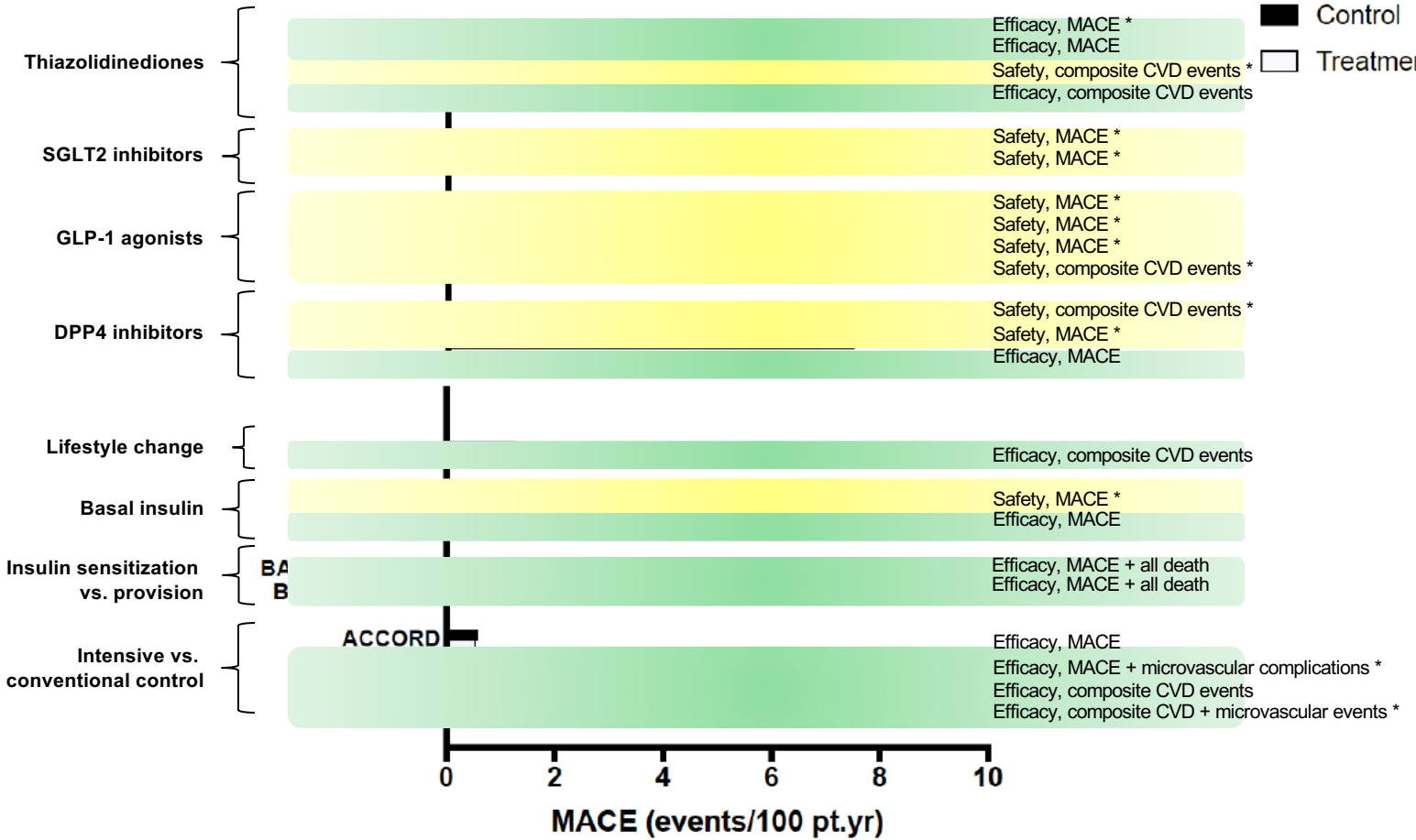
Les avancées dans les traitements



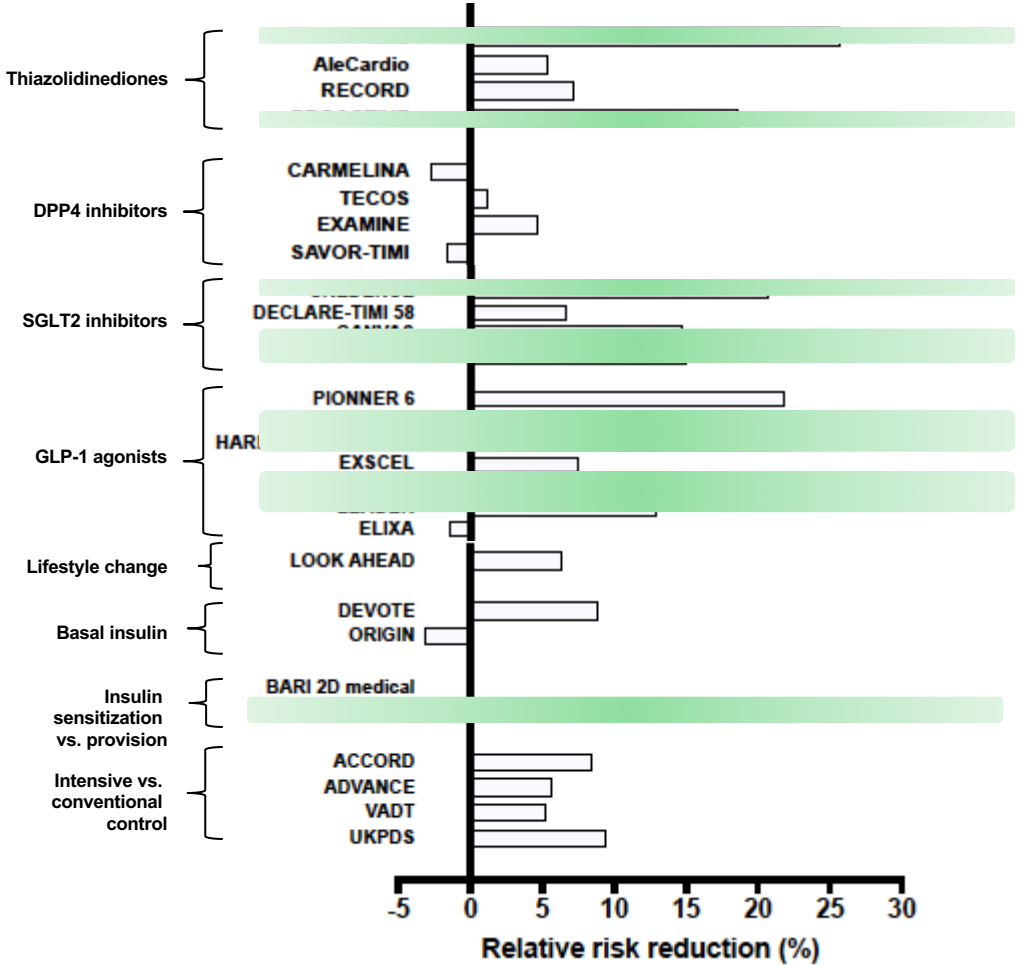
Une abondance d'études



Prévention des complications DM2



Traitement du DM2 et MACE



Primary outcome * (pioglitazone)

Secondary outcome * (pioglitazone)

Primary outcome * (canagliflozin)

Primary outcome * (canagliflozin)
Primary outcome * (empagliflozin)

Primary outcome * (dulaglutide)
Primary outcome * (albiglutide)

Primary outcome * (semaglutide)
Primary outcome * (liraglutide)

Secondary outcome, sub-analysis *

Quel était le l'objectif?

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Study	Drug	Aim	Population	Nb pt.year	MACE (per 100 pts.year)	RRR	HF + CVD death (per 100 pts.year)	RRR	Total death (per 100 pts.year	RRR
EMPAREG	empa	safety, MACE	T2D + CVD	21,762	**4,4**	15	1,5	35	2,9	32
CANVAS	cana	safety, MACE	T2D + CVD	36,511	**3,2**	15	0,9	37	2,0	11
DECLARE-TIMI 58	dapa	safety, MACE; efficacy, MACE + composite CVD, death, HF	T2D - CVD	72,072	2,4	7	1,5	17	1,6	8
VERTIS	ertu	safety, MACE	T2D + CVD	28,861	**4,0**	**3**	2,7	15	2,6	8
CREDENCE	cana	efficacy, CKD + CVD death	CKD + T2D	11,531	4,9	21	4,5	31	3,5	17
DAPA-HF	dapa	efficacy, HF + CVD death	HF ± T2D: 41,8%	7,116	-	-	**9,8**	30	9,5	17
EMPEROR REDUCED	empa	efficacy, HF + CVD death	HF ± T2D: 49,8%	4,961	-	-	**21,0**	25	10,7	6
DAPA-CKD	dapa	efficacy, CKD + CVD death	CKD ± T2D: 67,5%	10,330	-	-	3,0	27	3,1	29
SOLOIST-WHF	sota	efficacy, HF + CVD death	HF + T2D	917	-	-	**76,3**	33	16,3	17
SCORED	sota	efficacy, HF + CVD death	CKD + T2D	14,077	6,3	24	**7,5**	25	3,5	0

Quel était l'objectif?

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Study	Drug	Aim	Population	Nb pt.year	MACE (per 100 pts.year)	RRR	HF + CVD death (per 100 pts.year)	RRR	Total death (per 100 pts.year	RRR
ELIXA	lixisenatide	safety, composite CVD	T2D + CVD	12,743	7,4	-1	1,9	5	3,3	6
EXSCEL	exenatide	safety, MACE	T2D + CVD	47,206	**4,0**	**8**	1,0	10	2,3	13
LEADER	liraglutide	safety, MACE	T2D + CVD	35,492	**3,9**	13	1,4	14	1,6	25
SUSTAIN 6	semaglutide	safety, MACE	T2D + CVD	6,594	**4,4**	27	1,6	-9	1,8	-3
REWIND	dulaglutide	efficacy, MACE	T2D - CVD	53,465	**2,7**	11	0,9	7	2,3	10
HARMONY OUTCOME	albiglutide	safety, MACE	T2D + CVD	15,141	**5,9**	22	2,9	15	2,6	5
PIONNER 6	semaglutide (oral)	safety, MACE	T2D + CVD	4,138	**3,7**	**22**	1,2	17	2,2	50

Comment s'y retrouver?

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Special Article

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update — The User's Guide

Diabetes Canada Clinical Practice Guidelines Steering Committee

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[e] *Interdisciplinary School of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada*
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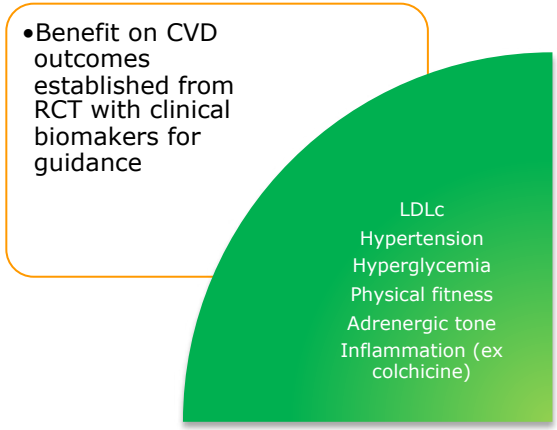
* Titration of basal insulin to achieve FPG target without hypoglycemia.
† And titrate dose of GLP1-RA, as tolerated.
†† Or fixed-ratio combination.
††† If eGFR >30 ml/min/1.73m², may be used for cardiorenal benefit.
** Sulfonylureas or meglitinides.

AHAs, antihyperglycemic agents; *A1C*, glycated hemoglobin; *DPP4i*, dipeptidyl peptidase-4 inhibitors; *eGFR*, estimated glomerular filtration rate; *GLP1-RA*, glucagon-like peptide-1 receptor agonists; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *SU*, sulfonylureas.

Figure 3. Starting or advancing insulin in type 2 diabetes.

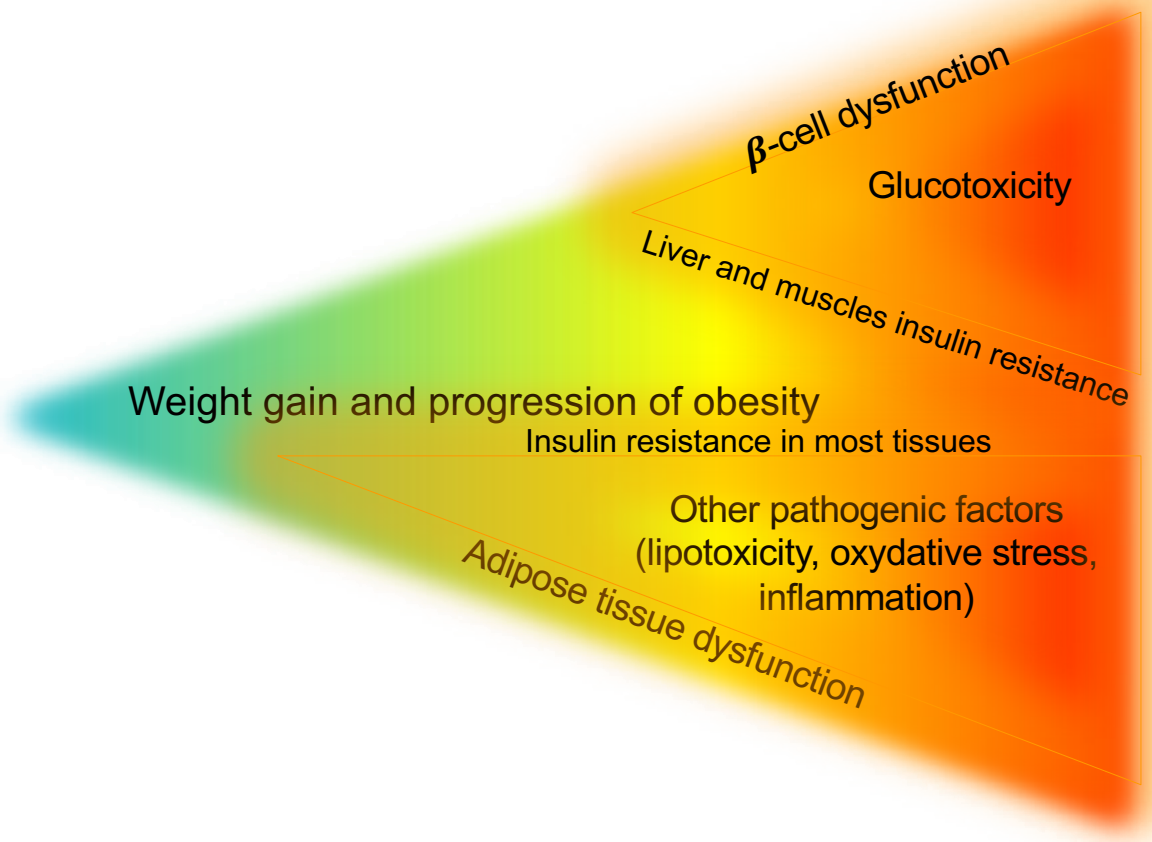
Can J Diabetes 44 (2020) 575–591
Can J Diabetes 44 (2020) 592–596

Interventions pour MCVAS



Carpentier AC *Unpublished*

De moins en moins glucocentrique…



Blindness

Hypoglycemic agents
Anti-VEGF
Fibrates

Kidney failure

Hypoglycemic agents
ACE inh, ARA
SGLT2 inh

Foot ulcers, amputation

Hypoglycemic agents
TG lowering?

Atherosclerotic events

LDLc lowering
ACE inh, ARA
Anti-platelet
GLP1 agonists
Pioglitazone
Cochicine
Icosapent ethyl

Heart failure

ACE inh, ARA
Beta-blockers
SGLT2 inh
Sacubitril - valsartan

NASH, cirrhosis

Statins
Pioglitazone
GLP1 agonists?

Cancers

Metformin?

Carpentier AC. Unpublished

Visceral obesity/ Ectopic fat

SGLT2 Inhibitors

Medical Treatment of CVD Risk Factors

Lifestyle Changes

Medical Treatment of CVD Risk Factors

SGLT2 Inhibitors

GLP1-RA

No Diabetes

Type 2 Diabetes

Massive obesity

SGLT2 Inhibitors

GLP1-RA or Medical or Surgical Rx of Obesity

Medical Treatment of CVD Risk Factors

Lifestyle Changes

Medical Treatment of CVD Risk Factors

Medical or Surgical Rx of Obesity

SGLT2 Inhibitors

No Diabetes

Preclinical Risk Factors — Clinical Risk Factors — Clinical Atherosclerosis — Cardiac and/or Renal Failure

Després JP, Carpentier AC, Poirier P, Neeland I. Submitted

Nouveautés pharmacologiques

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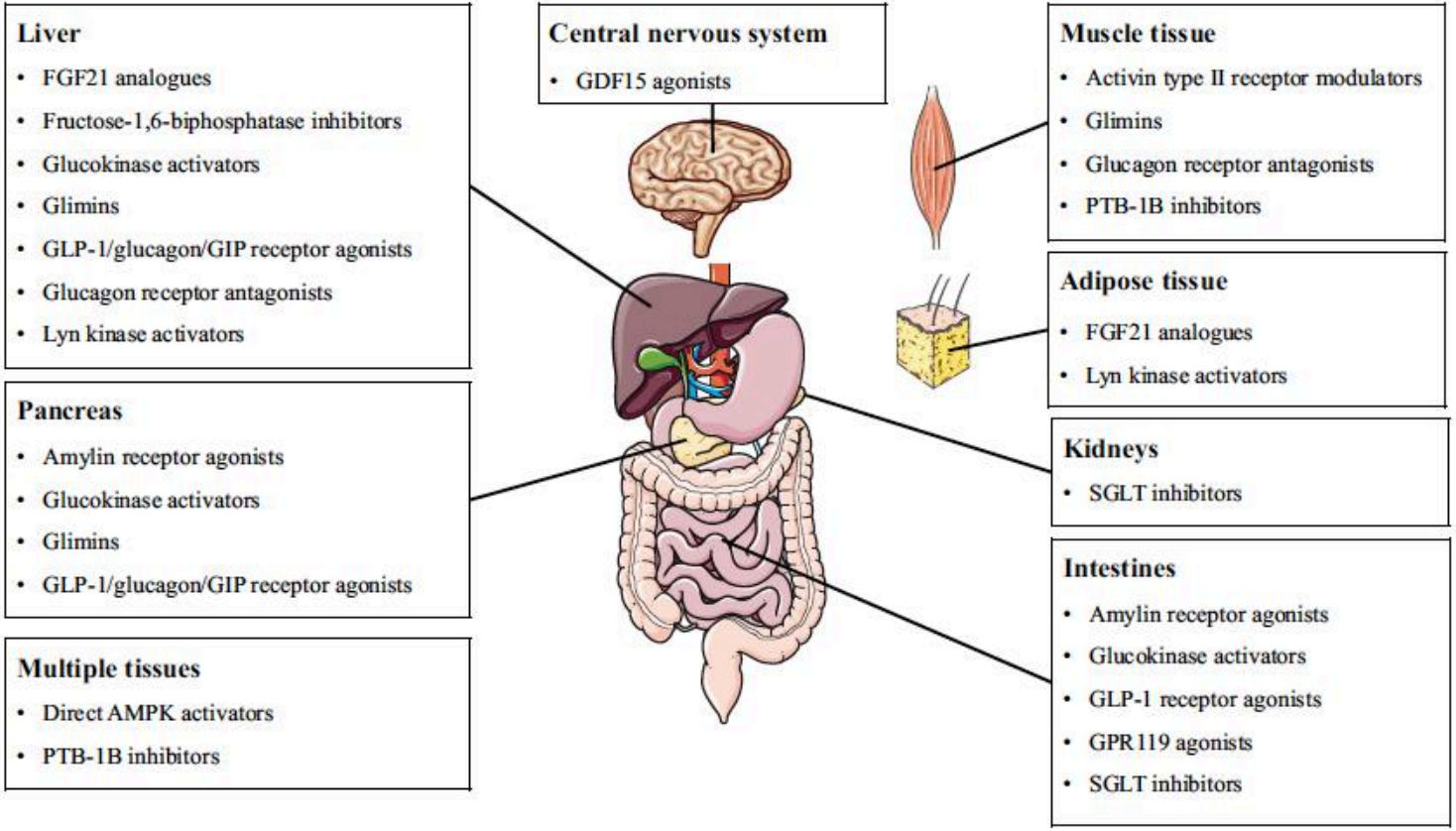
Table 1. Overview of antidiabetic drugs in clinical development. Drug name (name of developing company)

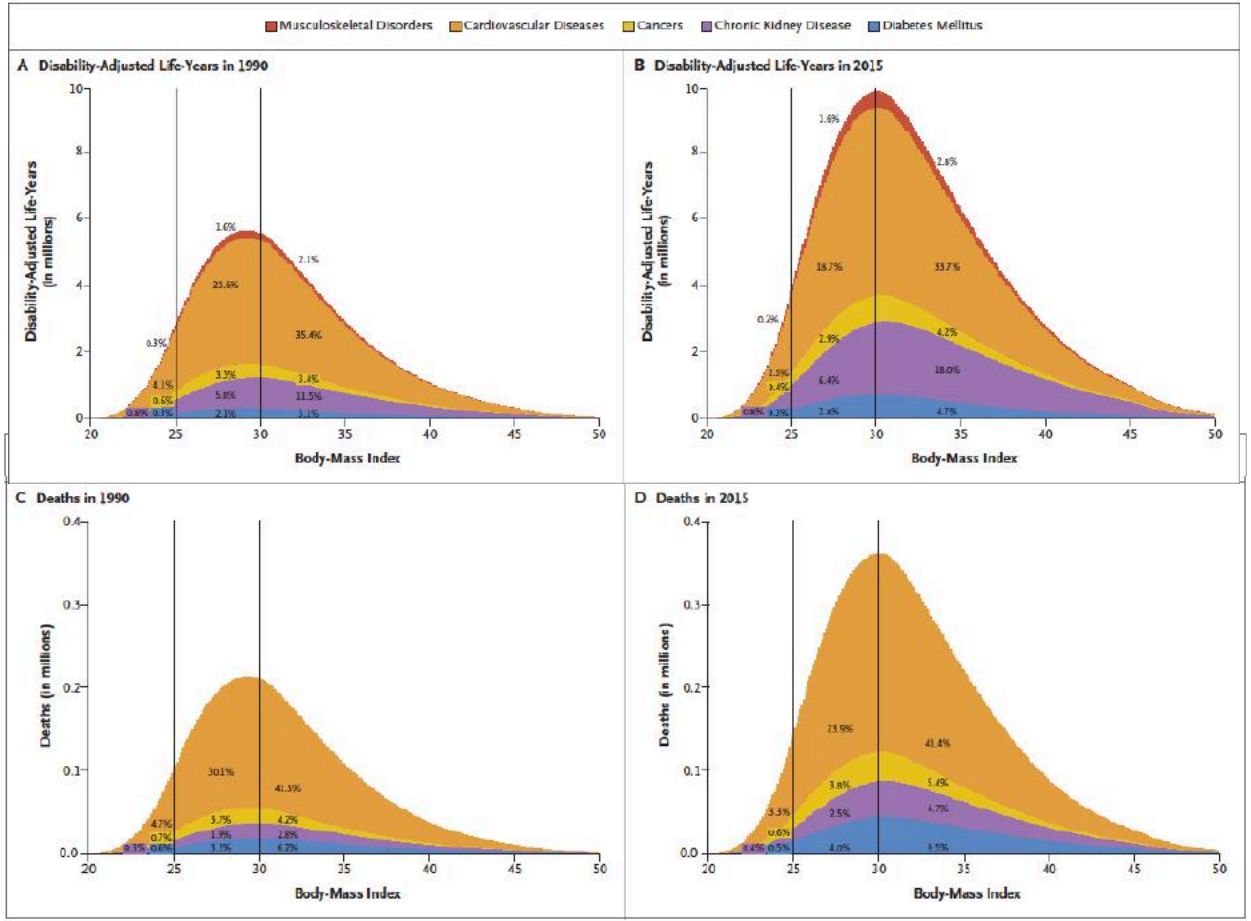


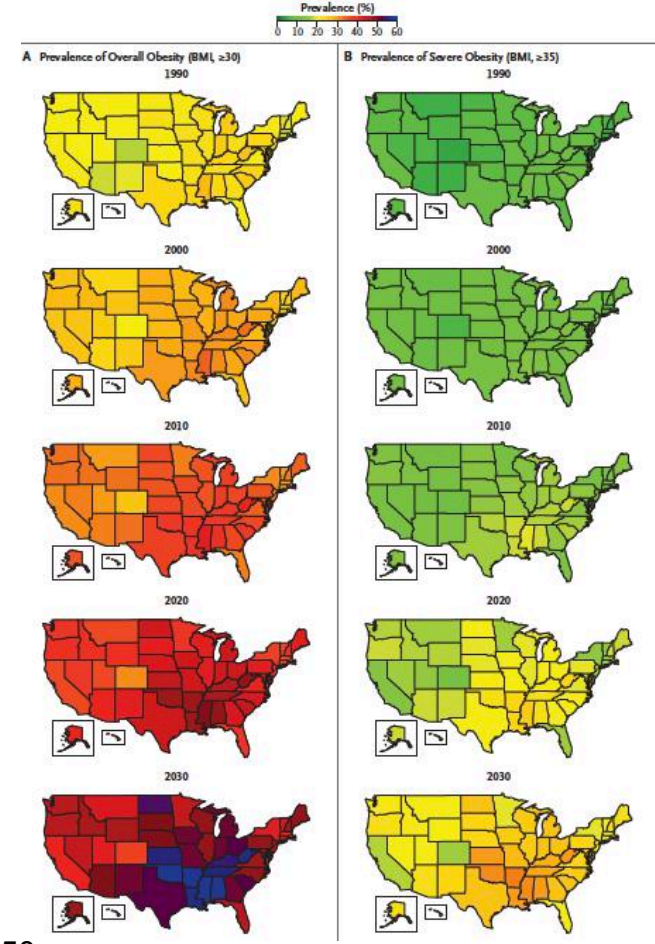
Pharmaceuticals)

AMPK, adenosine monophosphate-activated protein kinase; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; GPR119, G protein-coupled receptor 119; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; MetAP2, methionine aminopeptidase 2 inhibitor; PTB-1B, protein-tyrosine phosphatase; SGLT, sodium-glucose co-transporter.

Johansson KS et al. Expert Opin Drug Discov 2020;15:1253-1265

Progression de l'obésité et du DM2

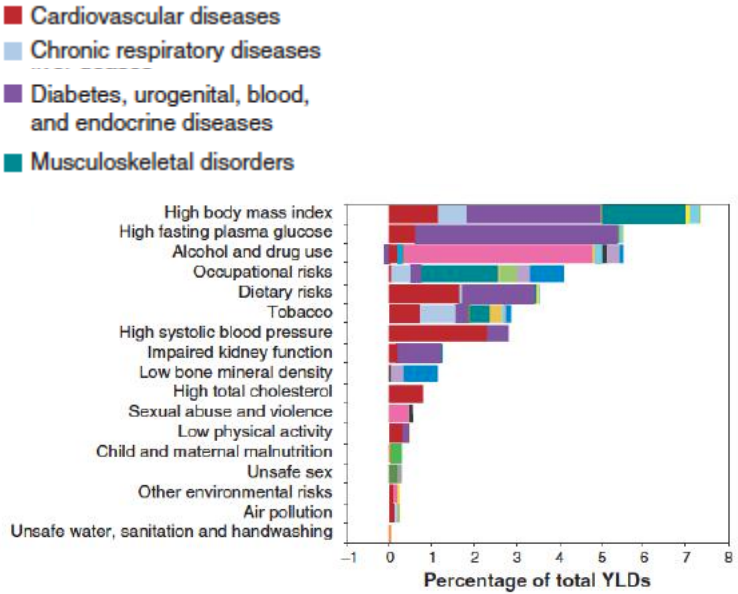




Obesity Collaborators NEJM 2017;377:13-27

Ward ZJ et al. NEJM 2019;381:2440-50

Causes de morbidité au Canada



Risk factors by attributable YLDs 1990	Risk factors by attributable YLDs 2016	% change all-age YLD rate (1990–2016)	% change age-standardized YLD rate (1990–2016)
1. Alcohol and drug use	1. High body mass index	61.0	24.3
2. High body mass index	2. High fasting plasma glucose	40.2	2.92
3. High fasting plasma glucose	3. Alcohol and drug use	11.2	16.0
4. Occupational risks	4. Occupational risks	16.3	3.97
5. Tobacco	5. Dietary risks	14.7	−15.4
6. Dietary risks	6. Tobacco	−17.8	−37.4
7. High systolic blood pressure	7. High systolic blood pressure	6.81	−26.0
8. Impaired kidney function	8. Impaired kidney function	39.3	1.90
9. High total cholesterol	9. Low bone mineral density	45.2	−1.93
10. Low bone mineral density	10. High total cholesterol	−1.01	−31.1
11. Sexual abuse and violence	11. Sexual abuse and violence	6.07	8.73
12. Low physical activity	12. Low physical activity	29.0	−11.3
13. Child and maternal malnutrition	13. Unsafe sex	31.2	24.6
14. Unsafe sex	14. Child and maternal malnutrition	−6.61	10.2
15. Air pollution	15. Other environmental risks	62.9	49.0
16. Other environmental risks	16. Air pollution	30.7	−6.73
17. Unsafe water, sanitation and handwashing	17. Unsafe water, sanitation and handwashing	−19.7	−15.2

CMAJ Open 2019. DOI:10.9778/cmajo.20180137

Populations vulnérables

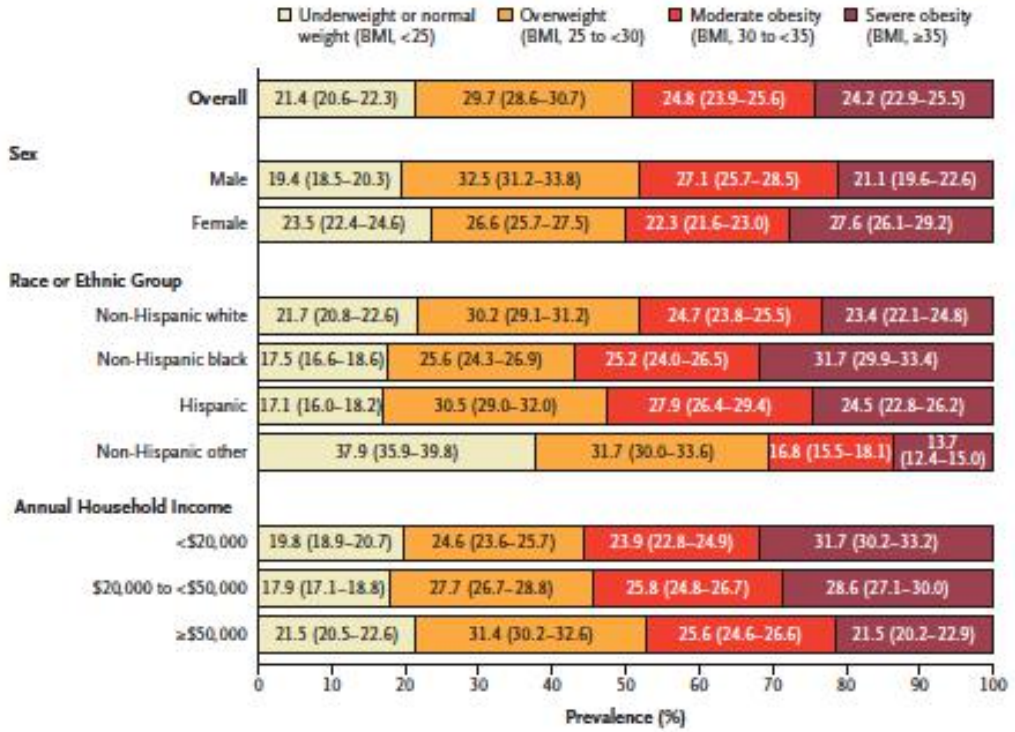
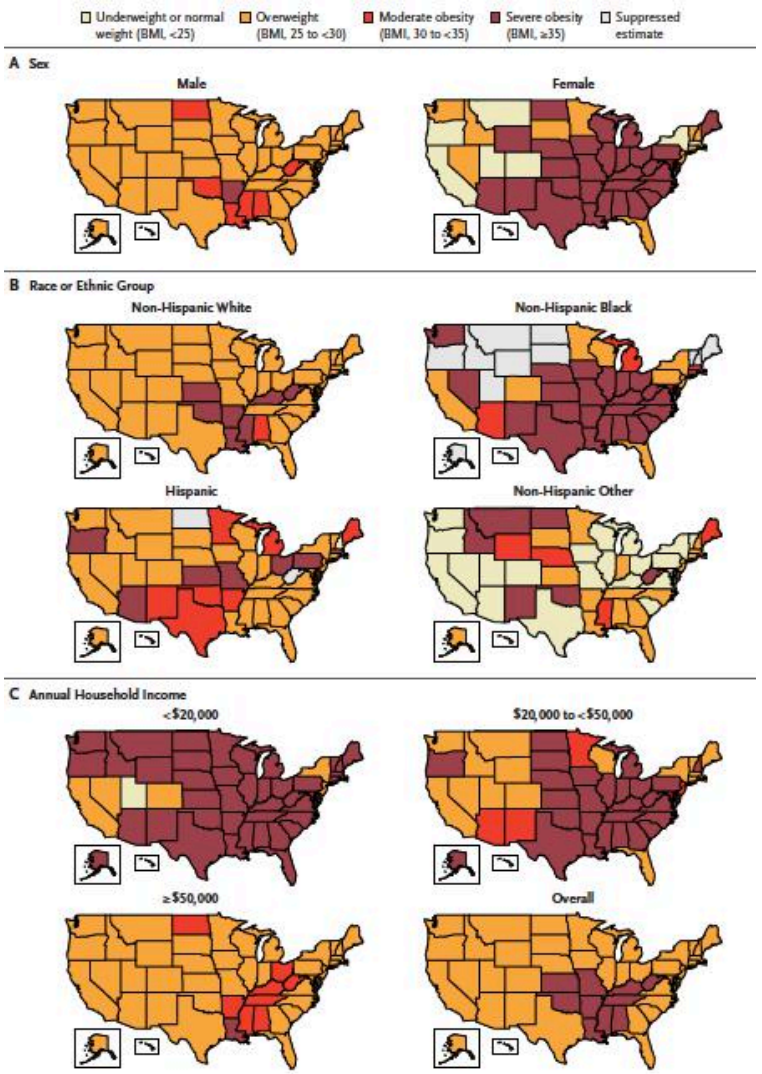
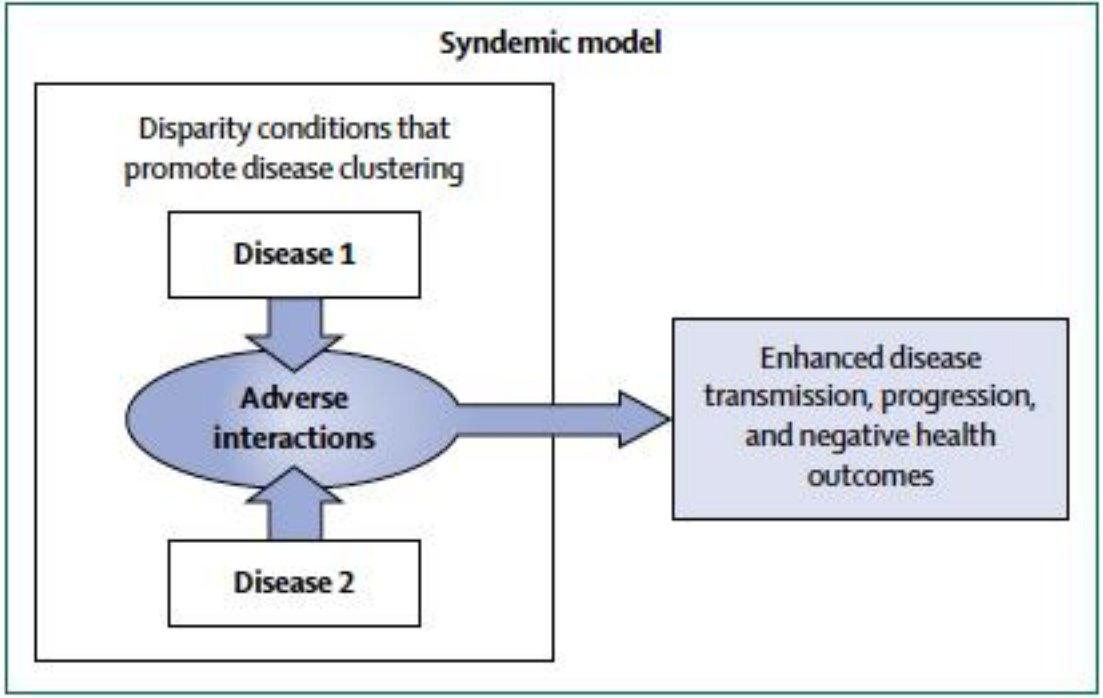


Figure 2. Projected National Prevalence of BMI Categories in 2030, According to Demographic Subgroup.
Shown is the projected national prevalence of BMI categories in 2030, according to sex, race or ethnic group, and annual household income.



Ward ZJ et al. NEJM 2019;381:2440-50

Covid 19, maladies cardiométaboliques et populations vulnérables = ‘syndémie’



The most important consequence of seeing COVID-19 as a syndemic is to underline its social origins. The vulnerability of older citizens, Black, Asian, and minority ethnic communities; and key workers who are commonly poorly paid with fewer welfare protections points to a truth so far barely acknowledged—namely, that no matter how effective a treatment or protective a vaccine, the

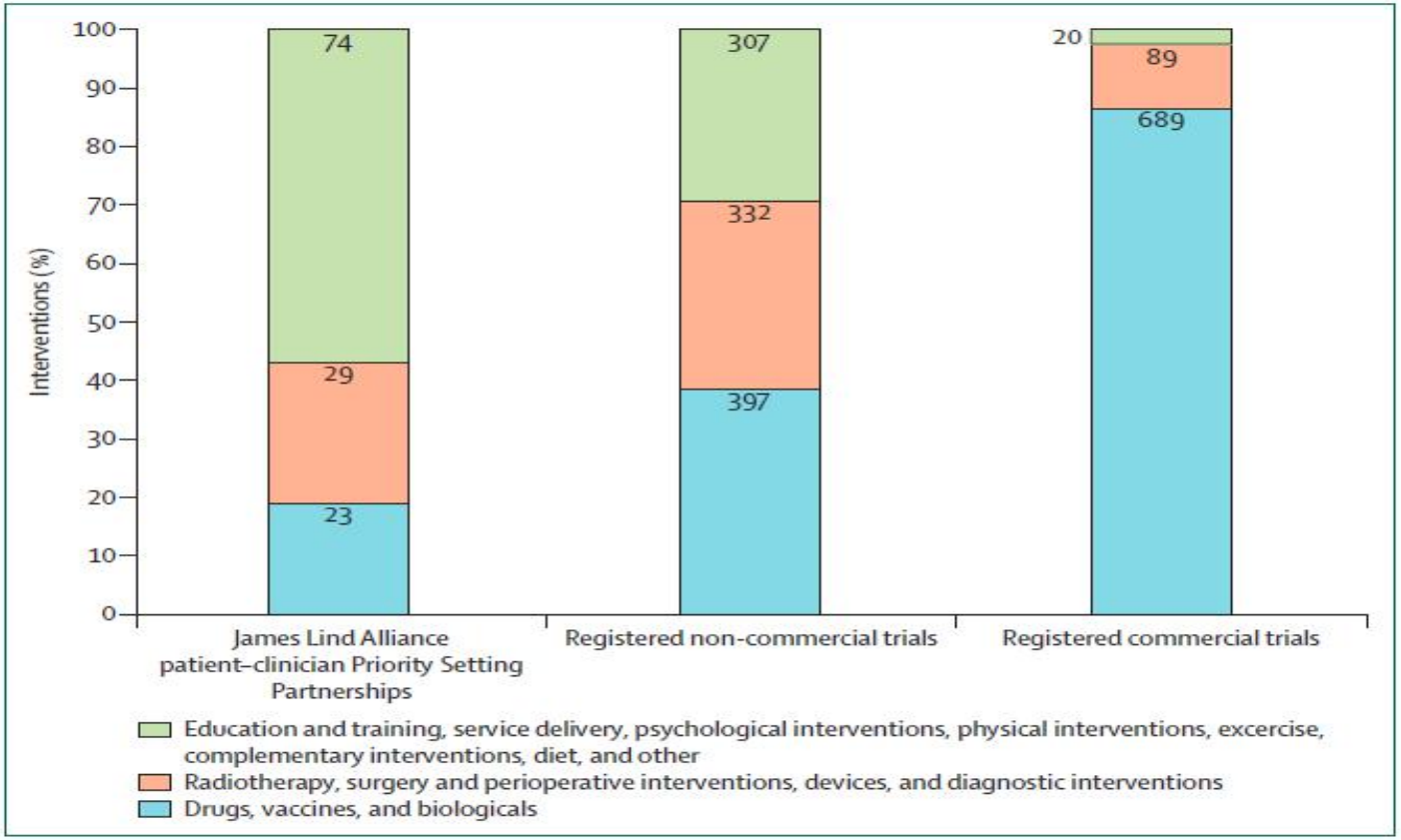
in 2017, “A syndemic approach provides a very different orientation to clinical medicine and public health by showing how an integrated approach to understanding and treating diseases can be far more successful than simply controlling epidemic disease or treating individual patients.” I would add one further advantage. Our

and treating diseases can be far more successful than simply controlling epidemic disease or treating individual patients.” I would add one further advantage. Our societies need hope. The economic crisis that is advancing towards us will not be solved by a drug or a vaccine. Nothing less than national revival is needed. Approaching COVID-19 as a syndemic will invite a larger vision, one encompassing education, employment, housing, food, and environment. Viewing COVID-19 only as a pandemic excludes such a broader but necessary prospectus.

Singer M et al. The Lancet 2017;389:941-950

Horton R. The Lancet 2020;396:874

Priorisation de la recherche



Chalmers I, et al. Lancet. 2014

Du biomédical vers une approche intégrée de la recherche en santé

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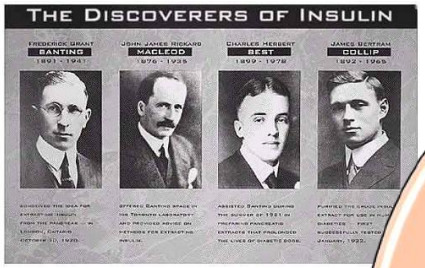

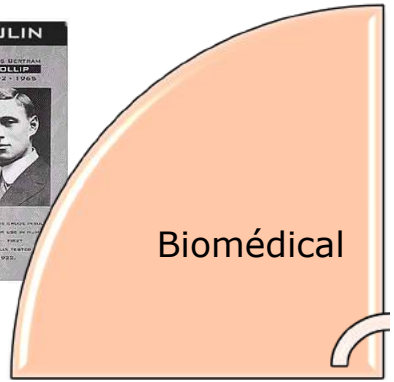

Activités du 100e anniversaire de la découverte de l'insuline

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