HTA applications in France

Understand key mechanisms

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Disclaimer : My participation and this presentation is personnal and the views presented here are my own and do not necessarily reflect the views of the University Hospital of Bordeaux, the HAS or its committees

Pay as you get

We must pay for clinical outcomes
not only for a marketing authorisation or an innovation as such

Economical rewards should go first to manufacturers providing new medicines representing **real, tangible medical progress**

This progress should be based on medical added value :

- Better efficacy, if possible better effectiveness but the latter is rarely available at the time of marketing authorisation (MA)
- And/or better safety , but data on both rare and serious adverse events is rarely available at the time of MA (role of pharmacovigilance and post-marketing studies)
- And/or substantial convenience of use with proof of better compliance with **positive clinical consequences**

Results should not only be **statistically** significant but should also be **clinically relevant**

Some definitions

Efficacy

Extent to which a drug has the ability to bring about its intended ***effect under ideal circumstances****, such as in a randomised clinical trial*

Q. Can this treatment work ? R. RCT, but limited extrapolability

Effectiveness

Extent to which a drug achieves its intended ***effect in the usual clinical setting***

Q. Does it work in pratice ? R. CER

Efficiency

Efficiency depends on ***whether a drug is worth its cost*** *to individuals or society*

Q. Is it worth it? R. HTA (cost-effectiveness studies, budget impact analysis)

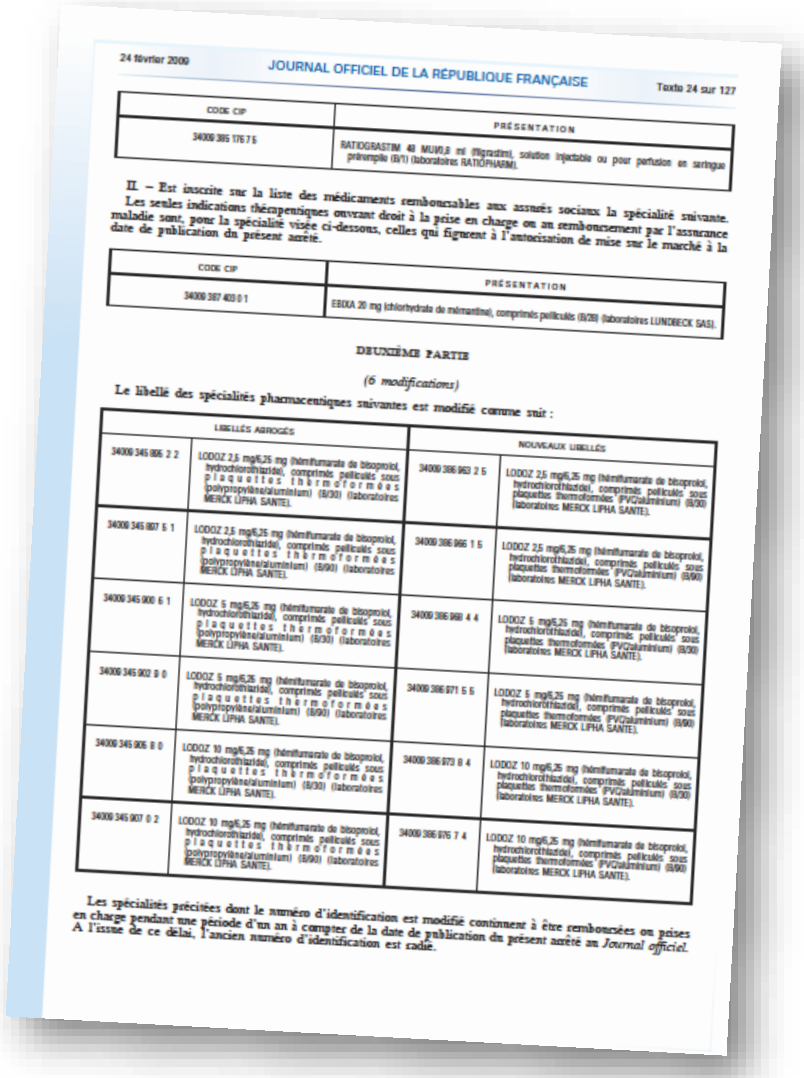
Br Med J 1999; 319: 652-3. Aust Prescr 2000; 23: 114–5

Evaluation of therapeutic value

Private and public "payers" have implemented various procedures to evaluate the **clinical value** of a new medicine, medical device or medical/surgical act

In France, for medicinal products, this process involves various actors, including :

- An **applicant**, holding a marketing authorisation
- The **HAS** (Haute Autorité de Santé, French Health Authority)
- The **Ministry of Health**
- The **National Health Fund** (CNAM, Caisse Nationale d'Assurance Maladie) : the main (and mandatory) **payer**



24 février 2009 JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE Texte 24 sur 127

CODE CIP	PRÉSENTATION
34009 385 176 7 6	RATIOGRASTIM 48 MUI/0,8 ml (filgrastim), solution injectable ou pour perfusion en seringue préremplie (B/1) (laboratoires RATIOPHARM).

II. – Est inscrite sur la liste des médicaments remboursables aux assurés sociaux la spécialité suivante. Les seules indications thérapeutiques ouvrant droit à la prise en charge ou au remboursement par l'assurance maladie sont, pour la spécialité visée ci-dessous, celles qui figurent à l'autorisation de mise sur le marché à la date de publication du présent arrêté.

CODE CIP	PRÉSENTATION
34009 387 403 0 1	EBIXA 20 mg (chlorhydrate de mémantine), comprimés pelliculés (B/28) (laboratoires LUNDBECK SAS).

DEUXIÈME PARTIE

(6 modifications)

Le libellé des spécialités pharmaceutiques suivantes est modifié comme suit :

LIBELLÉS ABROGÉS		NOUVEAUX LIBELLÉS	
34009 345 806 2 2	LODOZ 2,5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (polypropylène/aluminium) (B/30) (laboratoires MERCK LIPHA SANTÉ).	34009 386 963 2 5	LODOZ 2,5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (PVC/aluminium) (B/30) (laboratoires MERCK LIPHA SANTÉ).
34009 345 807 6 1	LODOZ 2,5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (polypropylène/aluminium) (B/90) (laboratoires MERCK LIPHA SANTÉ).	34009 386 966 1 5	LODOZ 2,5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (PVC/aluminium) (B/90) (laboratoires MERCK LIPHA SANTÉ).
34009 345 900 6 1	LODOZ 5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (polypropylène/aluminium) (B/30) (laboratoires MERCK LIPHA SANTÉ).	34009 386 968 4 4	LODOZ 5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (PVC/aluminium) (B/30) (laboratoires MERCK LIPHA SANTÉ).
34009 345 902 8 0	LODOZ 5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (polypropylène/aluminium) (B/90) (laboratoires MERCK LIPHA SANTÉ).	34009 386 971 5 6	LODOZ 5 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (PVC/aluminium) (B/90) (laboratoires MERCK LIPHA SANTÉ).
34009 345 906 8 0	LODOZ 10 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (polypropylène/aluminium) (B/30) (laboratoires MERCK LIPHA SANTÉ).	34009 386 973 8 4	LODOZ 10 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (PVC/aluminium) (B/30) (laboratoires MERCK LIPHA SANTÉ).
34009 345 907 0 2	LODOZ 10 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (polypropylène/aluminium) (B/90) (laboratoires MERCK LIPHA SANTÉ).	34009 386 976 7 4	LODOZ 10 mg/6,25 mg (hémifumarate de bisoprolol, hydrochlorothiazide), comprimés pelliculés sous plaquettes thermoformées (PVC/aluminium) (B/90) (laboratoires MERCK LIPHA SANTÉ).

Les spécialités précitées dont le numéro d'identification est modifié continuent à être remboursées ou prises en charge pendant une période d'un an à compter de la date de publication du présent arrêté au *Journal officiel*. A l'issue de ce délai, l'ancien numéro d'identification est radié.

HTA process in France

Marketing Authorisation Application evaluation
Quality, Safety, Efficacy → **Marketing authorisation**

CEESP
ECONOMIC & PUBLIC HEALTH EVALUATION COMMITTEE

SINCE OCT. 2013

FRENCH HEALTH AUTHORITY

Transparency Commission
Its evaluation includes :
- Clinical value (SMR)
- Clinical **added** value (ASMR
- Target population (size)

MINISTRY OF HEALTH
HEALTH PRODUCTS ECONOMICAL COMMITTEE

Price, price-volume agreement

NATIONAL HEALTH FUND

Level of reimbursement

SMR : Intrinsic value of a medicinal product

The (uncomparative) value of a medicine is in particular based on :

- The severity of the medical condition corresponding to the clinical indications validated in the SPC
- The clinical efficacy and safety of the medicine, including the **robustness and relevance** of the **methodologies and results** of the clinical trials
- The existence (or not) of alternative treatments and the conditions of use of possible alternative treatment/diagnosis/preventive options (not only medicines) : level of medical need
- The impact of the new medicinal product in terms of public health (burden of disease, health impact at the community/population level, external validity or generalisability of the results of CTs)

The level of 'SMR' will determine the reimbursement rate :

SMR	Serious disease	Usually non serious disease
Major/important	**65%**	**30%**
Moderate	**30%**	**30%**
Low	**15%**	**15%**

ASMR : The relative efficacy

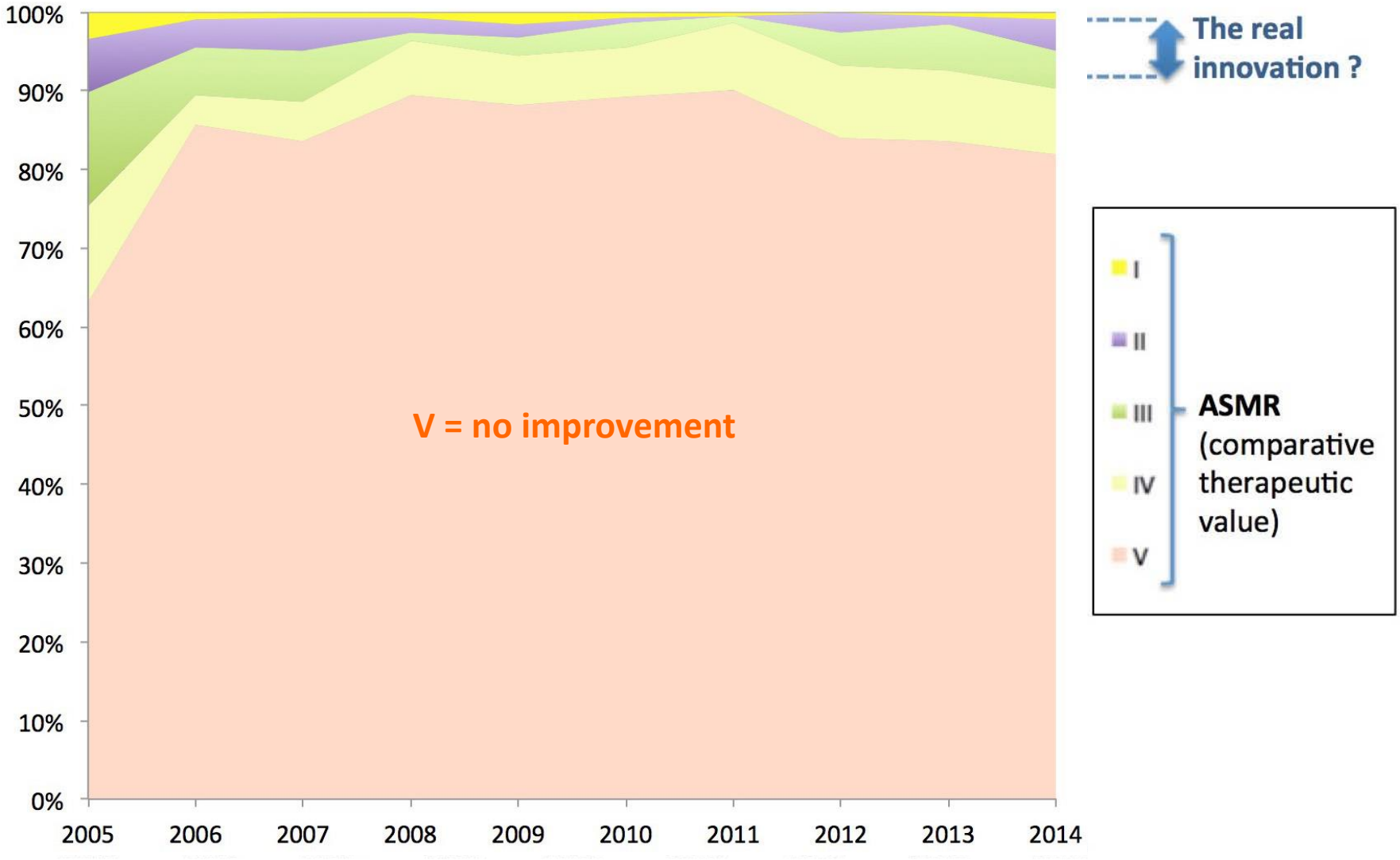
Evaluation of comparative efficacy/effectiveness

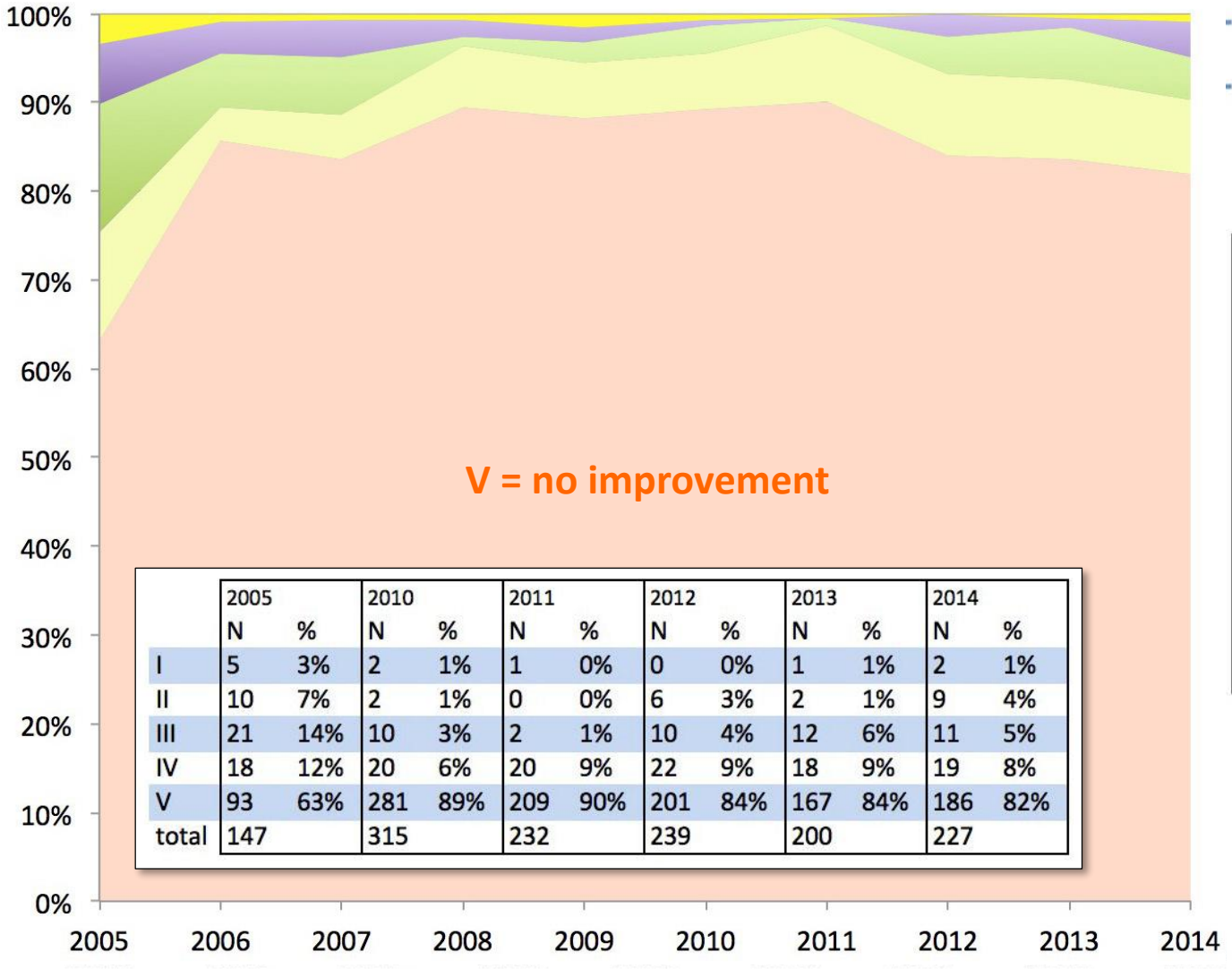
The therapeutic progress is quantified into levels of *ASMR* or **medical added value** which represents the "relative efficacy" of a drug compared with previously available treatments (if any, medicinal products or not).

Five levels of ASMR can be attributed by the Transparency Committee:

- ASMR I : major improvement over existing therapies
- ASMR II : important improvement over existing therapies
- ASMR III : moderate improvement over existing therapies
- ASMR IV : minor improvement over existing therapies
- ASMR V : no improvement over existing therapies

The level of ASMR will impact the price of a medicine (negociated by the Ministry of Health)


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
V = no improvement
The real innovation ?
I
II
III
IV
V
ASMR (comparative therapeutic value)



	2005		2010		2011		2012		2013		2014	
	N	%	N	%	N	%	N	%	N	%	N	%
I	5	3%	2	1%	1	0%	0	0%	1	1%	2	1%
II	10	7%	2	1%	0	0%	6	3%	2	1%	9	4%
III	21	14%	10	3%	2	1%	10	4%	12	6%	11	5%
IV	18	12%	20	6%	20	9%	22	9%	18	9%	19	8%
V	93	63%	281	89%	209	90%	201	84%	167	84%	186	82%
total	147		315		232		239		200		227	

The real innovation ?

I
II
III
IV
V

ASMR (comparative therapeutic value)

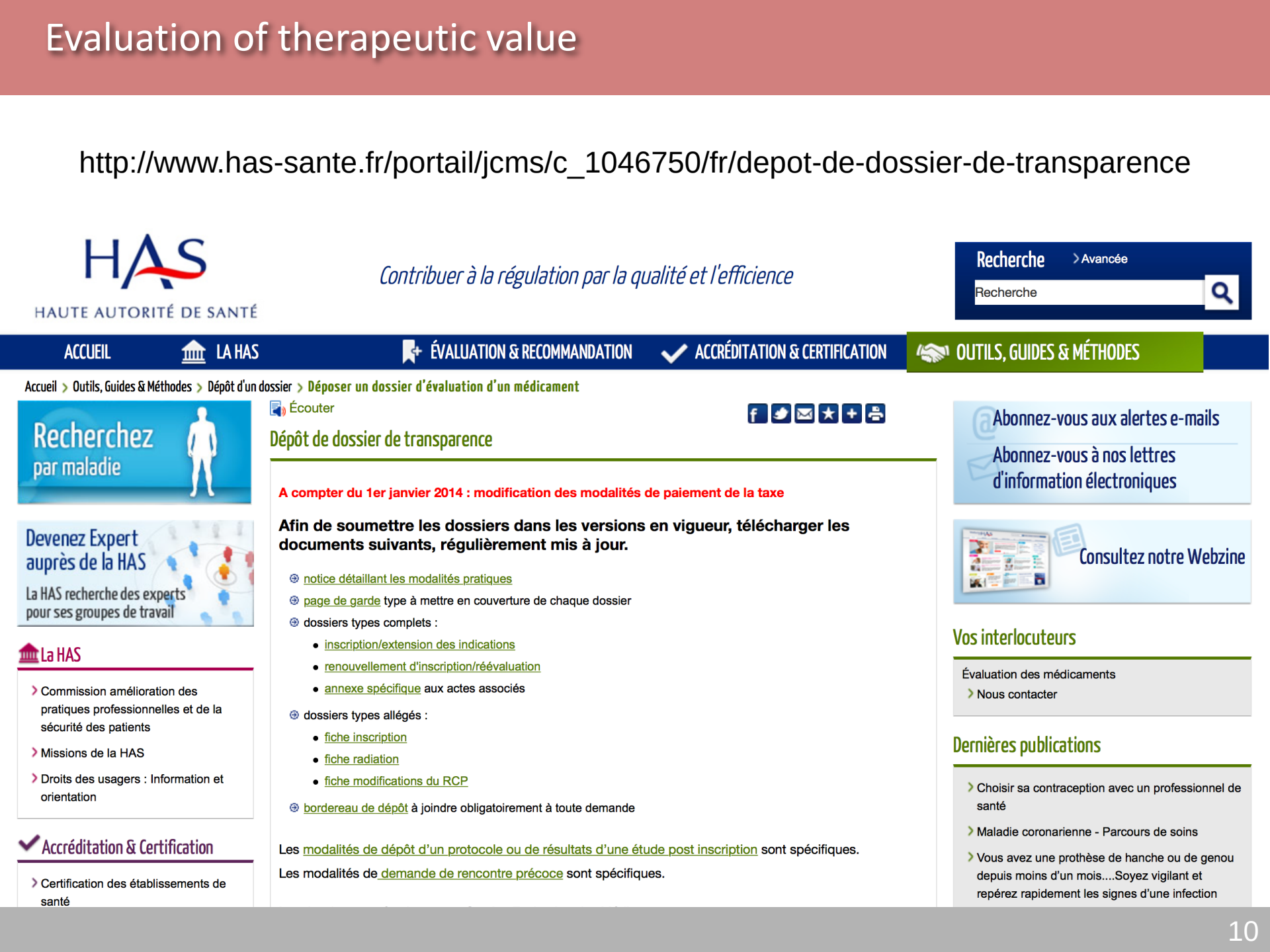
Evaluation of therapeutic value

Some key elements to reach high levels of "*ASMR*" (clinical added-value scale, progress)

- Clinical data based on **robust methodology** of clinical trials with head to head comparison
- Relevance of the **comparator** (gold standard or not ? Relevance of the doses, duration of treatment of the comparator…)
- Test of **superiority** design
- Nature of the clinical **evaluation criteria** : hard or surrogate marker ? (e.g. mortality vs biological marker)
- **Clinical relevance** of the size of the effect (statistical difference is not enough)
- **Duration** of the clinical effect
- **Sound clinical development program** (consistent, not always big)
- Unmet medical need ? Or few available efficient drugs with limited therapeutic effect (e.g. Alzheimer disease)

Evaluation of therapeutic value

http://www.has-sante.fr/portail/jcms/c_1046750/fr/depot-de-dossier-de-transparence



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NATIONAL HEALTH FUND

Level of reimbursement

Economic & Public Health Evaluation Committee

Décrets, arrêtés, circulaires

TEXTES GÉNÉRAUX

MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ

Décret nº 2012-1116 du 2 octobre 2012 relatif aux missions médico-économiques de la Haute Autorité de santé

NOR : *AFSS1208661D*

Publics concernés : Haute Autorité de santé (HAS), entreprises de produits de santé, régimes d'assurance maladie.

Objet : mise en œuvre de l'évaluation médico-économique nécessaire à l'évaluation des produits et des technologies de santé.

Entrée en vigueur : les dispositions de ce décret sont applicables aux demandes d'inscription ou de renouvellement d'inscription déposées par les entreprises à compter de l'expiration d'une période d'un an suivant la publication du présent décret.

Notice : ce décret précise les cas dans lesquels une évaluation médico-économique est requise pour les produits de santé, en raison notamment de l'amélioration du service médical rendu par le produit ou la technologie et des coûts prévisibles de son utilisation ou de sa prescription ; il précise également les conditions dans lesquelles elle est réalisée, notamment les critères d'appréciation et les délais applicables.

Une évaluation médico-économique est requise lorsqu'un produit de santé présente une amélioration du service attendu ou une amélioration du service médical rendu élevée et lorsqu'il est susceptible d'avoir un impact significatif sur les dépenses de l'assurance maladie. Cette évaluation intervient au moment du dépôt de la demande d'inscription au remboursement ou lors de son renouvellement. La commission évaluation

Economic & Public Health Evaluation Committee

Décrets, arrêtés, circulaires

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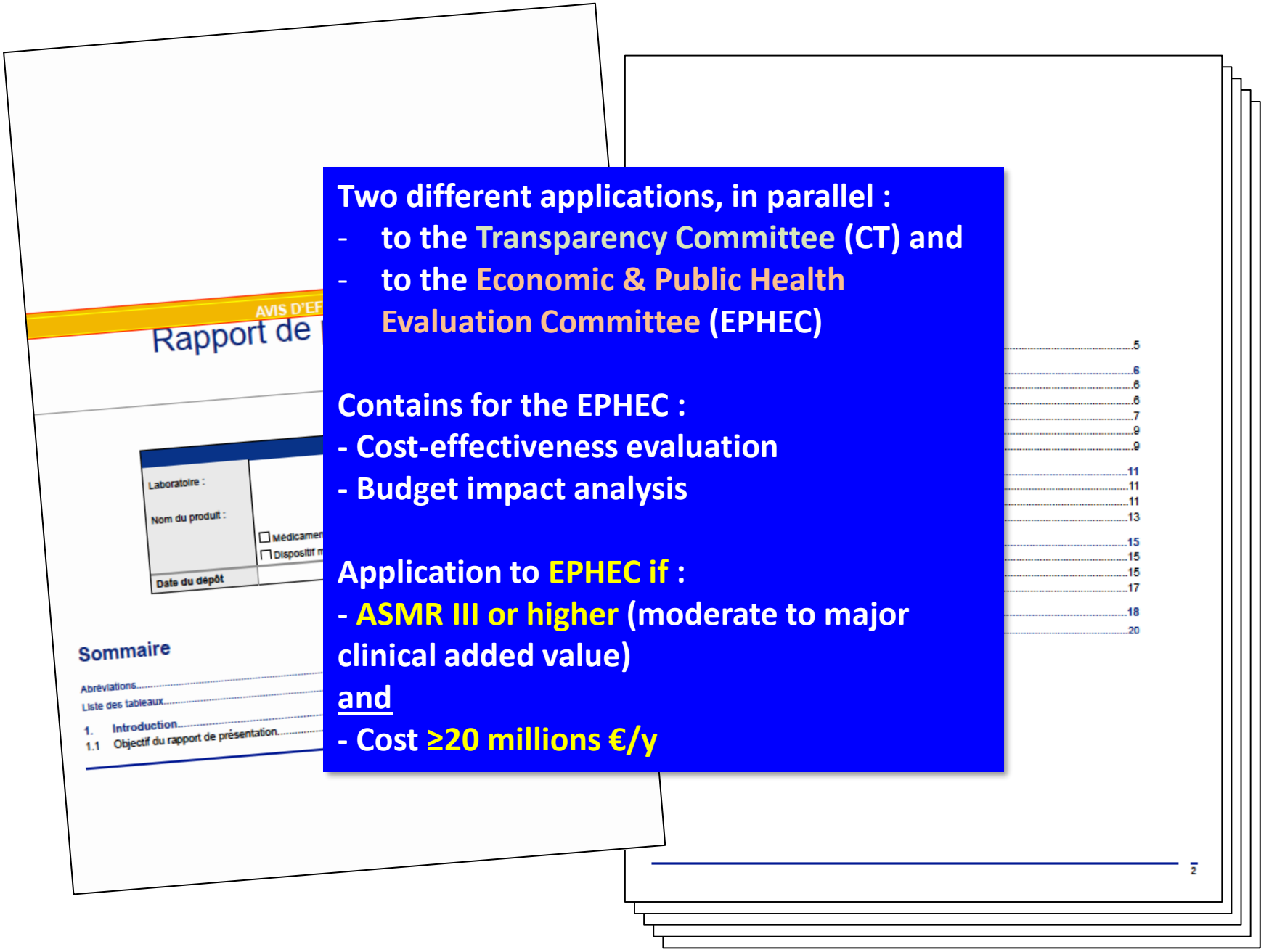
Includes :
- Cost-effectiveness evaluation
- Budget impact analysis

AVIS D'EFFICIENCE

Rapport de présentation

Laboratoire :	
Nom du produit :	☐ Médicament ☐ Dispositif médical ou technologie
Date du dépôt	

Sommaire



Two different applications, in parallel :

- **to the Transparency Committee (CT) and**
- **to the Economic & Public Health Evaluation Committee (EPHEC)**

Contains for the EPHEC :

- Cost-effectiveness evaluation

- Budget impact analysis

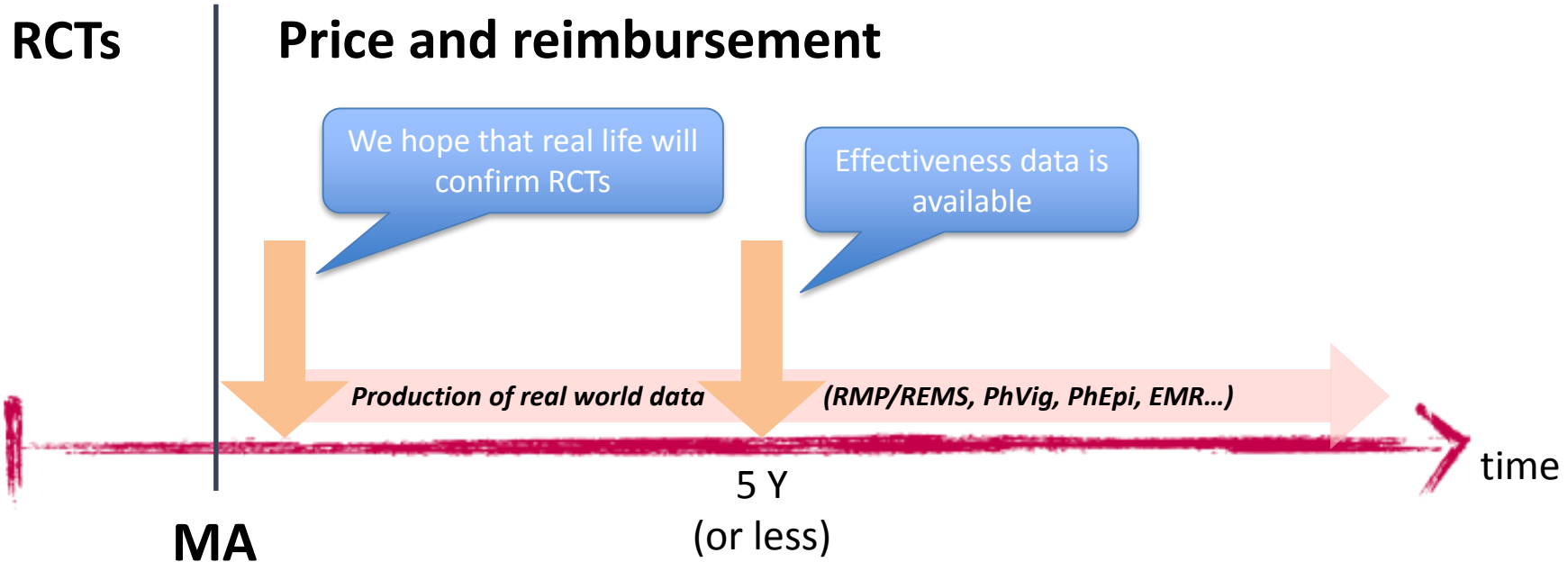
Application to EPHEC if :

- ASMR III or higher (moderate to major clinical added value)

and

- Cost ≥20 millions €/y

Multiple stages of evaluation



From HBM Hope-Based Medicine to EBM Evidence Based Medicine

Additional data from various sources, inc. 'Big Data', e.g. observational **post-marketing studies**

Field studies, e.g. drug utilisation studies

Database studies : Electronic medical records, claims' databases

Some definitions

Efficacy

Extent to which a drug has the ability to bring about its intended ***effect under ideal circumstances****, such as in a randomised clinical trial*

Q. Can this treatment work ? R. RCT, but limited extrapolability

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Br Med J 1999; 319: 652-3. Aust Prescr 2000; 23: 114–5

From efficacy to effectiveness

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

SHATTUCK LECTURE

Clinical Research to Clinical Practice — Lost in Translation?

Claude Lenfant, M.D.

Practice is science touched with emotion.

Confessio Medici
Stephen Paget, 1909

From the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md., and the Department of Health and Human Services, Washington, D.C. Address reprint requests to Dr. Lenfant at the National Heart, Lung, and Blood Institute, National Institutes of Health, 9000 Rockville Pike, Bldg. 31, Room 5A52, Bethesda, MD 20892.

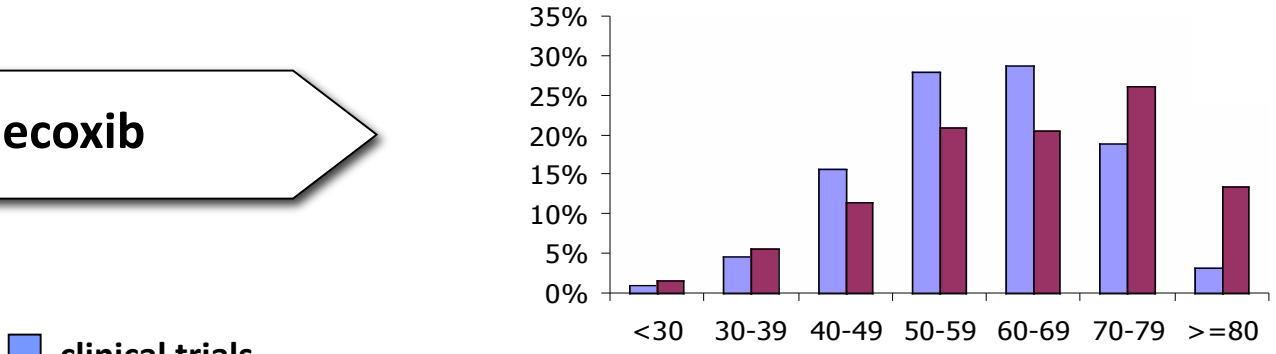
N Engl J Med 2003;349:868-74.

DURING THE 20TH CENTURY, ENORMOUS PROGRESS WAS MADE IN IMproving the health and therefore the life span of all Americans. The average life expectancy at birth increased by nearly 30 years between 1900 and 2000. Although the largest gains were made in the early part of the century, we still managed to add another 1.5 years between 1990 and 2000.

Much of our continued success in extending life expectancy over the past several decades is almost certainly due to research supported by the National Institutes of Health (NIH) and generously funded by the American public. NIH-supported research has not only made possible the development of new and improved treatments for a wide range

Pre-marketing CTs vs. reality

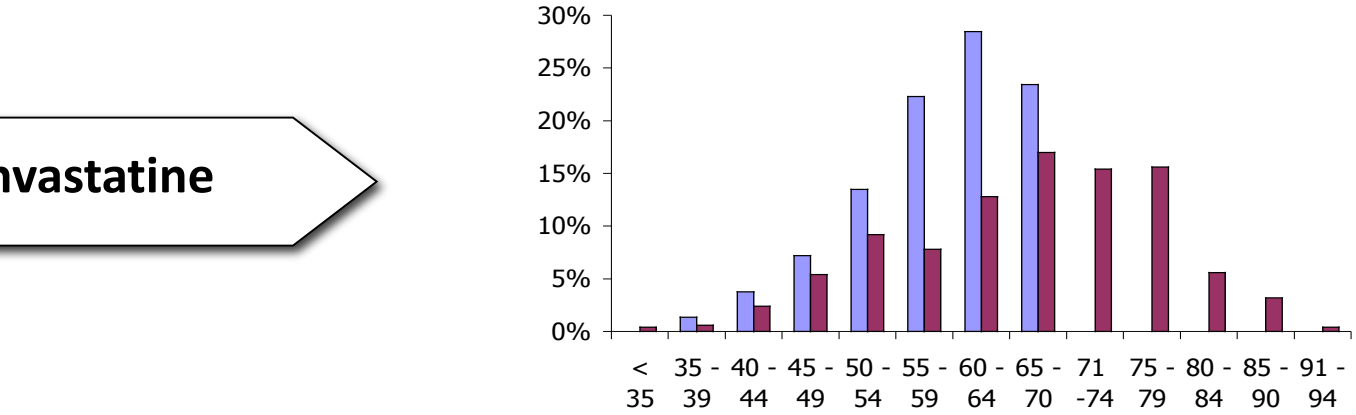
celecoxib



clinical trials

usual care

simvastatine



Martin K et al. J Clin Pharmacol 2004; 57: 86-92

From innovation to a clinical benefit

The link between innovation and value

Defining rewardable innovation in drug therapy. Aronson JK, Ferner RE, Hughes DA.
Nat Rev Drug Discov. 2012; 11: 253-4

COMMENT

Defining rewardable innovation in drug therapy

Jeffrey K. Aronson, Robin E. Ferner and Dyfrig A. Hughes

Implementing mechanisms for rewarding those who introduce innovative medicinal products requires a definition of 'rewardable innovation'. Here, we propose a definition of innovation with respect to medicinal products, accompanied by a ranking of the importance of different types of innovativeness, with the aim of providing a basis for rewarding such innovation.

The need to define innovation in relation to medicinal products stems in part from a desire to stimulate innovation by recognizing it and rewarding it appropriately. Indeed, innovativeness is increasingly becoming a major consideration in the valuation of new medicines: for example, with the forthcoming introduction of value-based pricing in the United Kingdom.

Not every medicine is innovative or, when innovative, to the same degree. We need to decide what is and what is not, to encourage innovation and to decide what is rewardable. Here, we propose a definition of innovation for medicinal products, accompanied by a rank order of the importance of different types of innovativeness in such products. Our aim is to provide a scale that can be used as a basis for assessing whether and to what extent the inventors of a new medicinal product should be rewarded for innovativeness.

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doi:10.1038/nrd3715

Innovation: an intensional definition

Previous definitions of innovation (Supplementary information S1 (table)) highlight some important aspects that should be included in any definition of rewardable innovation. The first aspect is novelty, which is not necessarily implied by newness. For example, a new beta blocker that shared all the attributes of a predecessor would not be novel; conversely, however, a novel use might be found for a compound that is not new, such as aspirin for preventing cardiovascular events. Deciding when newness constitutes true novelty may require value judgement.

The second aspect is usefulness. With regard to health, two general outcomes are crucial: health-related quality of life and survival, both of which are affected by the balance of clinical benefits and harms, which must be favourable for any innovative medicinal product. A possible rank order of usefulness that reflects the likelihood of these outcomes, from highest to lowest, is as follows: first, benefit in a condition with no existing effective treatment; second, improvement in the treatment of a condition that does not have a consistently satisfactory treatment; third, safer treatment (for example, owing to fewer adverse reactions or drug–drug interactions); fourth, more cost-effective treatment; and fifth, more convenient treatment (for example, oral versus intravenous administration). Non-health-related outcomes might also be considered (for example, improved employment, company profitability and increased national wealth). Different parties (patients, drug companies, health-care systems and governments) might have different views about the order of priorities in this list (Supplementary information S2 (table)), and the benefit that accrues from an innovation may affect only individuals or both individuals and their society (for example, immunization).

A third aspect is how the innovation arises, which can be either revolutionarily (by a single transformation) or evolutionarily (by gradual change, incrementally). In whatever way the innovation arises, it can have either a disruptive or sustaining effect on the market. Disruptive innovation occurs when a product emerges in a way that the market does not expect, whereas sustaining innovation produces improvement in an expected way and does not alter existing markets dramatically. Evolutionary innovations are not disruptive; revolutionary ones may be. There may be a fine line between drugs that are truly innovative and so-called 'me too' drugs, which are new but not novel. Indeed, small pharmacological differences between successive drugs may eventually lead to a major difference that can be regarded as being innovative in some respect, as exemplified by the beta blocker drug class (Supplementary information S3 (table)).

The aspects described above together lead to the concept of rewardable innovation[1]. Any inventor who desires that a product be regarded as innovative needs to demonstrate its usefulness, in the hope of thereby being rewarded. This idea has been recognized by the UK Office of Fair Trading, which — while not defining innovation — has stated that "innovation [should be] rewarded when new drugs provide medical

From innovation to a clinical benefit

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Previous definitions of innovation (Supplementary information S1 (table)) highlight some important aspects that should be included in any definition of rewardable innovation. The first aspect is novelty, which is not necessarily implied by newness. For example, a new beta blocker that shared all the attributes of a predecessor would not be novel; conversely, however, a novel use might be found for a compound that is not new, such as aspirin for preventing cardiovascular events. Deciding when newness constitutes true novelty may require value judgement.

The second aspect is usefulness. With regard to health, two general outcomes are crucial: health-related quality of life and survival, both of which are affected by the balance of clinical benefits and harms, which must be favourable for any innovative medicinal product. A possible rank order of usefulness that reflects the likelihood of these outcomes, from highest to lowest, is as follows: first, benefit in a condition with no existing effective treatment; second, improvement in the treatment of a condition that does not have a consistently satisfactory treatment; third, safer treatment (for example, owing to fewer adverse reactions or drug–drug interactions); fourth, more cost-effective treatment; and fifth, more convenient treatment (for example, oral versus intravenous administration). Non-health-related outcomes might also be considered (for example, improved employment, company profitability and increased national wealth). Different parties (patients, drug companies, health-care systems and governments) might have different views about the order of priorities in this list (Supplementary information S2 (table)), and the benefit that accrues from an innovation may affect only individuals or both individuals and their society (for example, immunization).

A third aspect is how the innovation arises, which can be either revolutionarily (by a single transformation) or evolutionarily (by gradual change, incrementally). In whatever way the innovation arises, it can have either a disruptive or sustaining effect on the market. Disruptive innovation occurs when a product emerges in a way that the market does not expect, whereas sustaining innovation produces improvement in an expected way and does not alter existing markets dramatically. Evolutionary innovations are not disruptive; revolutionary ones may be. There may be a fine line between drugs that are truly innovative and so-called 'me too' drugs, which are new but not novel. Indeed, small pharmacological differences between successive drugs may eventually lead to a major difference that can be regarded as being innovative in some respect, as exemplified by the beta blocker drug class (Supplementary information S3 (table)).

The aspects described above together lead to the concept of rewardable innovation[1]. Any inventor who desires that a product be regarded as innovative needs to demonstrate its usefulness, in the hope of thereby being rewarded. This idea has been recognized by the UK Office of Fair Trading, which — while not defining innovation — has stated that "innovation [should be] rewarded when new drugs provide medical

Economist Intelligence Unit Survey, September 2011

Perception of value

Which of these factors have the greatest influence on how your organisation currently assesses the value of a new drug?

	Biopharma-ceutical company	Biopharma-ceutical serv-ices provider	Generic pharmaceutical company	Health insurance company	Government payer	Regulatory agency
Degree of improved efficacy over existing products	63%	50%	44%	31%	26%	36%
Total patient outcomes	41%	39%	29%	34%	26%	29%
Whether it addresses an unmet medical need	54%	36%	27%	15%	39%	32%
Potential number of patients who could use the drug	23%	31%	54%	33%	10%	25%
Costs compared with competing products	14%	8%	37%	38%	29%	21%
Improved longevity of patient	14%	11%	20%	31%	36%	44%
Improved quality of life of patient	25%	31%	34%	65%	52%	52%

● 50% and over ● 40–49% ● 30–39% ● 20–29% ● 19% and under

Source: Economist Intelligence Unit survey, September 2011

Perception of value, priorities for data collection and evaluation

Which of these factors have the greatest influence on how your organisation currently assesses the value of a new drug?

	Biopharma-ceutical company	Biopharma-ceutical serv-ices provider	Generic pharmaceutical company	Health insurance company	Government payer	Regulatory agency
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● 50% and over ● 40–49% ● 30–39% ● 20–29% ● 19% and under

Source: Economist Intelligence Unit survey, September 2011

In summary

After marketing autorisation (EMA for innovative products, oncology, orphan drugs…), applicants for reimbursement of medicines in France must apply to the HAS :
- One application to the TC for evaluation of the clinical evaluation
- A different application to the CEESP for an economical evaluation in case of innovative and expensive products

With these two opinionss, the Ministry of Health negociates with the applicant on prices.
Commitments from all parties involved (Applicant, National Health Fund, Ministry of Health) with price-volume agreement (i.e. cap on expenditures)

Medicines can be lauched without submitting data to HAS but usually unapplicable
Re-evaluation on a periodic basis (max. 5 years)

EUNetHTA: forum for exchange of information, not binding, few applications

First example

An example : overweight & obesity

Obesity is a major public health issue

Worldwide obesity has nearly doubled since 1980

35% of adults aged 20 and over were overweight in 2008 (more than **1.4** billion adults), and **11% were obese** (over 200 million men and nearly 300 million women)

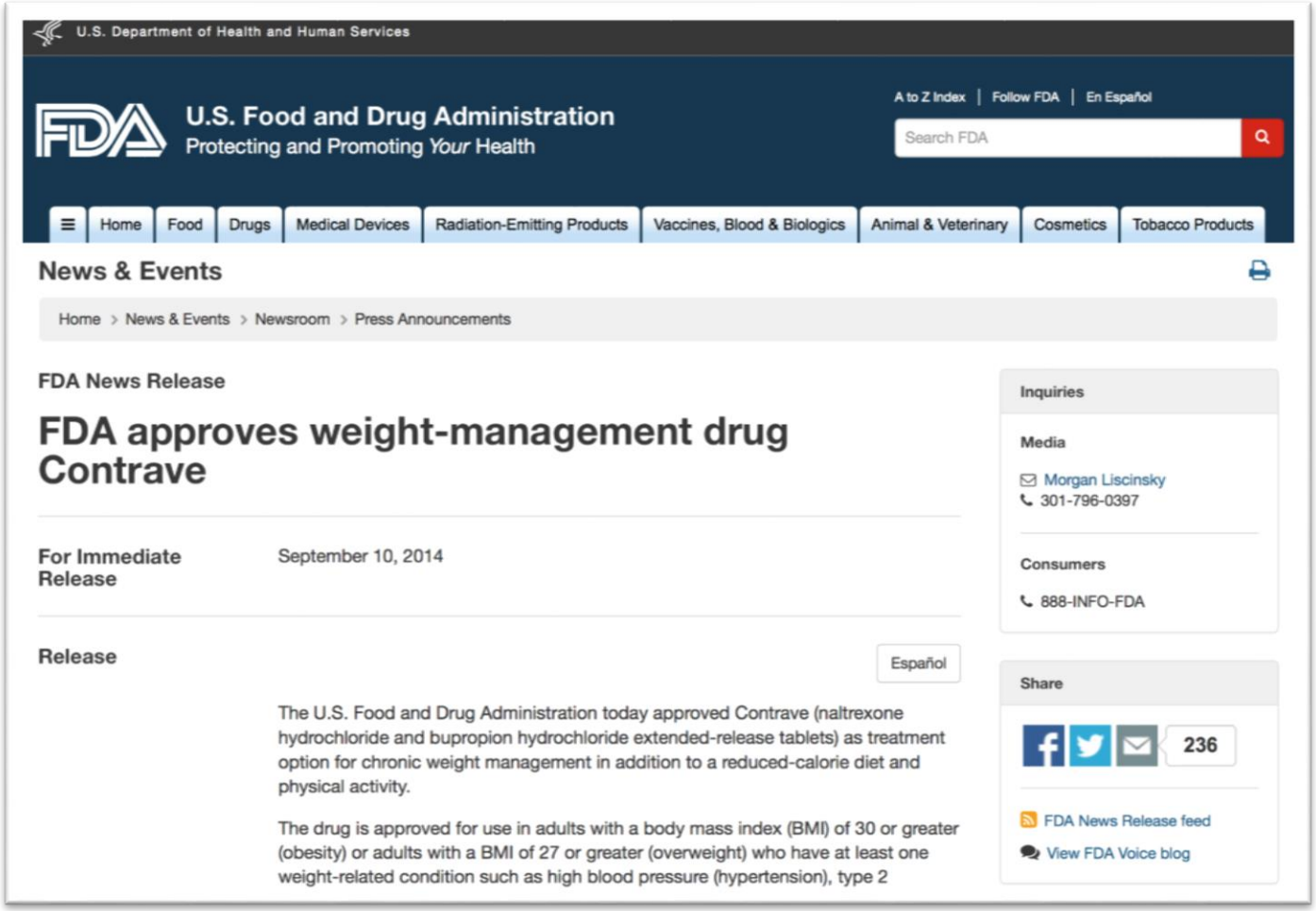
More than 40 million children under the age of 5 were overweight or obese in 2012

Huge population (and potential market), in particulier in rich countries : More than a third of the US population is obese, and two-thirds are either obese or overweight

Source : WHO

An example : overweight & obesity

Example of a medicinal product recently licensed by the FDA in this indication : Contrave, a fixed combination of naltrexone and bupropion



U.S. Department of Health and Human Services

U.S. Food and Drug Administration
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FDA News Release

FDA approves weight-management drug Contrave

For Immediate Release September 10, 2014

Release

Español

The U.S. Food and Drug Administration today approved Contrave (naltrexone hydrochloride and bupropion hydrochloride extended-release tablets) as treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity.

The drug is approved for use in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related condition such as high blood pressure (hypertension), type 2

Inquiries

Media

Morgan Liscinsky
301-796-0397

Consumers

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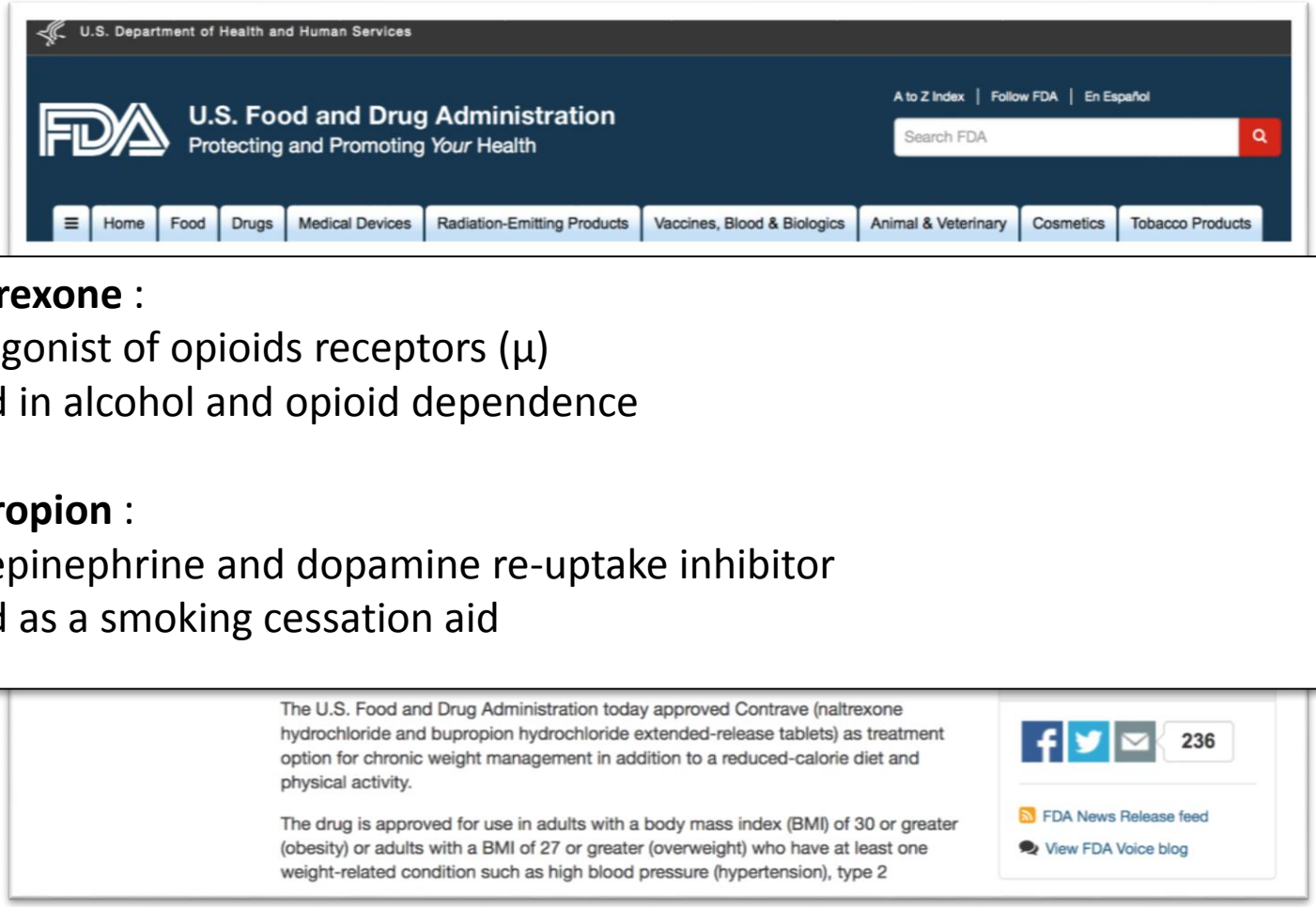
An example : overweight & obesity

Example of a medicinal product recently licensed by the FDA in this indication :
Contrave, a fixed combination of naltrexone and bupropion



Naltrexone :
Antagonist of opioids receptors (μ)
Used in alcohol and opioid dependence

Bupropion :
Norepinephrine and dopamine re-uptake inhibitor
Used as a smoking cessation aid

An example : overweight & obesity

Obesity or overweight as such do not directly kill (or exceptionally)

Morbidity and subsequent mortality is driven by **cardiovascular complications**

Am J Med Sci 2001; 321: 225–36
JACC 2009; 53: 1925–32

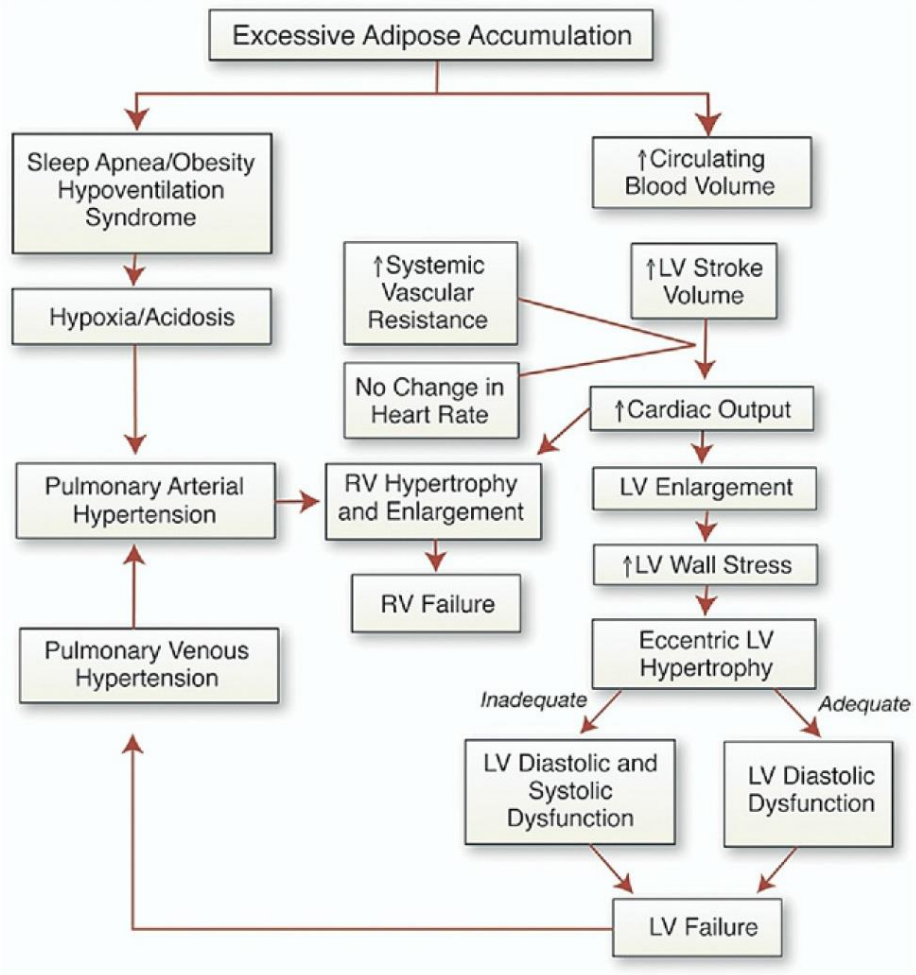


Figure 2 **Pathophysiology of Obesity and Cardiomyopathy**

LV = left ventricular; RV = right ventricular

1. Introduction

The price we are paying for an affl
a sedentary life style and faulty die
imbalance between energy intake a
in turn leads to obesity. Over we
rapidly growing threat to the health
number of countries [1].Obesity is l
and in the past 10 years in Europe
increase in obesity have occurred
Through the use of Body Mass Inde
that began in the 1980s has been
century. The original alarm was so
Center For Health Statistics in USA
the National Health And Nutrition

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AHA Scientific Statement

Obesity and Cardiovascular Disease: Pathophysiology, Evaluation, and Effect of Weight Loss

An Update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease From the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism

Paul Poirier, MD, PhD, FCRPC; Thomas D. Giles MD; George A. Bray, MD; Yuling Hong, MD, PhD; Judith S. Stern, ScD; F. Xavier Pi-Sunyer, MD, MPH; Robert H. Eckel, MD

Abstract— Obesity is becoming a global epidemic in both children and adults. It is associated with numerous comorbidities such as cardiovascular diseases (CVD), type 2 diabetes, hypertension, certain cancers, and sleep apnea/sleep-disordered breathing. In fact, obesity is an independent risk factor for CVD, and CVD risks have also been documented in obese children. Obesity is associated with an increased risk of morbidity and mortality as well as reduced life expectancy. Health service use and medical costs associated with obesity and related diseases have risen dramatically and are expected to continue to rise. Besides an altered metabolic profile, a variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts, even in the absence of comorbidities. Hence, obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, in addition to as-yet-unrecognized mechanisms. On the whole, overweight and obesity predispose to or are associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death because of their impact on the cardiovascular system. The pathophysiology of these entities that are linked to obesity will be discussed. However, the cardiovascular clinical evaluation of obese patients may be limited because of the morphology of the individual. In this statement, we review the available evidence of the impact of obesity on CVD with emphasis on the evaluation of cardiac structure and function in obese patients and the effect of weight loss on the cardiovascular system. (*Circulation*. 2006;113:898-918.)

Key Words: AHA Scientific Statements ■ obesity ■ cardiovascular diseases ■ heart diseases ■ diagnosis

Obesity is becoming a global epidemic,[1,2] and in the past 10 years in the United States, dramatic increases in obesity have occurred in both children and adults.[3–5] Historically, the Metropolitan Life Insurance Company data that express body fatness as percent ideal body weight have been used,[6] but currently overweight and obesity are classified by body mass index (BMI). BMI (weight in kilograms/height^2 in meters) is frequently used as a surrogate measure of fatness in children and adults. In adults, overweight is defined as a BMI of 25.0 to 29.9 kg/m^2; obesity is defined as a BMI ≥30.0 kg/m^2. Table 1 shows the classification developed by a National Heart, Lung, and Blood Institute task force, along with the associated disease risk with increasing BMI.[7]

Through the use of the BMI, the epidemic of obesity that began in the 1980s has been tracked through the end of the century.[4,8] The original alarm was sounded in 1994 by the National Center for Health Statistics when they reported their data from the first 3 years of the National Health and Nutrition Examination Survey (NHANES).[9] The authors observed that from 1988–1994 (NHANES III) to NHANES 1999–2000, the prevalence of overweight in adults increased from 55.9% to 64.5%. During that same period, the prevalence of obesity increased from 22.9% to 30.5%.[4,5,10] This sudden, unanticipated jump in the prevalence of obesity led the American Heart Association (AHA) to call for action to curb the consequences of this epidemic.[11,12] More recently,

Circulation is available at http://www.circulationaha.org

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Vol. 53, No. 21, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.12.068

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N), heart failure (HF), and
evidence from clinical co-
CV diseases indicates an
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of leptin, an adipocyte-
food intake and energy
related with CV disease
sewhere (Fig. 1) (10,11).
ay a role in the develop-

An example : overweight & obesity

Treatment rationale

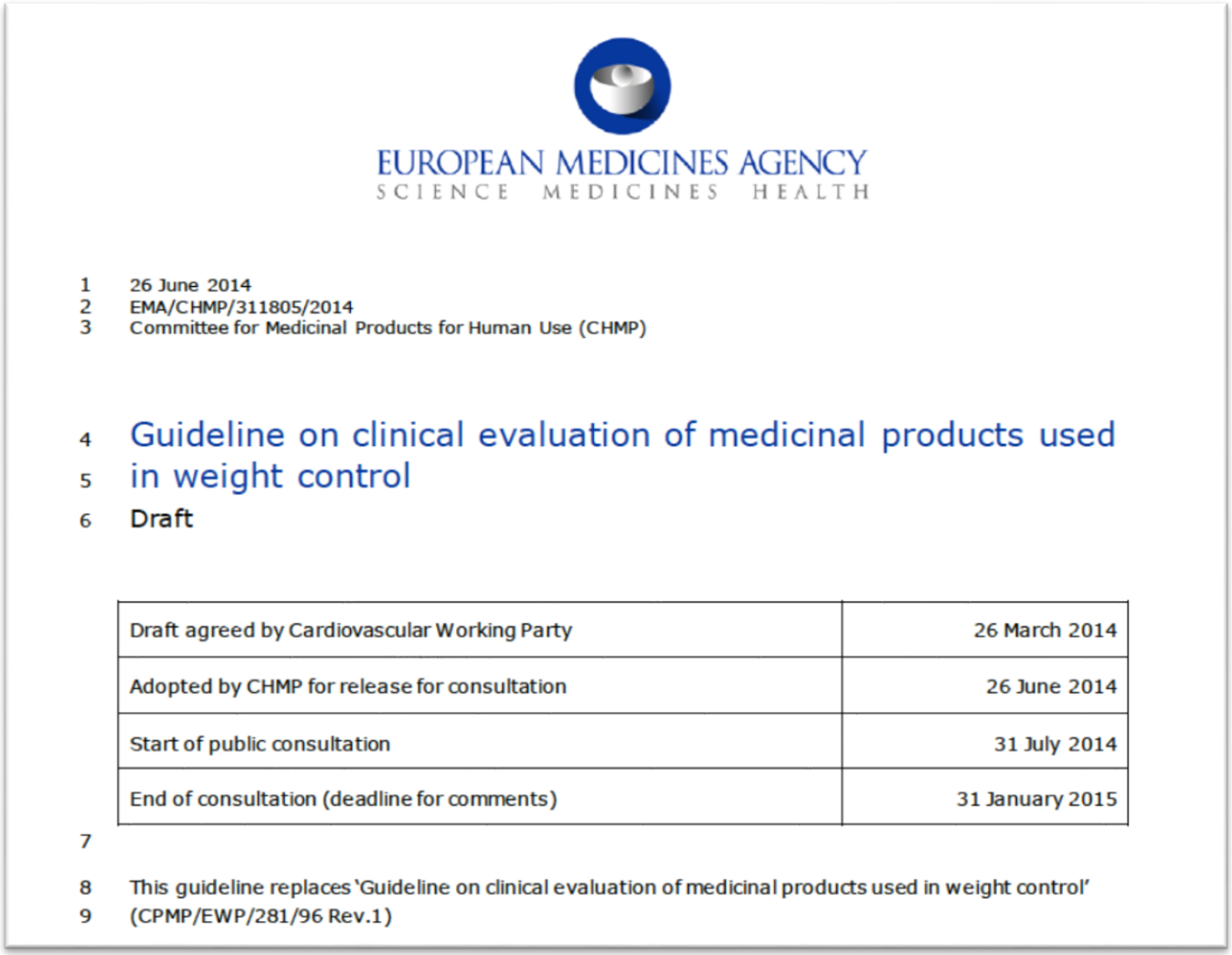
Obesity leads in particular to exposure to the following cardiovascular risk factors :

- Dyslipidemia
- Increase in heart rate
- Increase in systolic and diastolic blood pressure, hypertension (6 times more frequent in obese subjects)
- Glucose intolerance and diabetes
- Obstructive sleep apnea

Weight reduction leads to correction of these risk factors, source of favourable impact on potential clinical complications and mortality

An example : overweight & obesity

According to Authorities' guidelines, efficacy of these products should be established on the basis of at least a 5% weight reduction



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 26 June 2014
2 EMA/CHMP/311805/2014
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on clinical evaluation of medicinal products used
5 in weight control
6 Draft

Draft agreed by Cardiovascular Working Party	26 March 2014
Adopted by CHMP for release for consultation	26 June 2014
Start of public consultation	31 July 2014
End of consultation (deadline for comments)	31 January 2015

7

8 This guideline replaces 'Guideline on clinical evaluation of medicinal products used in weight control'
9 (CPMP/EWP/281/96 Rev.1)

An example : overweight & obesity

4. Efficacy criteria and methods to assess efficacy

4.1. Introduction

Reduction of body weight should be the primary efficacy endpoint in the clinical studies. However, it should preferably be supported by clinically relevant effects on endpoints reflecting the beneficial effect of the documented weight loss.

4.2. Reduction of body weight and related variables

Baseline weight is the subject's weight at randomisation. Weight loss should be documented both as absolute weight loss (kg) and percentage weight loss relative to baseline body weight. Demonstration of a clinically significant degree of weight loss of at least 5- 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.

Proportions of responders with ≥ 5% weight loss should be documented as a secondary endpoint.

Further, the predictive value of weight loss after e.g. 3 months treatment with respect to long term effects should be documented in order to identify a population with expected long term benefit.

Measurements of central adiposity (e.g. waist circumference or waist to hip ratio) should always be documented.

An example : overweight & obesity

4.3. Cardiovascular risk factors

A new weight-lowering agent should in general show a neutral or beneficial effect on parameters associated with cardiovascular risk (e.g. blood glucose, blood pressure, lipid levels). The impact on the risk of the development of diabetes is considered as an important secondary endpoint. For specific claims with respect to beneficial effects on cardiovascular endpoints other than body weight, relevant guidelines should be followed.

4.4. Cardiovascular morbidity and mortality

For products that have shown clinically relevant weight reductions, there will be no requirement to demonstrate a direct positive effect on cardiovascular morbidity or mortality prior to licensing unless specific claims are made. Any claim of a reduction of cardiovascular morbidity and/or mortality will need to be supported by well-designed clinical trials that enrol a representative, "real world" sample of patients with obesity.

An example : overweight & obesity

Phase III clinical trials of Contrave

Table 1. Phase III clinical trials for naltrexone SR/bupropion SR.

Trial	Abbreviation	Length of study (weeks)	Number of participants	Objective
Contrave Obese Research I (COR-I)	NB-301	56	1742	Compared safety and efficacy of two doses of naltrexone SR/bupropion SR in overweight and obese patients
Contrave Obese Research-Behavior Modification (COR-BMOD)	NB-302	56	793	Assessed safety and efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without behavior modification
Contrave Obese Research II (COR-II)	NB-303	56	1496	Tested efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without diet and exercise
Contrave Obese Research-Diabetes (COR-Diabetes)	NB-304	56	505	Determined safety and efficacy in overweight and obese patients with type 2 diabetes
Cardiovascular Outcomes Study of Contrave in Overweight and Obese Subjects With Cardiovascular Risk Factors	Light Study	Up to 4 years	Approximately 8900	Investigate cardiovascular health outcomes in overweight and obese individuals with cardiovascular risk factors. The study is designed to assess the occurrence of Major Adverse Cardiovascular Events

SR: Sustained-release.

Expert Opin Drug Saf 2014; 13: 831-841

An example : overweight & obesity

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-4.8%

-4.2%

-5.2%

-3.2%

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An example : overweight & obesity

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An example : overweight & obesity

Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

A Randomized, Phase 3 Trial of Naltrexone SR/Bupropion SR on Weight and Obesity-related Risk Factors (COR-II)

*Caroline M. Apovian[1], Louis Aronne[2], Domenica Rubino[3], Christopher Still[4], Holly Wyatt[5], Colleen Burns[6], Dennis Kim[6], Eduardo Dunayevich[6] for the COR-II Study Group**

Objective: To examine the effects of naltrexone/bupropion (NB) combination therapy on weight and weight-related risk factors in overweight and obese participants.
Design and Methods: CONTRAVE Obesity Research-II (COR-II) was a double-blind, placebo-controlled study of 1,496 obese (BMI 30-45 kg/m^2) or overweight (27-45 kg/m^2 with dyslipidemia and/or hypertension) participants randomized 2:1 to combined naltrexone sustained-release (SR) (32 mg/day) plus bupropion SR (360 mg/day) (NB32) or placebo for up to 56 weeks. The co-primary endpoints were percent weight change and proportion achieving ≥5% weight loss at week 28.
Results: Significantly ($P < 0.001$) greater weight loss was observed with NB32 versus placebo at week 28 (−6.5% vs. −1.9%) and week 56 (−6.4% vs. −1.2%). More NB32-treated participants ($P < 0.001$) experienced ≥5% weight loss versus placebo at week 28 (55.6% vs. 17.5%) and week 56 (50.5% vs. 17.1%). NB32 produced greater improvements in various cardiometabolic risk markers, participant-reported weight-related quality of life, and control of eating. The most common adverse event with NB was nausea, which was generally mild to moderate and transient. NB was not associated with increased events of depression or suicidality versus placebo.
Conclusion: NB represents a novel pharmacological approach to the treatment of obesity, and may become a valuable new therapeutic option.

Obesity (2013) **21**, 935-943. doi:10.1002/oby.20309

An example : overweight & obesity

TABLE 1 Demographics and baseline characteristics

Demographic/ characteristic[a]	Placebo *N* = 495	NB[b] *N* = 1001
Age, y	44.4 ± 11.4	44.3 ± 11.2
Gender (% female)	84.8	84.6
Race (% White/Black/Other)	84/15/2[c]	83/13/3[c]
Weight, kg	99.2 ± 15.9	100.3 ± 16.6
BMI, kg/m^2	36.1 ± 4.3	36.2 ± 4.5
Hypertension, %[d]	21.4	21.2
Dyslipidemia, %[e]	53.1	55.9

[a]Data are mean ± SD or % of participants for the Randomized population.
[b]NB group includes all participants randomized to NB32 at baseline, regardless of re-rand
[c]Perce
[d]Diagn
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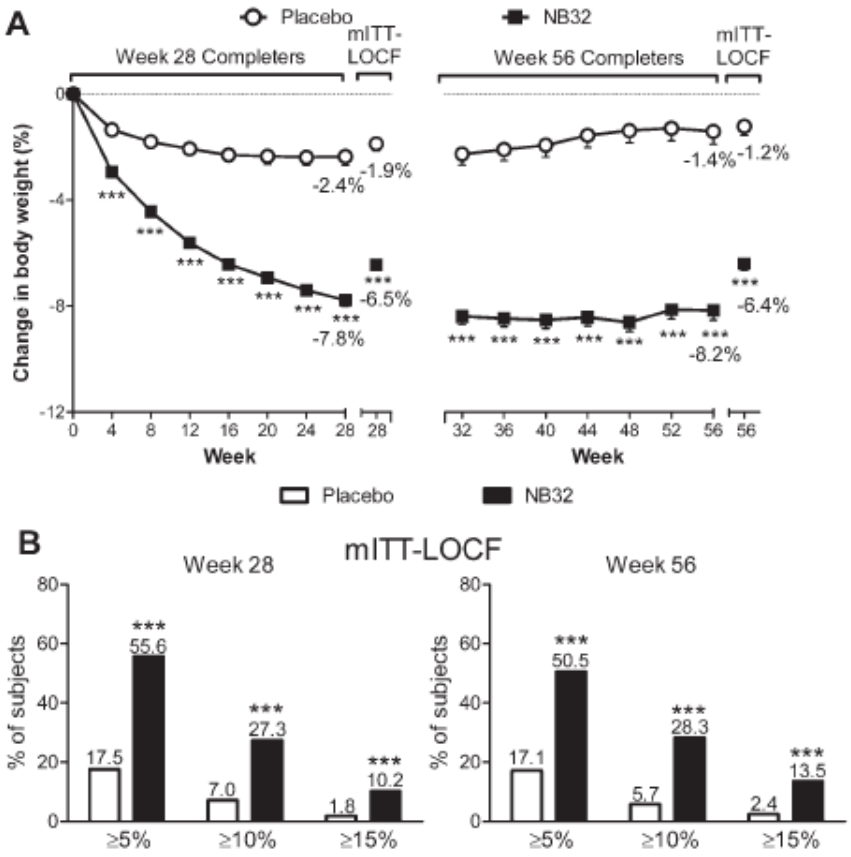
COR II : -5,2% (mITT considering the last weight reported in patients losts during follow-up). Completers at 56 weeks presented -6.8 % but **half** of the patients did not complete the one year treatment (**benefit is based on duration of weight control**). Diabetic patients excluded



An example : overweight & obesity

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Weight, kg	99.2 ± 15.9	100.3 ± 16.6
BMI, kg/m^2	36.1 ± 4.3	36.2 ± 4.5
Hypertension, %[d]	21.4	21.2
Dyslipidemia, %[e]	53.1	55.9

-1.2% → **98 kg**

-6.4% → **94 kg**

[a]Data are mean ± SD or % of participants for the Randomized population.
[b]NB group includes all participants randomized to NB32 at baseline, regardless of re-rand
[c]Perce
[d]Diagn
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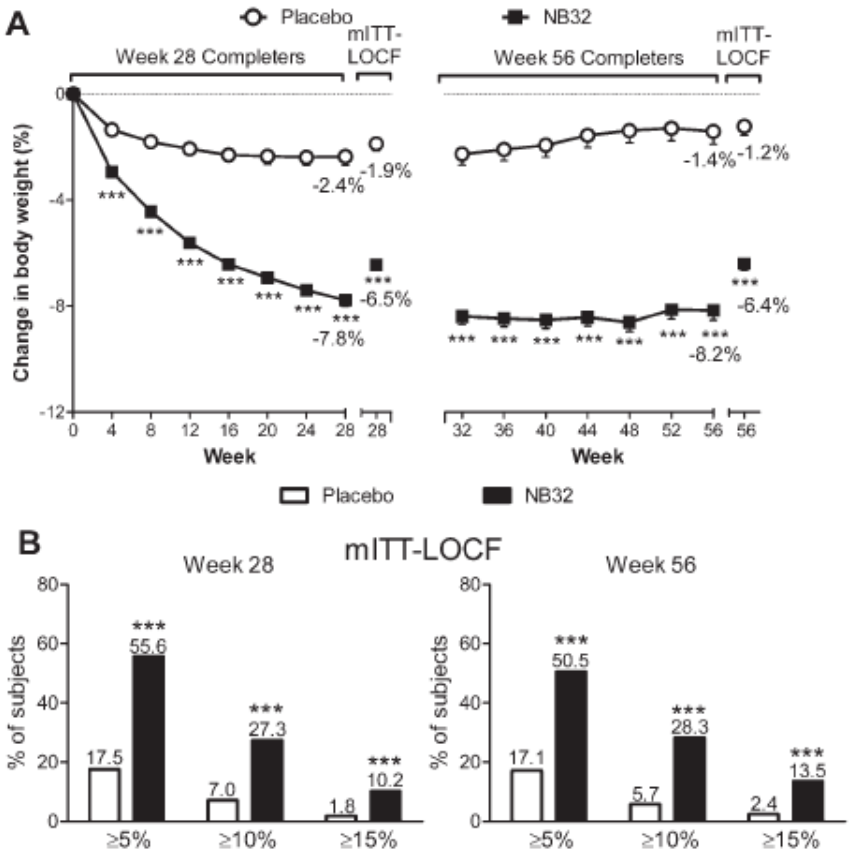

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An example : overweight & obesity

TABLE 3 Changes in secondary and additional endpoints

Measure[a]	Week 28 Placebo N = 456	Week 28 NB32 N = 825	Week 28 P-value	Week 56 Placebo N = 456	Week 56 NB32[b] N = 702	Week 56 P-value
Waist circumference, cm						
Baseline	108.9 ± 11.7	109.3 ± 11.9		108.6 ± 11.8	109.0 ± 11.8	
Change	−2.7 ± 0.4	−6.2 ± 0.3	<0.001[c]	−2.1 ± 0.5	−6.7 ± 0.3	<0.001
Triglycerides, mg/dL[d]						
Baseline	113.4 ± 1.6	119.0 ± 1.6		112.8 ± 1.6	118.9 ± 1.6	
Percent change (95% CI)	−1.4% (−5.0%, +2.4%)	−7.3% (−9.8%, −4.8%)	0.007[c]	−0.5% (−4.5%, +3.7%)	−9.8% (−12.4%, −7.1%)	<0.001
HDL-cholesterol, mg/dL						
Baseline	51.4 ± 13.1	51.4 ± 13.3		51.6 ± 12.9	51.8 ± 13.6	
Change	−1.4 ± 0.4	+1.2 ± 0.3	<0.001[c]	−0.9 ± 0.5	+3.6 ± 0.4	<0.001
LDL-cholesterol, mg/dL						
Baseline	117.1 ± 32.6	119.8 ± 30.2		116.8 ± 32.9	120.5 ± 30.2	
Change	0.0 ± 1.3	−4.4 ± 0.9	0.004	−2.1 ± 1.3	−6.2 ± 0.9	0.008
hsCRP, mg/L[d]						
Baseline	3.7 ± 2.7	3.9 ± 2.8		3.7 ± 2.8	3.8 ± 2.8	
Percent change (95% CI)	−1.1% (−9.1%, +7.5%)	−9.4% (−14.8%, −3.6%)	0.091	−8.3% (−17.2%, +1.6%)	−28.8% (−33.9%, −23.3%)	<0.001
Fasting blood glucose, mg/dL						
Baseline	94.2 ± 10.4	94.8 ± 11.2		94.2 ± 10.4	95.0 ± 11.3	
Change	−1.7 ± 0.5	−2.1 ± 0.4	0.544	−1.3 ± 0.6	−2.8 ± 0.5	0.051
Systolic blood pressure, mm Hg						
Baseline	118.2 ± 10.5	118.1 ± 10.0		118.2 ± 10.5	117.9 ± 10.0	
Change	−1.2 ± 0.4	−0.9 ± 0.3	0.556	−0.5 ± 0.4	+0.6 ± 0.3	0.039
Diastolic blood pressure, mm Hg						
Baseline	76.8 ± 7.0	76.8 ± 7.0		76.8 ± 7.0	76.7 ± 7.0	
Change	−0.7 ± 0.3	+0.2 ± 0.2	0.017	+0.3 ± 0.3	+0.4 ± 0.2	0.847

An example : overweight & obesity

Phase III clinical trials of Contrave

Table 1. Phase III clinical trials for naltrexone SR/bupropion SR.

Trial	Abbrevi	Length of study (weeks)	Number of participants	Objective
Contrave Obese Research I (COR-I)	NB-301	56	1742	Compared safety and efficacy of two doses of naltrexone SR/bupropion SR in overweight and obese patients
Contrave Obese Research-Behavior Modification (COR-BMOD)	NB-302	56	793	Assessed safety and efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without behavior modification
Contrave Obese Research II (COR-II)	NB-303	56	96	Tested efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without diet and exercise
Contrave Obese Research-Diabetes (COR-Diabetes)	NB-304	56	5	Determined safety and efficacy in overweight and obese patients with type 2 diabetes
Cardiovascular Outcomes Study of Contrave in Overweight and Obese Subjects With Cardiovascular Risk Factors	Light Study	Up to 4 years	Approximately 8900	Investigate cardiovascular health outcomes in overweight and obese individuals with cardiovascular risk factors. The study is designed to assess the occurrence of Major Adverse Cardiovascular Events

SR: Sustained-release.

-4.8%

-4.2%

-5.2%

-3.2%

Expert Opin Drug Saf 2014; 13: 831-841

An example : overweight & obesity

Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

*Frank L Greenway, Ken Fujioka, Raymond A Plodkowski, Sunder Mudaliar, Maria Guttadauria, Janelle Erickson, Dennis D Kim, Eduardo Dunayevich, for the COR-I Study Group**

Summary

Background Despite increasing public health concerns regarding obesity, few safe and effective drug treatments are available. Combination treatment with sustained-release naltrexone and bupropion was developed to produce complementary actions in CNS pathways regulating bodyweight. The Contrave Obesity Research I (COR-I) study assessed the effect of such treatment on bodyweight in overweight and obese participants.

Methods Men and women aged 18–65 years who had a body-mass index (BMI) of 30–45 kg/m^2 and uncomplicated obesity or BMI 27–45 kg/m^2 with dyslipidaemia or hypertension were eligible for enrolment in this randomised, double-blind, placebo-controlled, phase 3 trial undertaken at 34 sites in the USA. Participants were prescribed mild hypocaloric diet and exercise and were randomly assigned in a 1:1:1 ratio to receive sustained-release naltrexone 32 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB32), sustained-release naltrexone 16 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB16), or matching placebo twice a day, given orally for 56 weeks. The trial included a 3-week dose escalation. Randomisation was done by use of a centralised, computer-generated, web-based system and was stratified by study centre. Co-primary efficacy endpoints at 56 weeks were percentage change in bodyweight and proportion of participants who achieved a decrease in bodyweight of 5% or more. The primary analysis included all randomised participants with a baseline weight measurement and a post-baseline weight measurement while on study drug (last observation carried forward). This study is registered with ClinicalTrials.gov, number NCT00532779.

Findings 1742 participants were enrolled and randomised to double-blind treatment (naltrexone 32 mg plus bupropion, n=583; naltrexone 16 mg plus bupropion, n=578; placebo, n=581). 870 (50%) participants completed 56 weeks of treatment (n=296; n=284; n=290, respectively) and 1453 (83%) were included in the primary analysis (n=471; n=471; n=511). Mean change in bodyweight was –1·3% (SE 0·3) in the placebo group, –6·1% (0·3) in the naltrexone 32 mg plus bupropion group (p<0·0001 *vs* placebo) and –5·0% (0·3) in the naltrexone 16 mg plus bupropion group (p<0·0001 *vs* placebo). 84 (16%) participants assigned to placebo had a decrease in bodyweight of 5% or more compared with 226 (48%) assigned to naltrexone 32 mg plus bupropion (p<0·0001 *vs* placebo) and 186 (39%) assigned to naltrexone 16 mg plus bupropion (p<0·0001 *vs* placebo). The most frequent adverse event in participants assigned to combination treatment was nausea (naltrexone 32 mg plus bupropion, 171 participants [29·8%]; naltrexone 16 mg plus bupropion, 155 [27·2%]; placebo, 30 [5·3%]). Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups than in the placebo group. A transient increase of around

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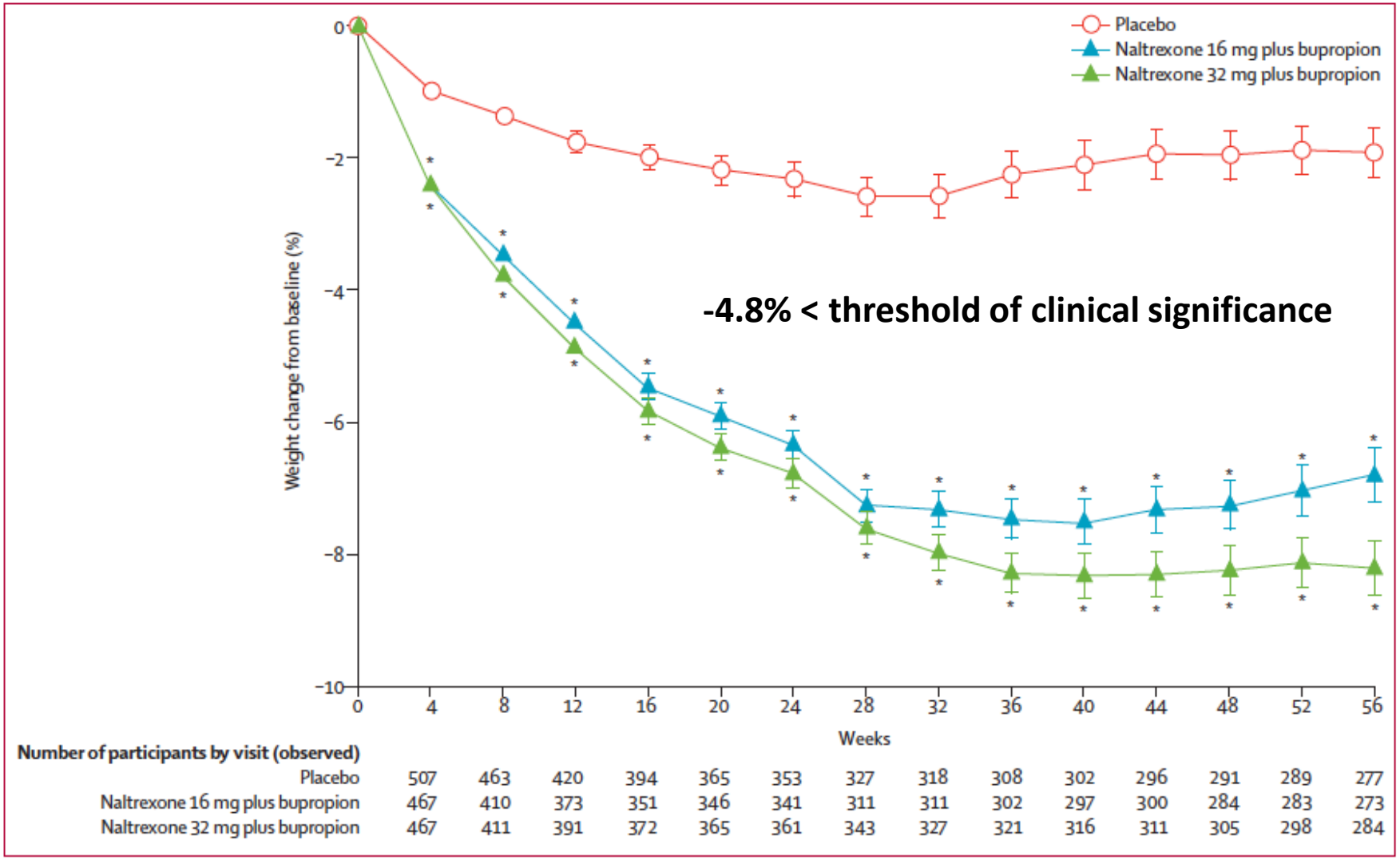
An example : overweight & obesity



Number of participants by visit (observed)														
Placebo	507	463	420	394	365	353	327	318	308	302	296	291	289	277
Naltrexone 16 mg plus bupropion	467	410	373	351	346	341	311	311	302	297	300	284	283	273
Naltrexone 32 mg plus bupropion	467	411	391	372	365	361	343	327	321	316	311	305	298	284

Figure 2: **Change in bodyweight**

Observed least squares mean (SE) percentage change from baseline in bodyweight and number of participants at each visit during 56 weeks. *p<0·0001 compared with placebo.

	Placebo	Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion	p value for comparison with placebo	
				Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion
Waist circumference (cm)					
Baseline	110·0 (12·2)	109·8 (11·2)	108·8 (11·3)	..	..
Change	−2·5 (−3·3 to −1·6)	−5·0 (−5·9 to −4·2)	−6·2 (−7·1 to −5·4)	<0·0001*	<0·0001*
Triglycerides (mmol/L)†					
Baseline	1·28 (0·02)	1·33 (0·02)	1·31 (0·02)	..	..
Percentage change	−3·1% (−6·6 to 0·6)	−8·0% (−11·4 to −4·4)	−12·7% (−15·8 to 9·5)	0·0461*	<0·0001*
HDL cholesterol (mmol/L)					
Baseline	1·35 (0·35)	1·35 (0·35)	1·34 (0·35)	..	..
Change	0·00 (−0·02 to 0·02)	0·09 (0·06 to 0·11)	0·09 (0·07 to 0·11)	<0·0001*	<0·0001*
Percentage change	0·8% (−1·0 to 2·5)	7·6% (5·9 to 9·4)	8·0% (6·3 to 9·7)	..	..
LDL cholesterol (mmol/L)					
Baseline	3·10 (0·90)	3·23 (0·84)	3·08 (0·84)	..	..
Change	−0·08 (−0·15 to −0·02)	−0·10 (−0·16 to −0·03)	−0·11 (−0·17 to −0·05)	0·8112	0·4838
Percentage change	−0·5% (−2·6 to 1·6)	−1·5% (−3·6 to 0·6)	−2·0% (−4·0 to 0·1)	..	..
hsCRP (mg/L)†					
Baseline	3·57 (2·81)	3·89 (2·64)	3·83 (2·80)	..	..
Percentage change	−16·7% (−23·7 to −9·0)	−28·0% (−34·1 to −21·4)	−29·0% (−34·8 to −22·7)	0·0159*	0·0076*
Fasting insulin (pmol/L†)					
Baseline	78·7 (12·9)	79·0 (13·5)	77·2 (13·3)	..	..
Percentage change	−4·6% (−10·5 to 1·6)	−11·8% (−17·3 to −6·0)	−17·1% (−22·0 to −12·0)	0·0628	0·0007*
Fasting blood glucose (mmol/L)					
Baseline	5·21 (0·62)	5·28 (0·64)	5·23 (0·67)	..	..
Change	−0·07 (−0·13 to −0·01)	−0·13 (−0·19 to −0·07)	−0·18 (−0·24 to −0·12)	0·1584	0·0104*
Percentage change	−0·7% (−1·9 to 0·5)	−1·9% (−3·1 to −0·7)	−2·6% (−3·7 to −1·4)	..	..
HOMA-IR†					
Baseline	2·6 (2·0)	2·6 (2·0)	2·6 (2·0)	..	..
Percentage change	−5·9% (−12·1 to 0·7)	−14·3% (−20·1 to −8·1)	−20·2% (−25·3 to −14·8)	0·0442	0·0003*
IWQOL-Lite total score‡					
Baseline	71·8 (17·2)	70·7 (17·0)	70·3 (16·5)	..	..
Change	8·6 (−7·5 to 9·6)	11·7 (10·6 to 12·7)	12·7 (11·6 to 13·8)	<0·0001*	<0·0001*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IDS-SR total score§					
Baseline	6·2 (5·0)	6·5 (5·5)	6·7 (5·5)	..	..
Change	−0·7 (−1·1 to −0·3)	0·0 (−0·4 to 0·4)	−0·3 (−0·7 to 0·1)	0·0080	0·1017

Data are for the primary analysis population. Baseline values are mean (SD); change and percentage change values are least squares mean (95% CI). hsCRP=high-sensitivity C-reactive protein. HOMA-IR=homoeostasis model assessment for insulin resistance. IWQOL-Lite=Impact of Weight on Quality of Life-Lite questionnaire. IDS-SR=Inventory of Depressive Symptomatology Self Report. *Endpoints that were significant according to the prespecified sequential closed testing procedure undertaken to correct for multiple comparisons. †Values that were $\log_{10}$ transformed before statistical analyses (to reduce skewness). Baseline values are geometric mean (SD); percentage change values are least squares geometric mean minus one (95% CI). ‡IWQOL-Lite total score is based on a scale from 0 to 100, where a score of 0–70 indicates severe impairment, 71–79 indicates moderate impairment, 80–87 indicates mild impairment, and 88–100 indicates no impairment. §IDS-SR total score is based on 30 items, where the score can range from 0 to 84; a total score of 13 or lower indicates no depression.

Table 3: **Secondary endpoints at 56 weeks**

	Placebo	Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion	p value for comparison with placebo	
				Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion
Waist circumference (cm)					
Baseline	110·0 (12·2)	109·8 (11·2)	108·8 (11·3)	..	..
Change	−2·5 (−3·3 to −1·6)	−5·0 (−5·9 to −4·2)	−6·2 (−7·1 to −5·4)	<0·0001*	<0·0001*
Triglycerides (mmol/L)†					
Baseline	1·28 (0·02)	1·23 (0·02)	1·31 (0·02)	..	..
Percentage change	−3·1% (−6·6 to 0·6)	−8·0% (−11·4 to −4·4)	−12·7% (−15·8 to −9·5)	0·0461*	<0·0001*
HDL cholesterol (mmol/L)					
Baseline	1·35 (0·35)	1·35 (0·35)	1·34 (0·35)	..	..
Change	0·00 (−0·02 to 0·02)	0·09 (0·06 to 0·11)	0·09 (0·07 to 0·11)	<0·0001*	<0·0001*
Percentage change	0·8% (−1·0 to 2·5)	7·6% (5·9 to 9·4)	8·0% (6·3 to 9·7)	..	..
LDL cholesterol (mmol/L)					
Baseline	3·10 (0·90)	3·23 (0·84)	3·08 (0·84)	..	..
Change	−0·08 (−0·15 to −0·02)	−0·10 (−0·16 to −0·03)	−0·11 (−0·17 to −0·05)	0·8112	0·4838
Percentage change	−0·5% (−2·6 to 1·6)	−1·5% (−3·6 to 0·6)	−2·0% (−4·0 to 0·1)	..	..
hsCRP (mg/L)†					
Baseline	3·57 (2·81)	3·89 (2·64)	3·83 (2·80)	..	..
Percentage change	−16·7% (−22·7 to −9·9)	−28·0% (−34·1 to −21·4)	−29·0% (−34·8 to −22·7)	0·0150*	0·0076*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IWQOL-Lite total score‡					
Baseline	71·8 (17·2)	70·7 (17·0)	70·3 (16·5)	..	..
Change	8·6 (−7·5 to 9·6)	11·7 (10·6 to 12·7)	12·7 (11·6 to 13·8)	<0·0001*	<0·0001*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IDS-SR total score§					
Baseline	6·2 (5·0)	6·5 (5·5)	6·7 (5·5)	..	..
Change	−0·7 (−1·1 to −0·3)	0·0 (−0·4 to 0·4)	−0·3 (−0·7 to 0·1)	0·0080	0·1017

Data are for the primary analysis population. Baseline values are mean (SD); change and percentage change values are least squares mean (95% CI). hsCRP=high-sensitivity C-reactive protein. HOMA-IR=homoeostasis model assessment for insulin resistance. IWQOL-Lite=Impact of Weight on Quality of Life-Lite questionnaire. IDS-SR=Inventory of Depressive Symptomatology Self Report. *Endpoints that were significant according to the prespecified sequential closed testing procedure undertaken to correct for multiple comparisons. †Values that were $\log_{10}$ transformed before statistical analyses (to reduce skewness). Baseline values are geometric mean (SD); percentage change values are least squares geometric mean minus one (95% CI). ‡IWQOL-Lite total score is based on a scale from 0 to 100, where a score of 0–70 indicates severe impairment, 71–79 indicates moderate impairment, 80–87 indicates mild impairment, and 88–100 indicates no impairment. §IDS-SR total score is based on 30 items, where the score can range from 0 to 84; a total score of 13 or lower indicates no depression.

Table 3: Secondary endpoints at 56 weeks

	Placebo	Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion	p value for comparison with placebo	
				Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion
Waist circumference (cm)					
Baseline	110·0 (12·2)	109·8 (11·2)	108·8 (11·3)	..	..
Change	−2·5 (−3·3 to −1·6)	−5·0 (−5·9 to −4·2)	−6·2 (−7·1 to −5·4)	<0·0001*	<0·0001*
Triglycerides (mmol/L)†					
Baseline	1·28 (0·02)	1·23 (0·02)	1·31 (0·02)	..	..
Percentage change	−3·1% (−6·6 to 0·6)	−8·0% (−11·4 to −4·4)	−12·7% (−15·8 to −9·5)	0·0461*	<0·0001*
HDL cholesterol (mmol/L)					
Baseline	1·35 (0·35)	1·35 (0·35)	1·34 (0·35)	..	..
Change	0·00 (−0·02 to 0·02)	0·09 (0·06 to 0·11)	0·09 (0·07 to 0·11)	<0·0001*	<0·0001*
Percentage change	0·8% (−1·0 to 2·5)	7·6% (5·9 to 9·4)	8·0% (6·3 to 9·7)	..	..
LDL cholesterol (mmol/L)					
Baseline	3·10 (0·90)	3·23 (0·84)	3·08 (0·84)	..	..
Change	−0·08 (−0·15 to −0·02)	−0·10 (−0·16 to −0·03)	−0·11 (−0·17 to −0·05)	0·8112	0·4838
Percentage change	−0·5% (−2·6 to 1·6)	−1·5% (−3·6 to 0·6)	−2·0% (−4·0 to 0·1)	..	..
hsCRP (mg/L)†					
Baseline	3·57 (2·81)	3·89 (2·64)	3·83 (2·80)	..	..
Percentage change	−16·7% (−33·7 to 0·0)	−28·0% (−34·1 to −21·4)	−29·0% (−34·8 to −22·7)	0·0150*	0·0076*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IWQOL-Lite total score‡					
Baseline	71·8 (17·2)	70·7 (17·0)	70·3 (16·5)	..	..
Change	8·6 (−7·5 to 9·6)	11·7 (10·6 to 12·7)	12·7 (11·6 to 13·8)	<0·0001*	<0·0001*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IDS-SR total score§					
Baseline	6·2 (5·0)	6·5 (5·5)	6·7 (5·5)	..	..
Change	−0·7 (−1·1 to −0·3)	0·0 (−0·4 to 0·4)	−0·3 (−0·7 to 0·1)	0·0080	0·1017

Data are for the primary analysis population. Baseline values are mean (SD); change and percentage change values are least squares mean (95% CI). hsCRP=high-sensitivity C-reactive protein. HOMA-IR=homoeostasis model assessment for insulin resistance. IWQOL-Lite=Impact of Weight on Quality of Life-Lite questionnaire. IDS-SR=Inventory of Depressive Symptomatology Self Report. *Endpoints that were significant according to the prespecified sequential closed testing procedure undertaken to correct for multiple comparisons. †Values that were $\log_{10}$ transformed before statistical analyses (to reduce skewness). Baseline values are geometric mean (SD); percentage change values are least squares geometric mean minus one (95% CI). ‡IWQOL-Lite total score is based on a scale from 0 to 100, where a score of 0–70 indicates severe impairment, 71–79 indicates moderate impairment, 80–87 indicates mild impairment, and 88–100 indicates no impairment. §IDS-SR total score is based on 30 items, where the score can range from 0 to 84; a total score of 13 or lower indicates no depression.

Table 3: Secondary endpoints at 56 weeks

Bupropion is considered fairly safe as a treatment for smoking cessation. However, patients can have insomnia, and generalised seizures occur in 0·1–0·4% of patients.[5] Other side-effects are agitation and anxiety. Bupropion is associated with a slight increase in blood pressure and heart rate, and perhaps even suicidal behaviour.[6–8] These side-effects are major problems when treating obese patients who often have hypertension and other cardiovascular risk factors.

Naltrexone is an opioid-receptor antagonist and several relevant adverse events have been reported in the management of opioid-addiction disorders, such as difficulty sleeping, anxiety, nervousness, and headache. Naltrexone might also increase blood pressure during stress.[9] If the adverse effects of bupropion and naltrexone are additive, the combination could be expected to produce frequent CNS (insomnia, anxiety) and cardiovascular effects (increased blood pressure) that are difficult to accept for a weight-loss compound.

…y weight-loss drugs?

Published Online July 30, 2010 DOI:10.1016/S0140-6736(10)60999-3

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…propion is considered fairly safe as a treatment …smoking cessation. However, patients can have …nnia, and generalised seizures occur in 0·1–0·4% of …nts.[5] Other side-effects are agitation and anxiety. …opion is associated with a slight increase in blood …ure and heart rate, and perhaps even suicidal …viour.[6–8] These side-effects are major problems when …ing obese patients who often have hypertension …other cardiovascular risk factors.

…ltrexone is an opioid-receptor antagonist and …al relevant adverse events have been reported in …nanagement of opioid-addiction disorders, such as …ulty sleeping, anxiety, nervousness, and headache. …exone might also increase blood pressure …g stress.[9] If the adverse effects of bupropion and …exone are additive, the combination could be …cted to produce frequent CNS (insomnia, anxiety) …cardiovascular effects (increased blood pressure) …are difficult to accept for a weight-loss compound.

…oday's trial, the most relevant adverse events were …ea (combination treatment, highest dose 30% *vs* …bo 5%), headache (14% *vs* 9%), and dizziness (9% *vs* …but combination treatment was not associated with …ening on various anxiety, depression, or suicidal …cale scores, nor were there more adverse events or …drawals due to these psychiatric conditions. These …ngs suggest that the combination might have …r adverse psychiatric effects than its components given separately, but a meta-analysis of all continuing or completed phase 3 studies of this combination treatment is needed to assess this effect more accurately.[10]

CNS effects and biomarkers of cardiovascular safety in the early stages of the development of anti-obesity drugs.

In *The Lancet* today, Frank Greenway and colleagues[4]

Lancet 2010; 376: 567-568

New obesity pill: new hopes, old fears

Corbis

On Dec 7, 2010, the US Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee gave a positive recommendation for the use of Contrave in the treatment of obesity and weight management, signalling a potentially major shift in attitude towards the disorder. Contrave, if finally approved by the FDA on Jan 31, 2011, will be the first new weight-loss drug to be approved for 10 years. The drug is a combination of bupropion, an antidepressant used to help patients to quit smoking, and naltrexone, an opioid antagonist prescribed for alcohol and drug addiction, thought to affect the reward pathway (system in which behaviour is regulated by induction of pleasure).

The use of such a drug to tackle a complex problem like obesity is worrying, especially when the benefits seem modest (a decrease in bodyweight of 5%) compared with the potential risks. Albeit no serious side-effects were recorded in the four phase-3 trials for Contrave (one of which was published in this journal), there are indices of serious risks associated with bupropion, such as suicidal thoughts, seizures, and serious cardiovascular effects. The FDA committee and the drug's manufacturer, Orexigen, agreed that a large trial to assess the risk of major cardiac events associated with Contrave was needed, but that this study could wait until after the approval.

Research into obesity has been fraught with difficulty, with many drugs having been withdrawn from the market in the past for safety reasons. The flexibility shown by the FDA in its ruling on Contrave may be motivated by a desire to encourage pharmaceutical companies to commit more funding into obesity research, as rates of obesity continue to soar. More than a third of the US population is obese, and two-thirds are either obese or overweight. But this drug showed weight loss only when combined with lifestyle modification, and should not be seen as a magic bullet. Governments should address the obesity epidemic through a comprehensive approach, focusing on the underlying causes of obesity, and not promoting medication of a disorder that should be treated with modifications of lifestyle, diet, and exercise. ■ *The Lancet*

For more on **the US Food And Drug Association** see http://www.fda.gov/

For more on the **Contrave phase-3 trial** see Articles *Lancet* 2010; **376**: 595–605

For more on **obesity statistics** see http://www.cdc.gov/obesity/data/index.html

An example : overweight & obesity

Finally :

A very limited size effect related to the evaluation criteria for efficacy

A concern related to the safety profile, including an effect on blood pressure opposite to the objective of protection against cardiovascular complications

An example : overweight & obesity

US labeling

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

SUICIDALITY AND ANTIDEPRESSANT DRUGS

CONTRAVE® is not approved for use in the treatment of major depressive disorder or other psychiatric disorders. CONTRAVE contains bupropion, the same active ingredient as some other antidepressant medications (including, but not limited to, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL and APLENZIN). Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older. In patients of all ages who are started on CONTRAVE, monitor closely for worsening, and for the emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. CONTRAVE is not approved for use in pediatric patients *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.

NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

Serious neuropsychiatric reactions have occurred in patients taking bupropion for smoking cessation *[see Warnings and Precautions (5.2)]*. The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke. Although CONTRAVE is not approved for smoking cessation, observe all patients for neuropsychiatric reactions. Instruct the patient to contact a healthcare provider if such reactions occur *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

CONTRAVE is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

An example : overweight & obesity

Finally :

A very limited size effect related to the evaluation criteria for efficacy

A concern related to the safety profile, including an effect on blood pressure opposite to the objective of protection against cardiovascular complications

And other issues such as the level of compliance to treatment during clinical trials (usually worse in current care conditions)

Should we consider this example* as a **real, tangible medical progress** ?

* Excerpts of publications and other public data are used in this presentation only for illustrative purpose.

An example : overweight & obesity

Second example in oncology

Another example

HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 December 2007

TARCEVA 25 mg, film-coated tablet (369 232-3)
TARCEVA 100 mg, film-coated tablet (369 234-6)
TARCEVA 150 mg, film-coated tablet (369 235-2)
Pack of 30

Applicant: ROCHE

erlotinib

List I
Medicine for hospital prescription only.
To be prescribed only by oncologists or haematologists, or doctors competent in oncology.
Medicinal product requiring specific monitoring during treatment.

*Extension of indication: Treatment of metastatic **pancreatic cancer**, in combination with gemcitabine*

http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/tarceva_ct_5077.pdf

Another example

285 patients received gemcitabine combined with **Tarceva** (261 patients with 100 mg and 24 patients with 150 mg) and 284 patients gemcitabine alone

Table 1 (results for the primary endpoint)

	Tarceva (months)	Placebo (months)	Δ (months)	CI of Δ	HR	CI of HR	p
Overall population							
Median overall survival	6.4	6.0	0.41	-0.54-1.64	0.82	0.69-0.98	0.028
Mean overall survival	8.8	7.6	1.16	-0.05-2.34			
Metastatic population							
Median overall survival	5.9	5.1	0.87	-0.26-1.56	0.80	0.66-0.98	0.029
Mean overall survival	8.1	6.7	1.43	0.17-2.66			
Population with locally advanced disease							
Median overall survival	8.5	8.2	0.36	-2.43-2.96	0.93	0.65-1.35	0.713
Mean overall survival	10.7	10.5	0.19	-2.43-2.69			

The ITT results for the primary endpoint showed a median survival of 6.4 months in the Tarceva-gemcitabine combination group vs 6 months for the gemcitabine monotherapy group showing an absolute **gain of 12 days (p=0.028)**.
An absolute **gain of 26 days (p=0.029)** was observed in favour of the group treated with the combination (5.9 months vs 5.1) in terms of median survival in the metastatic subgroup.
The following **adverse events were more frequent** in patients who received Tarceva: rash (69% vs 30%), diarrhoea (48% vs 36%), weight loss (39% vs 29%) and stomatitis (22% vs 12%).

Another example

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Applicant: ROCHE

erlotinib

List I
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To be prescribed only by oncologists or haematologists, or doctors competent in oncology.
Medicinal product requiring specific monitoring during treatment.

The Transparency Committee **did not recommend inclusion on the list of medicines reimbursed by National Insurance** and on the list of medicines approved for hospital use and various public services in this extension of indication

http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/tarceva_ct_5077.pdf

Third example on use of statins

Use of statins in primary prevention in elderly

Elders and exposure to statins (French statistics from the National Health Fund, 2012)

22% of 75+ were treated with statins
More than **50%** for primary prevention*

* Patients without a previous diagnosis of coronary artery disease, peripheral vascular disease or cerebrovascular disease

thebmj

BMJ 2014;349:g7820 doi: 10.1136/bmj.g7820 (Published 29 December 2014)

NEWS

Half of over 75s in US are taking cholesterol lowering drugs, report says

Jeanne Lenzer

New York

Nearly half (48%) of all US adults aged 75 or older are taking cholesterol lowering drugs, says a report by the Centers for Disease Control and Prevention's National Center for Health Statistics.[1] However, some professional groups have challenged the report's conclusion that "there is extensive and consistent evidence supporting the use of cholesterol-lowering medication

A professional association that participated in the Choosing Wisely campaign initiated by the American Board of Internal Medicine Foundation has called for doctors to stop routinely prescribing lipid lowering drugs to people over 70. In response to the Choosing Wisely campaign the association, known as AMDA (the Society for Post-Acute and Long-Term Care

Use of statins in primary prevention in elderly

Majority of patients included in CTs of statins in primary prevention are <75

An exception :

PROSPER - PROspective Study of Pravastatin in the Elderly at Risk (Lancet 2002; 360: 1623)

Ages between 70 and 82

Inclusion in case of either :

- Pre-existing vascular disease (coronary, cerebral or peripheral)
- Or raised risk of such disease because of smoking, hypertension, or diabetes.

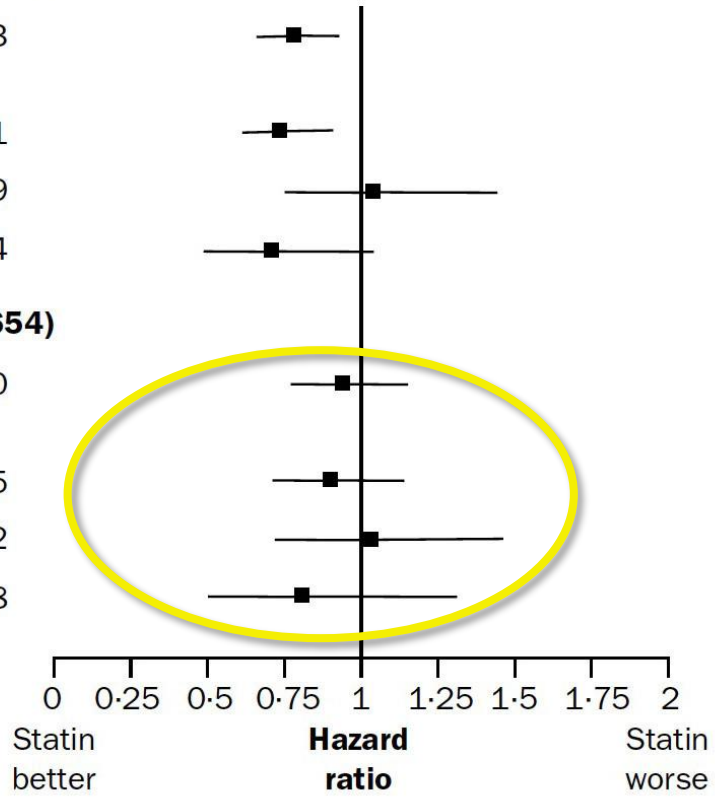
Plasma total cholesterol was required to be 4–9 mmol/L and their triglyceride concentrations less than 6 mmol/L.

Objective : evaluate if treatment with pravastatin reduces the risk of cardiac events, stroke, cognitive decline and disability in those with existing (secondary prevention) and in those at high risk of developing (primary prevention) vascular disease.

No benefit was found in the primary prevention group

Use of statins in primary prevention in elderly

	Pravastatin	Placebo
Secondary prevention	**(n=1306)**	**(n=1259)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	227	273
CHD death, non-fatal MI	166	211
Fatal and non-fatal stroke	74	69
TIA	47	64
Primary prevention	**(n=1585)**	**(n=1654)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	181	200
CHD death, non-fatal MI	126	145
Fatal and non-fatal stroke	61	62
TIA	30	38



Major cardiovascular outcomes, according to primary or secondary prevention status of participants

CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

Use of statins in primary prevention in elderly

Meta-analysis aggregating data from 61 prospective studies, total of 900,000 adults, nearly 12 million person years at risk between the ages of 40 and 89 years

Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths

*Prospective Studies Collaboration**

Summary

Background Age, sex, and blood pressure could modify the associations of total cholesterol (and its main two fractions, HDL and LDL cholesterol) with vascular mortality. This meta-analysis combined prospective studies of vascular mortality that recorded both blood pressure and total cholesterol at baseline, to determine the joint relevance of these two risk factors.

Methods Information was obtained from 61 prospective observational studies, mostly in western Europe or North America, consisting of almost 900 000 adults without previous disease and with baseline measurements of total cholesterol and blood pressure. During nearly 12 million person years at risk between the ages of 40 and 89 years, there were more than 55 000 vascular deaths (34 000 ischaemic heart disease [IHD], 12 000 stroke, 10 000 other). Information about HDL cholesterol was available for 150 000 participants, among whom there were 5000 vascular deaths (3000 IHD, 1000 stroke, 1000 other). Reported associations are with usual cholesterol levels (ie, corrected for the regression dilution bias).

Findings 1 mmol/L lower total cholesterol was associated with about a half (hazard ratio 0·44 [95% CI 0·42–0·48]), a third (0·66 [0·65–0·68]), and a sixth (0·83 [0·81–0·85]) lower IHD mortality in both sexes at ages 40–49, 50–69, and 70–89 years, respectively, throughout the main range of cholesterol in most developed countries, with no apparent threshold. The proportional risk reduction decreased with increasing blood pressure, since the absolute effects of cholesterol and blood pressure were approximately additive. Of various simple indices involving HDL cholesterol, the

Lancet 2007; 370: 1829–39

See **Comment** page 1803

*Collaborators listed in full at end of paper

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Use of statins in primary prevention in elderly

For patients of 70–89 y.o. :

- **No impact of lower cholesterol on mortality**
- Decrease in cardiovascular mortality, lower ischaemic heart disease mortality, increase in other causes of death

	Hazard ratio (95% CI)		
	IHD	Stroke	Other vascular
40–49 years	0·45 (0·42–0·47)	0·87 (0·76–1·00)	0·62 (0·55–0·69)
50–59 years	0·57 (0·55–0·58)	0·91 (0·85–0·97)	0·75 (0·71–0·79)
60–69 years	0·68 (0·66–0·69)	0·93 (0·89–0·97)	0·83 (0·80–0·86)
70–79 years	0·79 (0·78–0·81)	1·02 (0·97–1·06)	0·89 (0·85–0·92)
80–89 years	0·85 (0·82–0·89)	1·05 (0·98–1·11)	1·02 (0·96–1·09)

Hazard ratios for IHD (ischaemic heart disease), stroke and other vascular mortality for 1 mmol/L lower usual total cholesterol

A previous meta-analysis (Ann Epidemiol 2004; 14: 705) reported that total cholesterol showed an inverse relationship with all-cause mortality in elderly over the age of 80

Use of statins in primary prevention in elderly

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PRACTICE GUIDELINE

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults☆

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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The American College of Cardiology requests that this document be cited as follows: Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.

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Individuals >75 years of age

Few data were available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD.

Therefore, initiation of statins for primary prevention of ASCVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care.

Use of statins in primary prevention in elderly

Large use of statins in elderly, especially for primary prevention of cardiovascular events

Lack of strong evidence on benefit in primary prevention, in particular in a context of relatively limited life expectancy and possible co-morbidities

Increase of mortality with low values of cholesterol

Risk of frequent adverse events (myalgia, athralgia, digestive disorders,…), risk of drug interactions

Consequences at distance of initial market access

Do we need to treat ?
Need for **real life studies** to better assess the use and evaluate impacts on morbidity, QoL and mortality ?
Need for guidelines adapted to these populations to answer precisely to practical situations :
- **Initiation or not** in elderly ? At what age ?
- **When to discontinue a pre-existing statin therapy** ?

Thank you for your attention

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