Hôpital du Valais
Spital Wallis

Mucoviscidose: de l'enfance à l'âge adulte

Pierre-Olivier Bridevaux
Anne Mornand

Sion
le 6 novembre 2015

Plan

Définition de la mucoviscidose (cystic fibrosis CF)

Survie actuelle

Epidémiologie

Traitements (Dr Anne Mornand)

Mucoviscidose - Définition

Une maladie génétique rare (env 1 naissance / 2000 à 4000)
~35’000 patients en Europe
Manifestations cliniques multiples

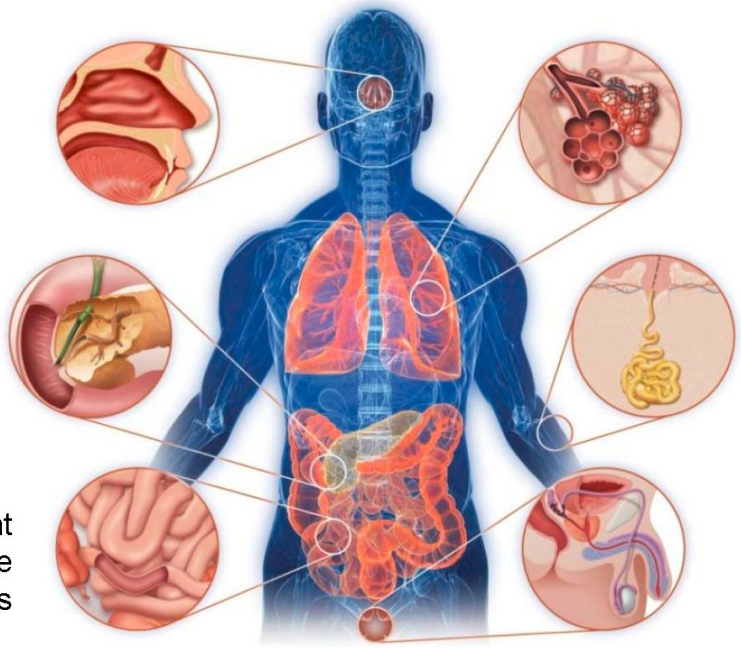
Sinus infections

Nasal polyps

Exocrine pancreatic insufficiency and resulting malnutrition

Endocrine insufficiency and resulting CF-related diabetes

Failure to thrive/gain weight due to pancreatic insufficiency, digestive problems, and intestinal blockages



Reduced lung function

Frequent lung infections, inflammation, and progressive lung disease

Abnormally high excretion of sodium and chloride (salt) in the sweat

Infertility

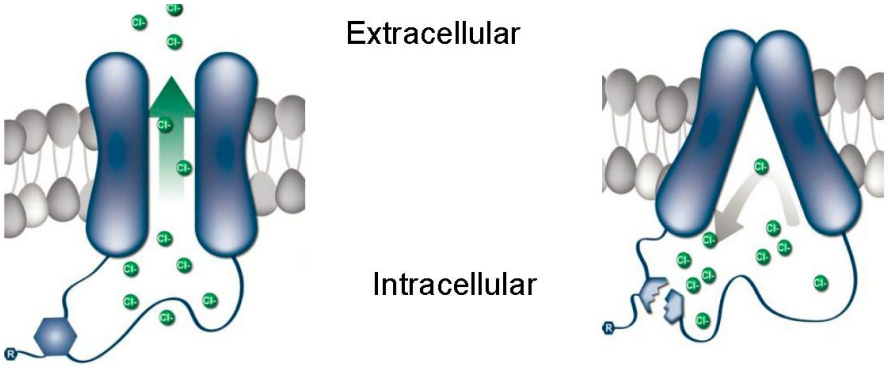
Congenital bilateral absence of the vas deferens (CBAVD) in men

1. Cystic Fibrosis Foundation (CFF) Patient Registry. 2012 Annual Data Report. Bethesda, MD: CFF; 2013.
2. Cystic Fibrosis Canada Patient Registry. 2011 Annual Data Report. Toronto, ON
3. European Cystic Fibrosis Patient Registry. 2008-2009 Annual Report. Denmark

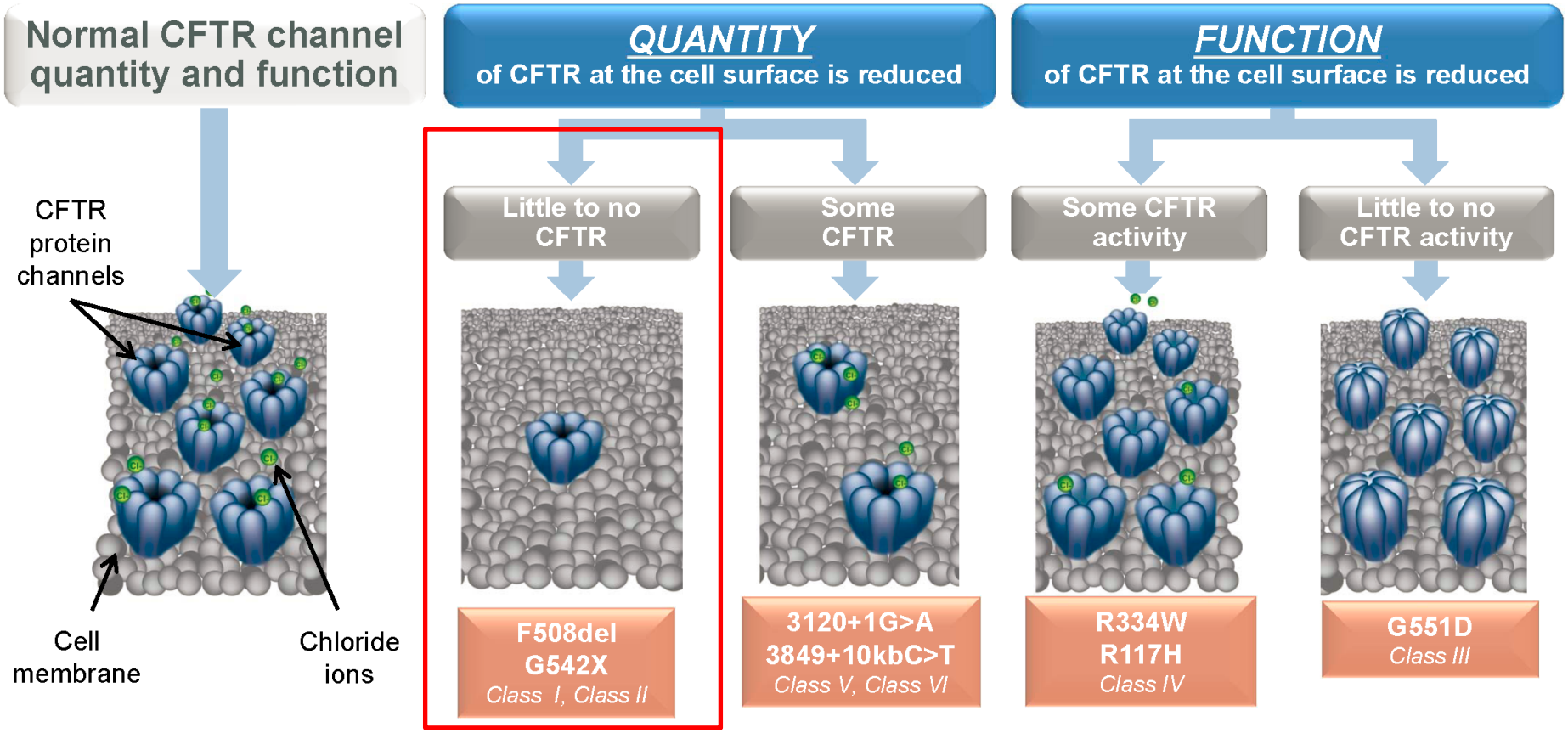
La dysfonction du CFTR

(Cystic Fibrosis Transmembrane Conductance Regulator)

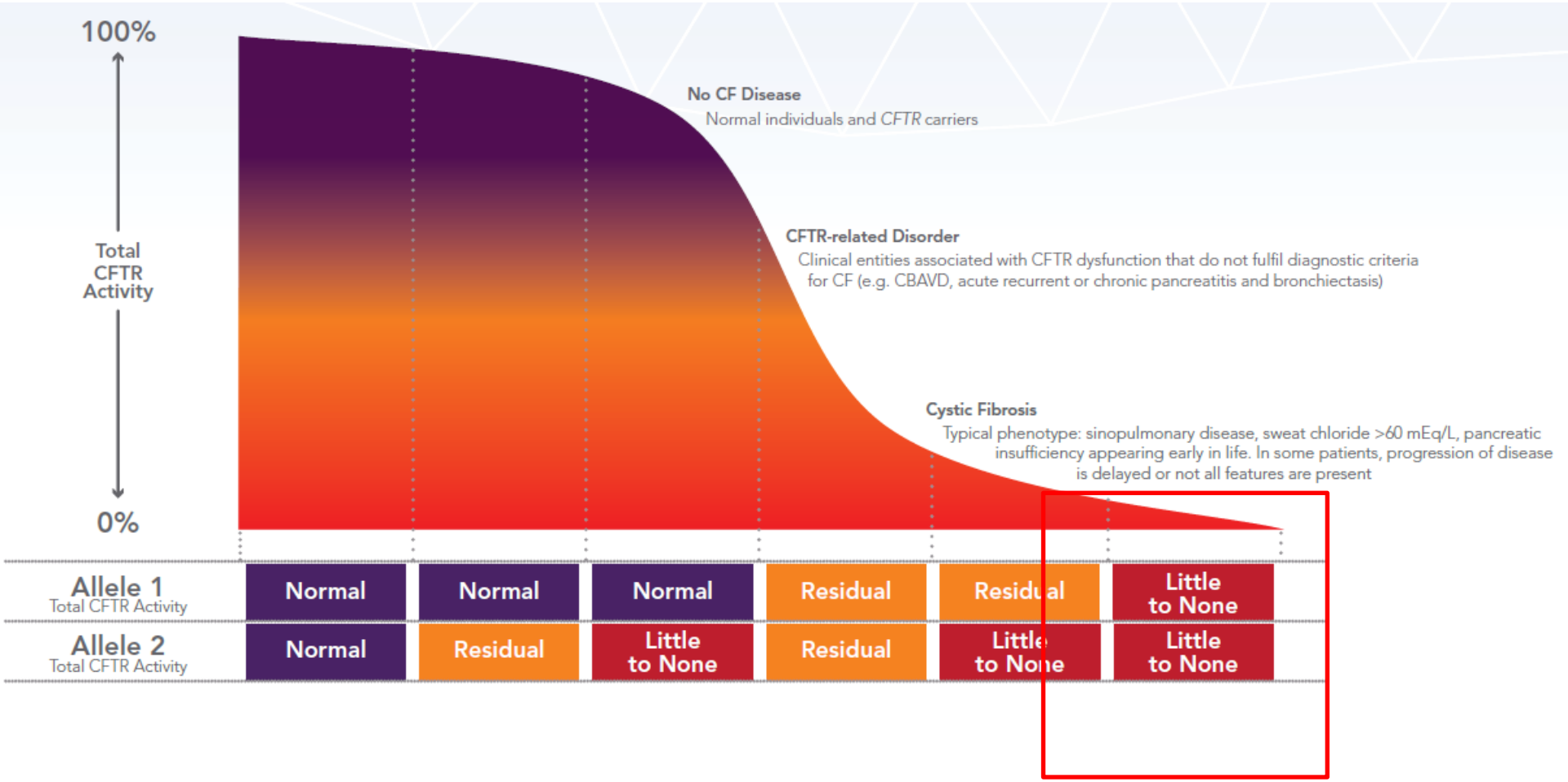
- Le gène CFTR code pour la protéine CFTR
- La protéine CFTR régule le transport du chlore
- La mucoviscidose est causée par une protéine CFTR dysfonctionnelle



Dysfonction du CFTR et mutations génétiques



Les phénotypes de la mucoviscidose



Adapted from Zielenski J. Respiration 2000;67:117–33

Survie actuelle des patients souffrant de mucoviscidose

- Nouveaux antibiotiques inhalés (colistine, tobramycine)
- Eradication de Pseudomonas aeruginosa
- Mucolytiques (DNAse)
- Transplantation pulmonaire
- Recherche active des complications
- Nouveaux médicaments (Modulateurs/potentiateur du CFTR)
- Dépistage des nouveaux nés
- Centres de compétence

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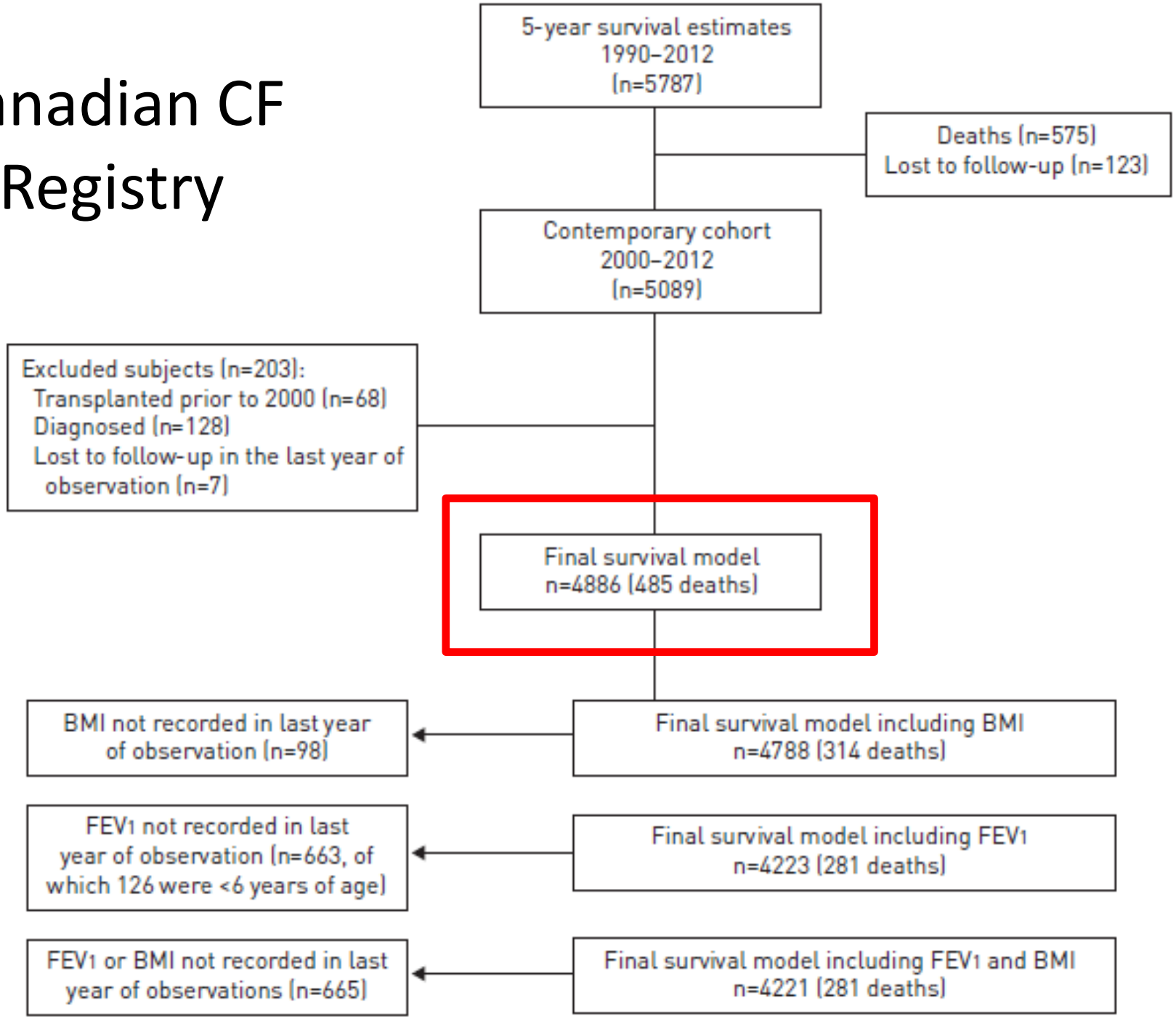
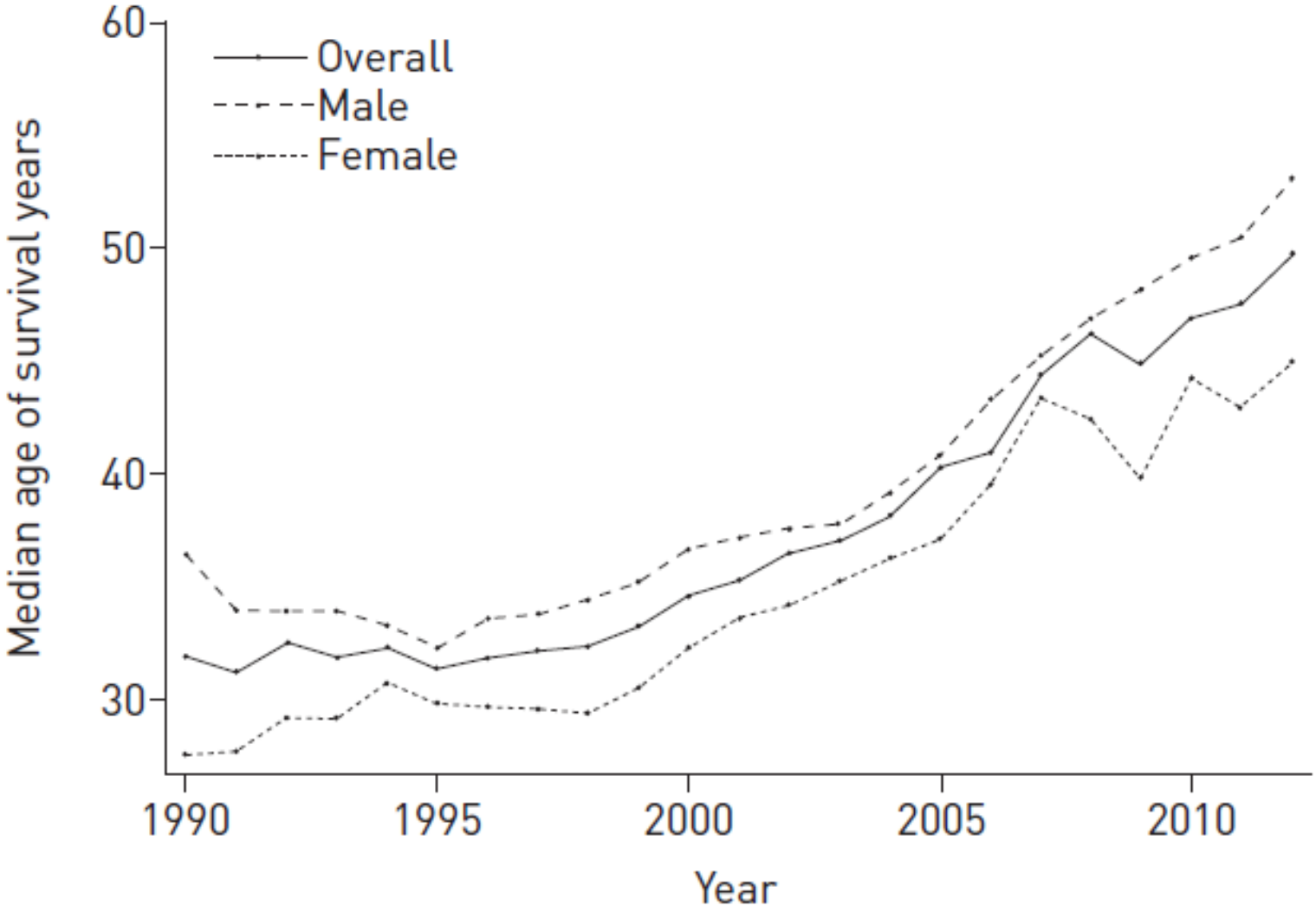
A contemporary survival analysis of individuals with cystic fibrosis: a cohort Study.
Anne L. Stephenson, Shawn D. Aaron, G.A. Whitmore Sanja Stanojevic,
Eur Respir J, March 2015; 45: 670–679

Canadian CF Registry



Age médian de survie de 1990 à 2010



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CF - Prédicteurs de la survie

	Univariate	Multivariate
Sex		
Male	Ref.	Ref.
Female	1.35 (1.12–1.61)	1.28 (1.00–1.63)
Genotype		
Other	Ref.	
Homozygous ΔF508	1.54 (1.08–2.21)	
Heterozygous ΔF508	1.20 (0.84–1.73)	
Missing	3.01 (1.89–4.81)	
Pancreatic insufficiency		
Sufficient	Ref.	Ref.
Insufficient	3.18 (2.19–4.61)	2.19 (1.15–4.17)
Age at diagnosis		
<2 years	Ref.	Ref.
2–18 years	0.62 (0.50–0.77)	0.79 (0.59–1.06)
>18 years	0.30 (0.20–0.44)	0.55 (0.28–1.11)
Longest time in a region		
Quebec	Ref.	
East	1.53 (1.13–2.09)	
Ontario	1.01 (0.81–1.28)	
West	1.27 (1.00–1.61)	
Exacerbations per year		
0	Ref.	Ref.
1–2	6.17 (3.69–10.31)	2.98 (2.14–4.15)
⩾3	11.12 (5.58–21.78)	4.53 (3.19–6.43)
CF-related diabetes	2.26 (1.36–3.78)	
Microbiology#		
Burkholderia cepacia complex	2.51 (1.40–4.50)	1.89 (1.44–2.49)
Staphylococcus aureus	0.32 (0.19–0.53)	
Pseudomonas aeruginosa	2.05 (0.98–4.27)	
Stenotrophomonas maltophilia	1.17 (0.73–1.86)	0.75 (0.58–0.97)
MRSA	0.70 (0.25–1.94)	
BMI categories		
Adequate weight	Ref.	Ref.
Overweight	0.22 (0.06–0.80)	0.80 (0.47–1.35)
Underweight	12.44 (6.26–24.75)	2.12 (1.60–2.82)
FEV1% predicted	0.91 (0.89–0.93)	0.95 (0.94–0.96)
Birth year	0.96 (0.93–0.99)	

Espérance de vie des patients CF

Age médian au décès augmente

-Meilleure nutrition

-Meilleure fonction pulmonaire

-Burckholderia Cepacia Complex ↓

Facteurs pronostiques favorables

-Peu ou pas d'exacerbation

-BMI normal

-Sexe masculin

-Génotype non DeltaF508/DeltaF508

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Mucoviscidose:
Prévisions épidémiologiques pour l'Europe

4 catéories de pays
Q: Registre de qualité [>4 ans & >85%]
G: GNI per capita [23'000 Euros]

A (Q+G+)
Belgium, Czech Republic, Denmark, France, UK and the Netherlands

B (Q+G-)
Germany, Hungary, Ireland, Israel, Latvia, Moldova, Serbia, Sweden, Slovenia and Slovakia

C (Q- H+)
Austria, Switzerland, Cyprus, Spain, Finland, Greece, Italy, Luxemburg, Malta and Portugal

D (Q-H-)
Bulgaria, Belarus, Estonia, Lithuania, Poland, Romania, Russian Federation, Ukraine

Future trends in cystic fibrosis demography in 34 European countries
Pierre-Régis Burgel, Gil Bellis, Hanne V. Olesen, Laura Viviani, Anna Zolin, Francesco Blasi and J. Stuart Elborn, ERJ, july 2015

	CF prevalence per 10 000¶		CF prevalence per 10 000¶
Belgium	1.030	Switzerland	0.737
Czech Rep.	0.556	Cyprus	0.335
Denmark	0.761	Spain	0.546
France	0.750	Finland	0.123
UK	1.370	Greece	0.521
Netherlands	0.781	Italy	0.872
Germany	0.829	Luxembourg	0.431
Hungary	0.409	Malta	0.579
Ireland	2.980	Portugal	0.271
Israel	0.564	Bulgaria	0.226
Latvia	0.104	Belarus	0.191
Moldova	0.100	Estonia	0.618
Serbia	0.166	Lithuania	0.130
Sweden	0.403	Poland	0.256
Slovenia	0.328	Romania	0.106
Slovakia	0.627	Russian Fed.	0.191
Austria	0.839	Ukraine	0.191

No data for CH. Mean of EU

Prévalence 2010 et 2025 de la mucoviscidose en Europe

Group	Country	Children age ⩽17 years			Adults age ⩾18 years			Total		
		2010	2025	Growth rate %	2010	2025	Growth rate %	2010	2025	Growth rate %
A	Belgium	559	661	18.3	615	1093	77.7	1174	1754	49.4
	Czech Republic	293	313	6.8	230	372	61.7	523	685	31.0
	Denmark	192	192	0.0	265	337	27.2	457	529	15.8
	France	3040	3599	18.4	2718	4776	75.7	5758	8375	45.5
	UK	4435	5539	24.9	4,950	8876	79.3	9385	14415	53.6
	The Netherlands	591	659	11.5	715	1402	96.1	1306	2061	57.8
	All in group	9110	10963	20.3	9493	16856	77.6	18603	27819	49.5
B	Germany	2413	2976	23.3	2590	4380	69.1	5003	7356	47.0
	Hungary	339	388	14.5	218	506	132.1	557	894	60.5
	Ireland	527	640	21.4	554	915	65.2	1081	1555	43.9
	Israel	268	327	22.0	284	476	67.6	552	803	45.5
	Latvia	22	19	−13.6	8	12	50.0	30	31	3.3
	Moldova	34	36	5.9	8	25	212.5	42	61	45.2
	Serbia	86	109	26.7	35	94	168.6	121	203	67.8
	Sweden	264	315	19.3	329	523	59.0	593	838	41.3
	Slovenia	55	74	34.6	25	66	164.0	80	140	75.0
	Slovakia	151	202	33.8	182	292	60.4	333	494	48.4
	All in group	4159	5086	22.3	4233	7289	72.2	8392	12375	47.5

Mucoviscidose- Prévisions pour la Suisse

Country	Children age ⩽17 years				Adults age ⩾18 years				Total			
	2010	2015	2020	2025	2010	2015	2020	2025	2010	2015	2020	2025
Switzerland	294	320	341	353	281	360	433	500	575	680	774	853
				+20.0%				+77.9%				+ 34.6%

Epidémiologie - Discussion

Augmentation importante de la prévalence:
+ 77% c/o adultes in CH from 280 (2010)à 500 (2025)

Effet du dépistage néonatal:
Augmentation de l'incidence?
Diminution de l'incidence par le screening des porteurs sains?

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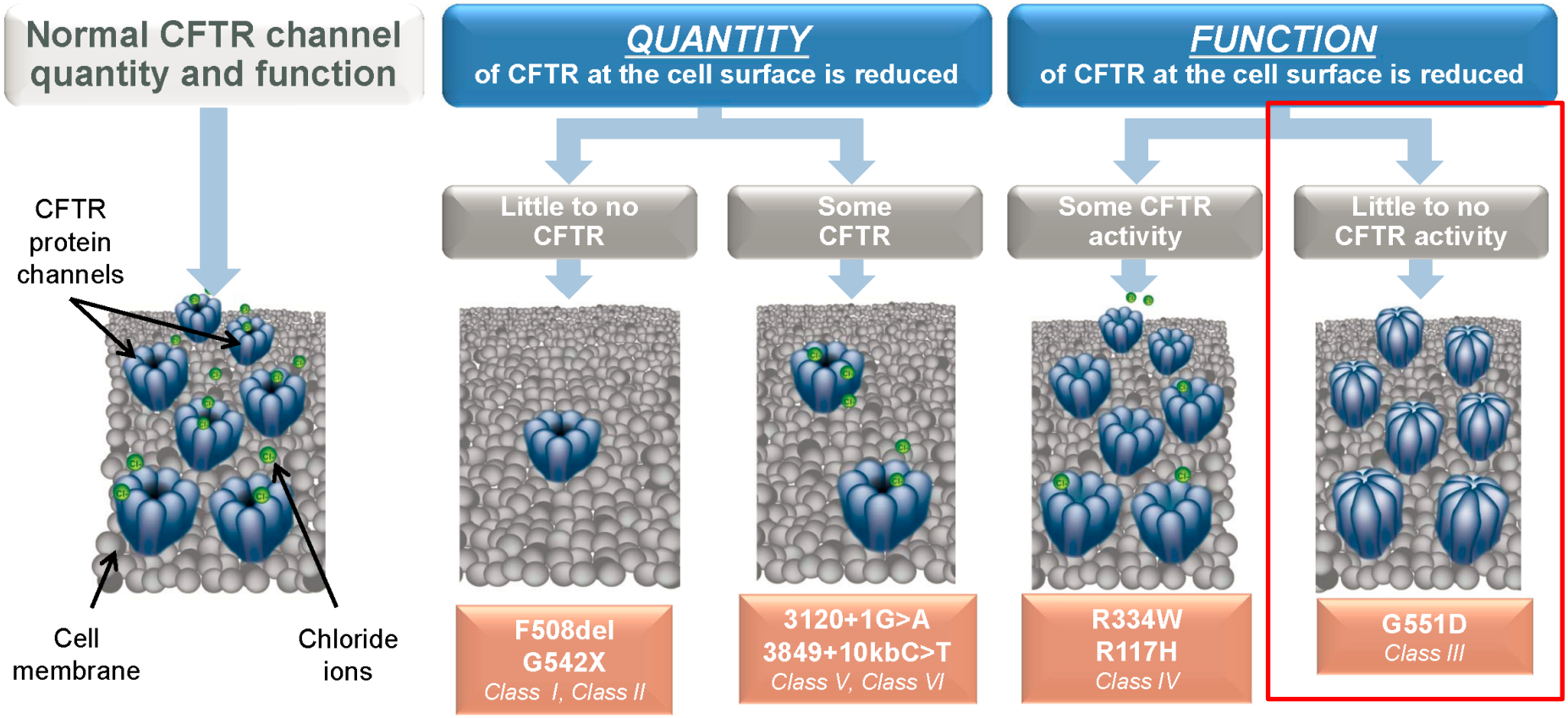
Anne Mornand

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Dysfonction du CFTR
mutations génétiques et nouveaux traitements
(ivacaftor et ivacaftor/lumacaftor)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, M.S., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

G551D / -- 5% des patients avec mucoviscidose

Dysfonction du CFTR mutations génétiques et nouveaux traitement (ivacaftor et ivacaftor/lumacaftor)

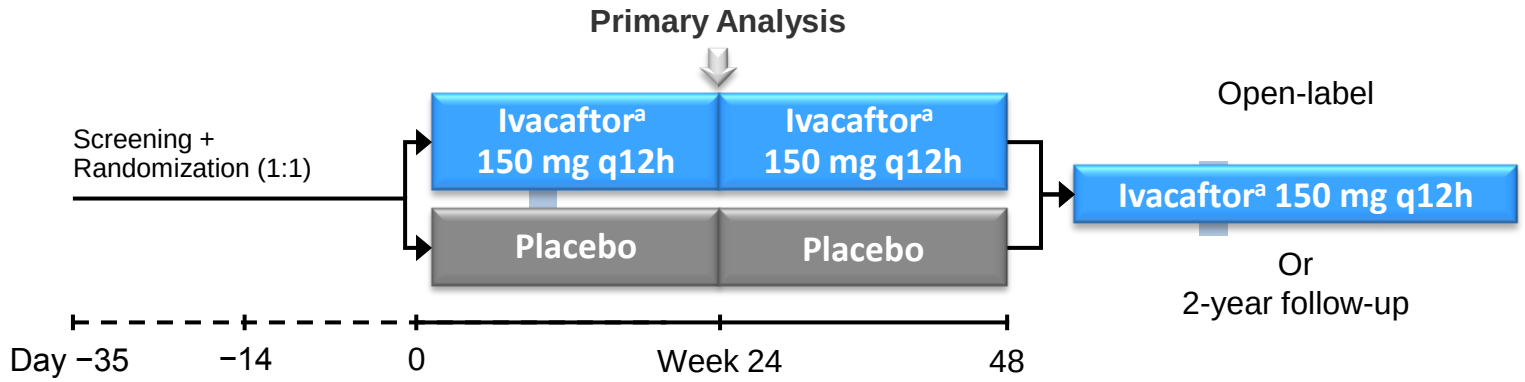
***G551D* sur une au moins des allèles**

Ivacaftor Maintien du CFTR fonctionnel

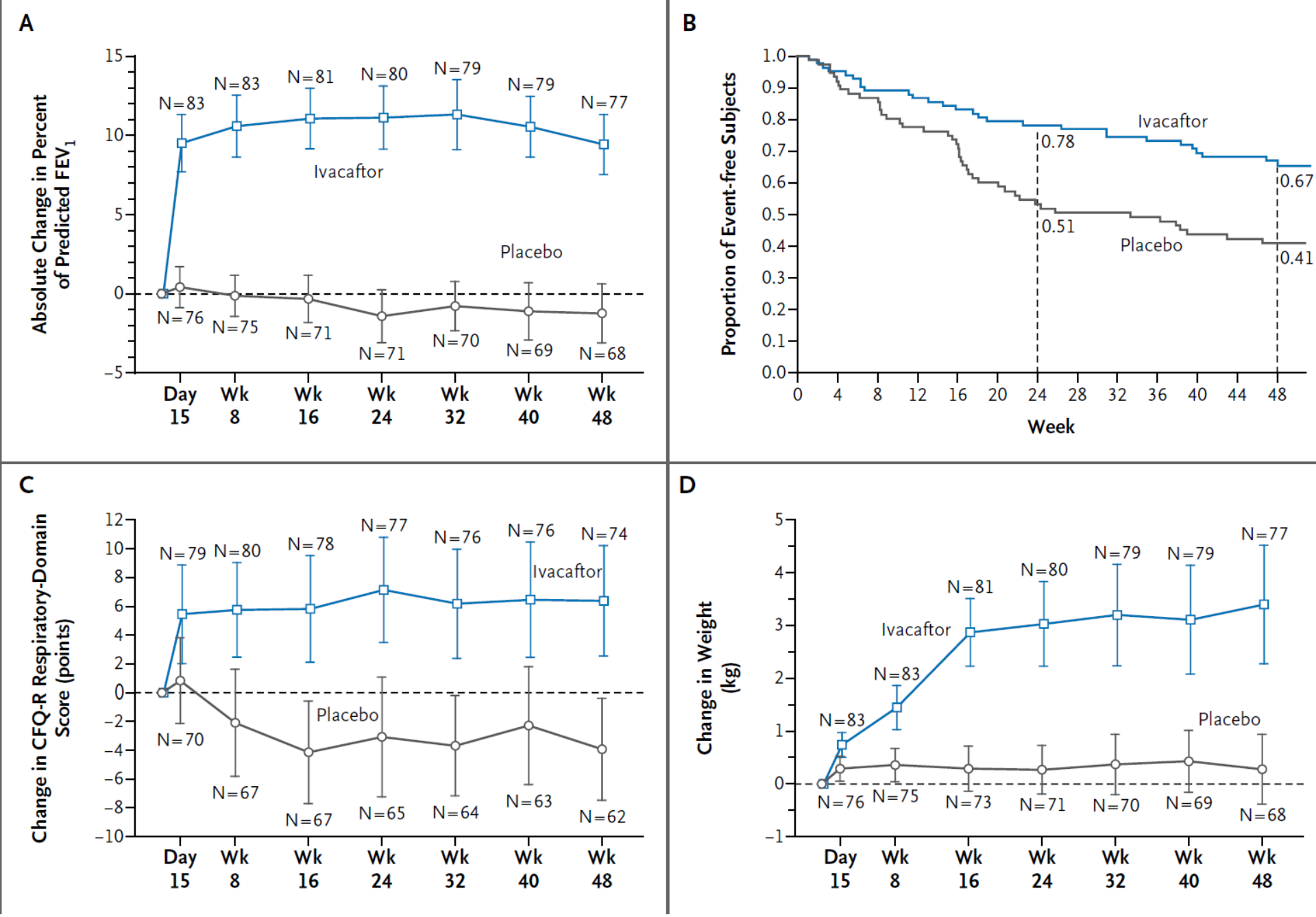
161 adultes ≥ 12 ans avec FEV_1 entre 40-90% de la valeur prédite

Age moyen 26 ans (range: 12-53)

FEV_1 moyen 64% vp (range: 32-98%)



1. Ramsey BW et al. *N Engl J Med*. 2011;365:1663-1672.



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mutations génétiques et nouveaux traitements
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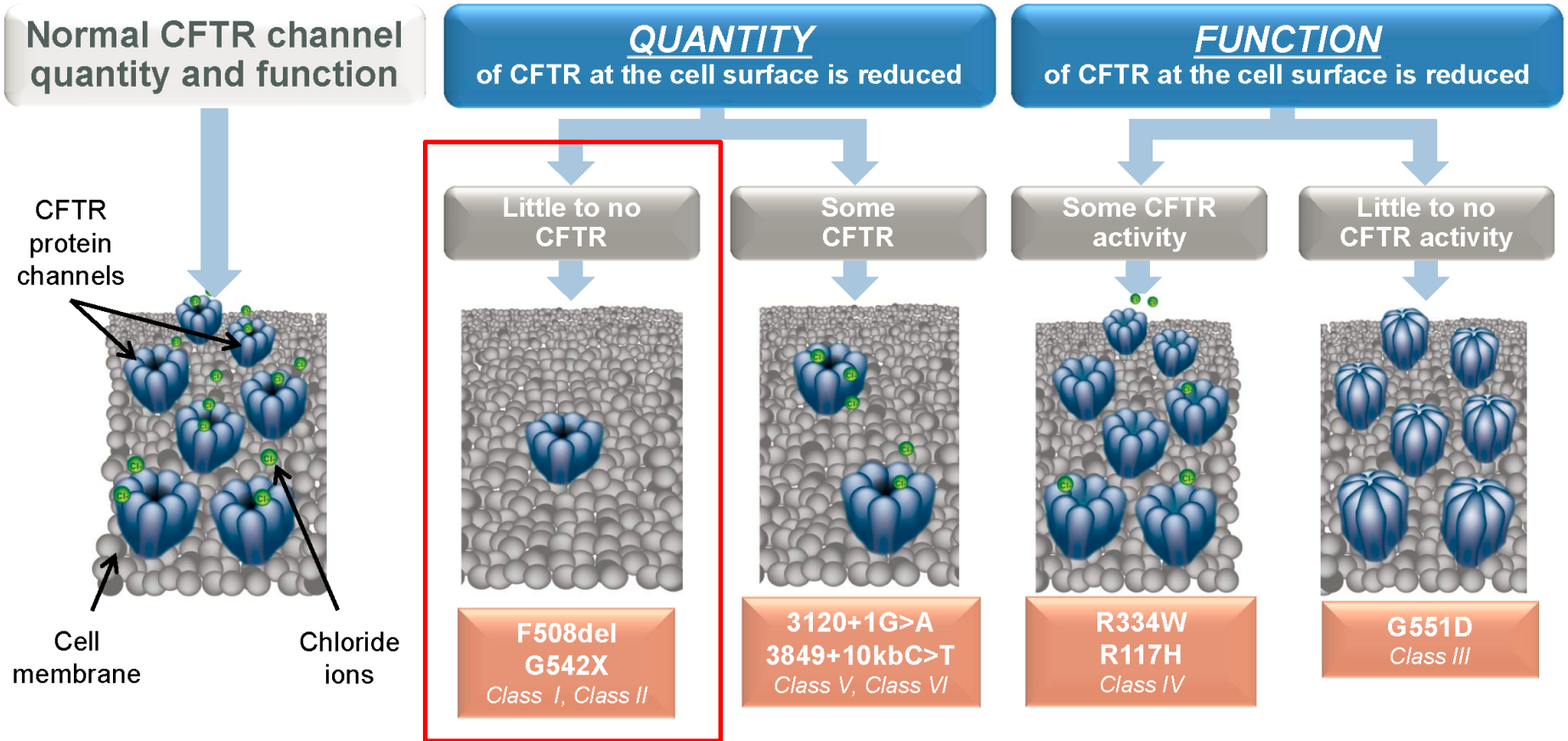


The NEW ENGLAND JOURNAL of MEDICINE

Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*

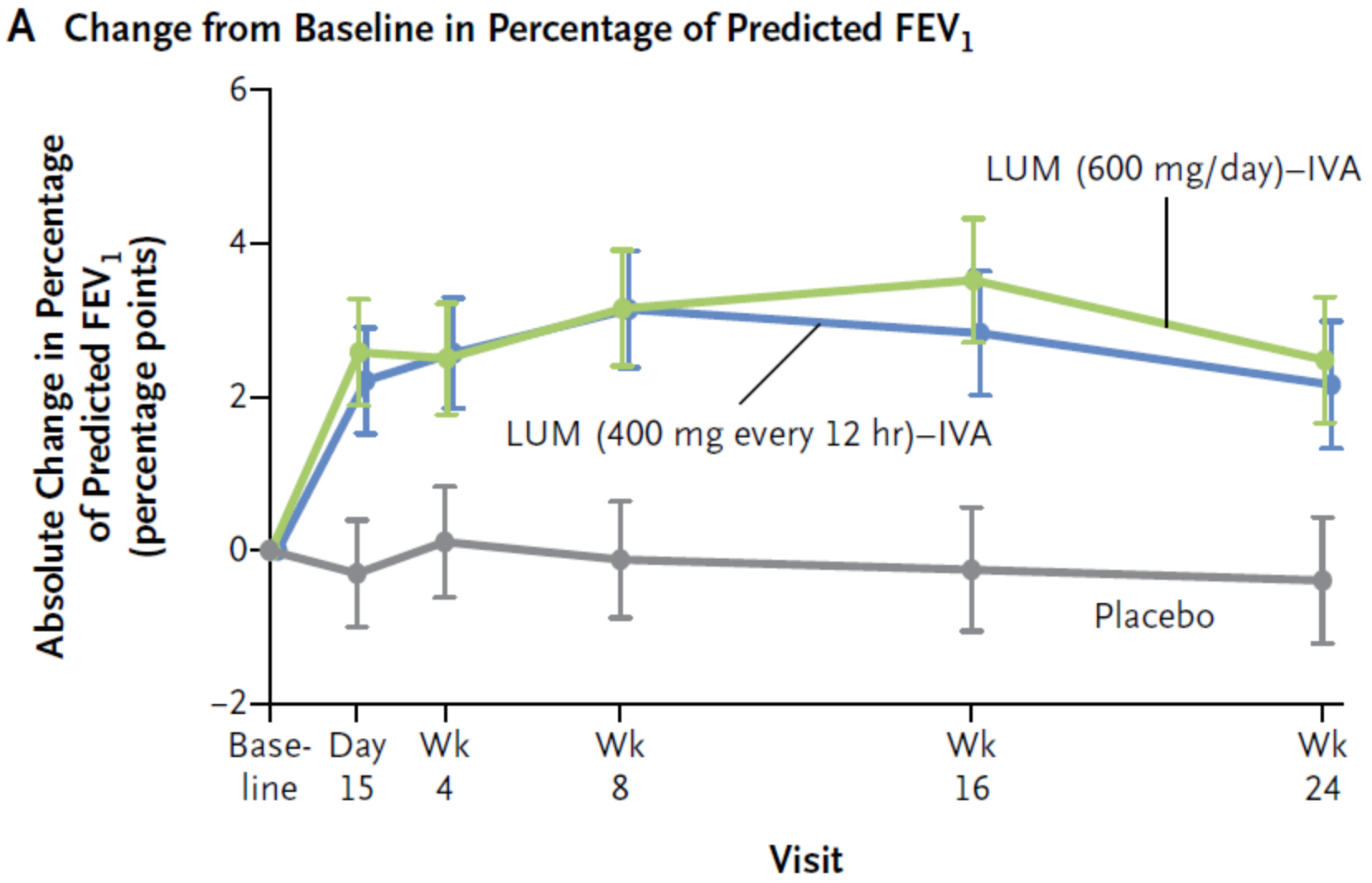
C.E. Wainwright, J.S. Elborn, B.W. Ramsey, G. Marigowda, X. Huang, M. Cipolli, C. Colombo, J.C. Davies, K. De Boeck, P.A. Flume, M.W. Konstan, S.A. McColley, K. McCoy, E.F. McKone, A. Munck, F. Ratjen, S.M. Rowe, D. Waltz, and M.P. Boyle, for the TRAFFIC and TRANSPORT Study Groups.*

JULY 16, 2015

DeltaF508 / DeltaF508 45% des patients avec mucoviscidose

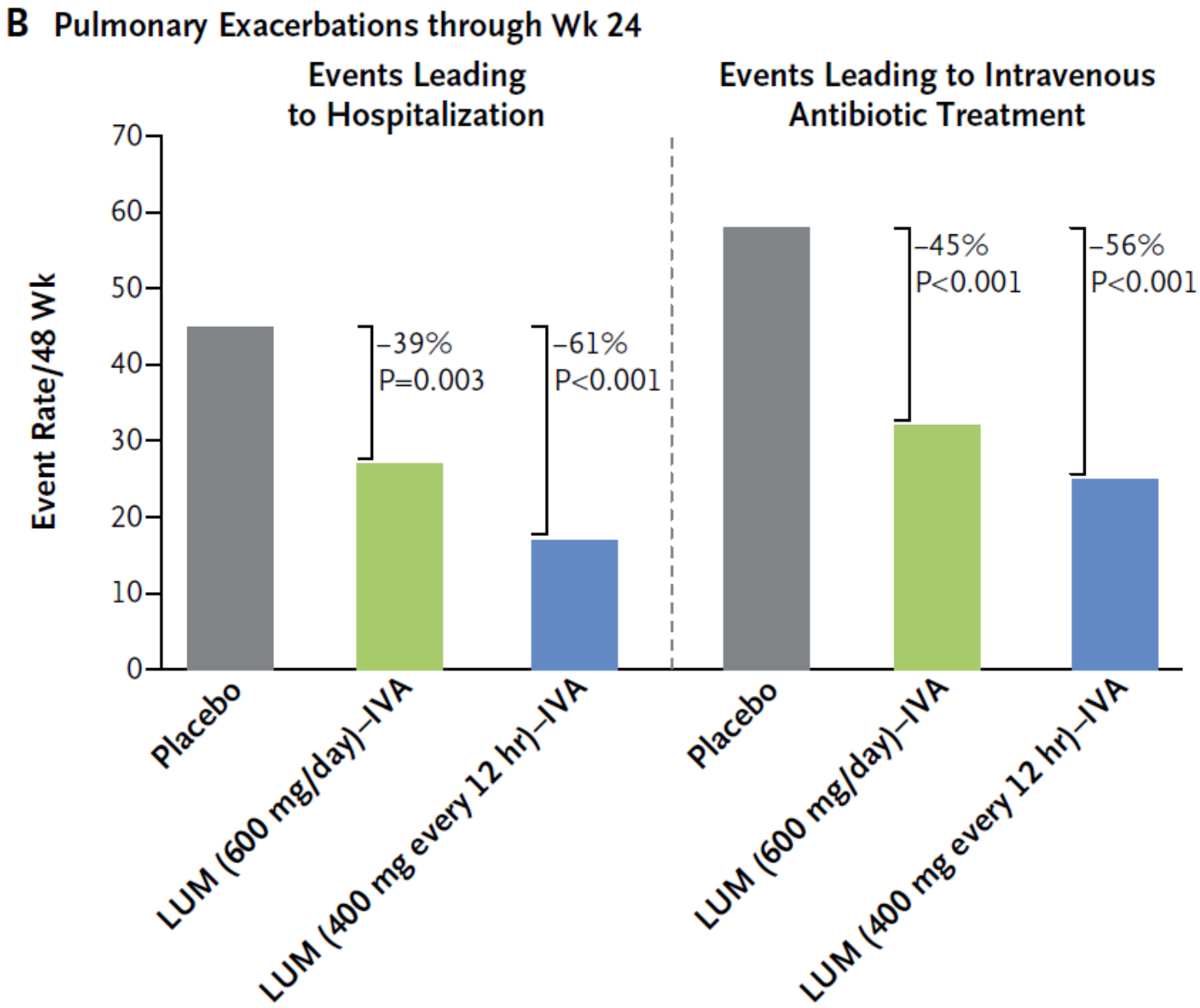
Wainright et al *N Engl J Med*. 2015

DeltaF508/DeltaF508 (ivacaftor/lumacaftor)



Wainright et al *N Engl J Med*. 2015

DeltaF508/DeltaF508 (ivacaftor/lumacaftor)



Wainright et al *N Engl J Med*. 2015

Mucoviscidose – conclusions

Survie nettement améliorée

Augmentation importante de la prévalence en particulier chez l'adulte

Nouvelles possibilités thérapeutique (CFTR modulateur et potentiateur)

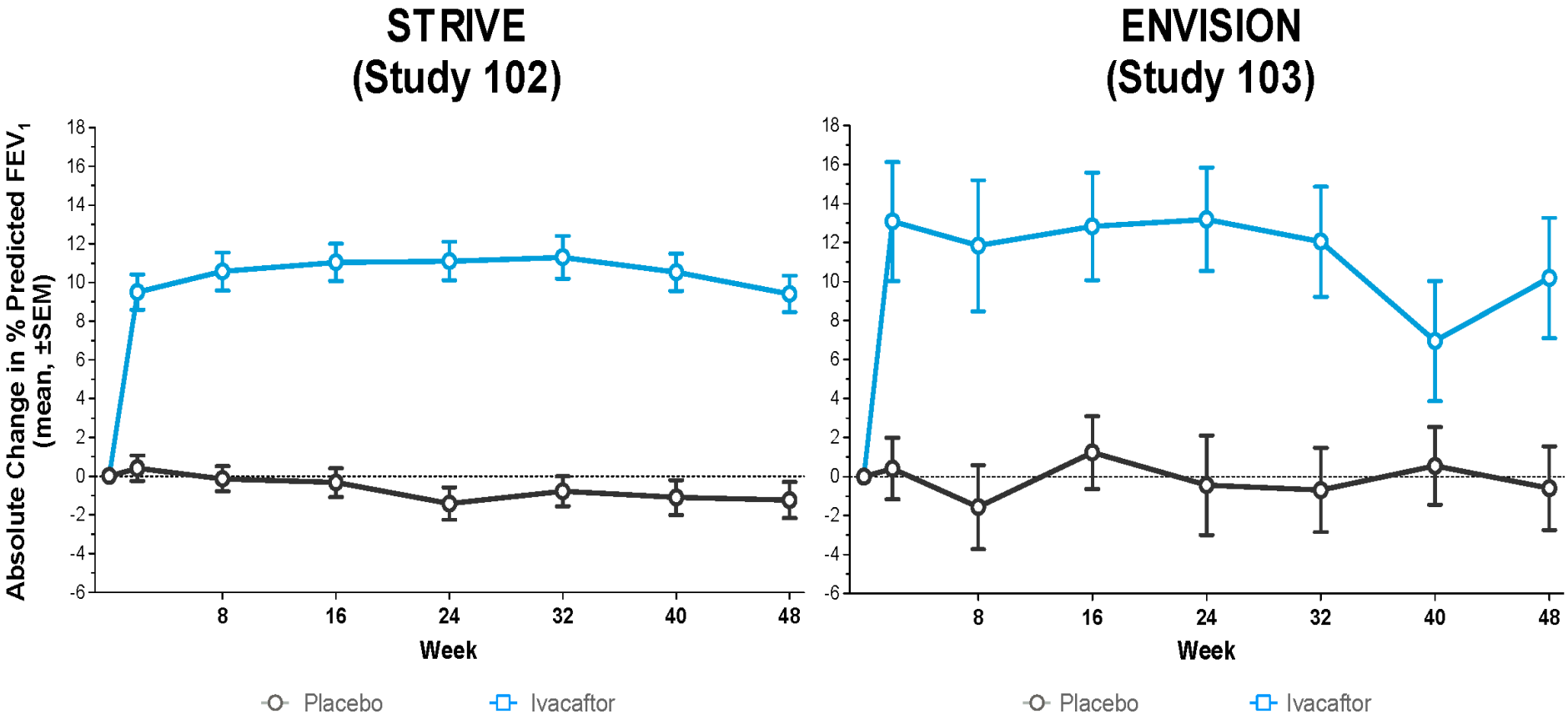
Subjects n	4886
Newly diagnosed cases n	1498
Females	46.9
Caucasians	92.8
Age at last visit years	22.0 (0–79.3)
Age at diagnosis years median	0.5
Age at diagnosis	
0–2 years	66.8
2–18 years	26.2
>18 years	6.9
Genotype	
Homozygous ΔF508	48.1
Heterozygous ΔF508	38.1
Other	9.9
Missing	4.0
FEV_1% predicted	67.7 (9.5–145.1)
BMI category	
Normal weight	59.0
Overweight	13.4
Underweight	17.9
Missing	9.8
Microbiology¶	
Pseudomonas aeruginosa	79.3
Staphylococcus aureus	87.8
Stenotrophomonas maltophilia	37.8
Burkholderia cepacia complex	11.6
MRSA	9.0
Pancreatic insufficiency	85.9
CF-related diabetes	24.1

Total deaths n	485
Males	227 (46.6)
Females	260 (53.4)

Canadian CF Registry

STRIVE & ENVISION Primary Endpoint:

Mean Absolute Change from Baseline in % Predicted FEV_1 Through Week 24

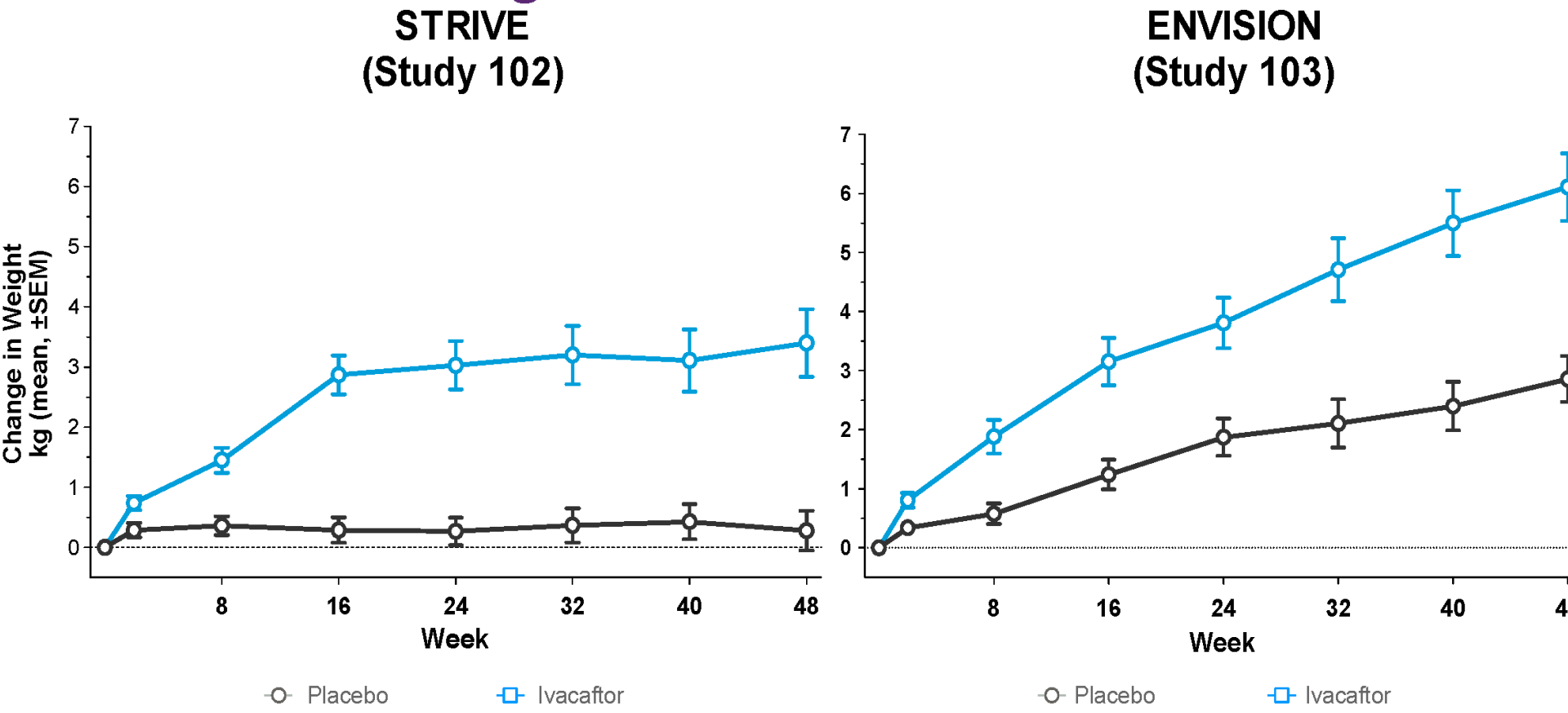


	STRIVE[1]		ENVISION[2]	
Endpoint	Treatment difference[a] (95% CI)	P value	Treatment difference[a] (95% CI)	P value
Mean absolute change from baseline in percent predicted FEV_1 (% Points)				
Through Week 24	10.6 (8.6, 12.6)	<0.0001	12.5 (6.6, 18.3)	<0.0001
Through Week 48	10.5 (8.5, 12.5)	<0.0001	10.0 (4.5, 15.5)	0.0006

CI=confidence interval.

a Treatment difference = effect of ivacaftor – effect of placebo

STRIVE & ENVISION: Absolute Change from Baseline in Weight at Weeks 24 and 48



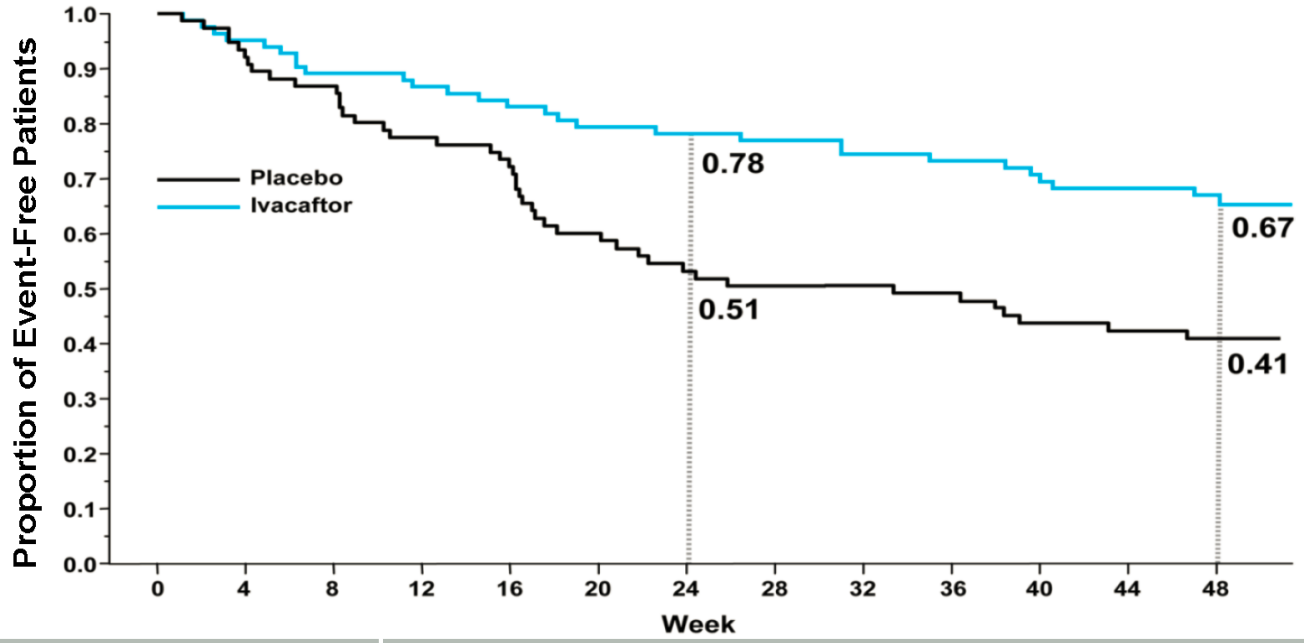
	STRIVE[1]		ENVISION[2]	
Endpoint	Treatment difference[a] (95% CI)	P value	Treatment difference[a] (95% CI)	P value
Mean absolute change from baseline in body weight (kg)				
At Week 24	2.8 (1.8, 3.7)	<0.0001	1.9 (0.9, 2.9)	0.0004
At Week 48	2.7 (1.3, 4.1)	0.0001	2.8 (1.3, 4.2)	0.0002

CI=confidence interval.

a Treatment difference = effect of ivacaftor – effect of placebo

STRIVE: Risk of Pulmonary Exacerbation Through Weeks 24 and 48

- At Week 48, a total of 67% of patients in the ivacaftor group, as compared with 41% in the placebo group, were free from pulmonary exacerbations, corresponding to a hazard ratio with ivacaftor of 0.455 (*P*=0.001), or a 55% reduction in the risk of pulmonary exacerbation[1]



	STRIVE	
Endpoint	Treatment difference[a] (95% CI)	P value
Relative risk of pulmonary exacerbation		
Through Week 24	0.40[b]	0.0016
Through Week 48	0.46[b]	0.0012