

ORIGINAL ARTICLE

Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations

McKeever et al. NEJM 2018

CREMA

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Conclusion

- Un plan d'auto-gestion de l'asthme proposant un quadruplement temporaire des doses de corticostéroïdes inhalés quand le contrôle de l'asthme commence à se détériorer, résulte en moins d'exacerbations sévères que lorsque les doses ne sont pas augmentées.



Méthode

- Essai clinique randomisé
- Non aveugle
- Suivi 12 mois

Recrutement

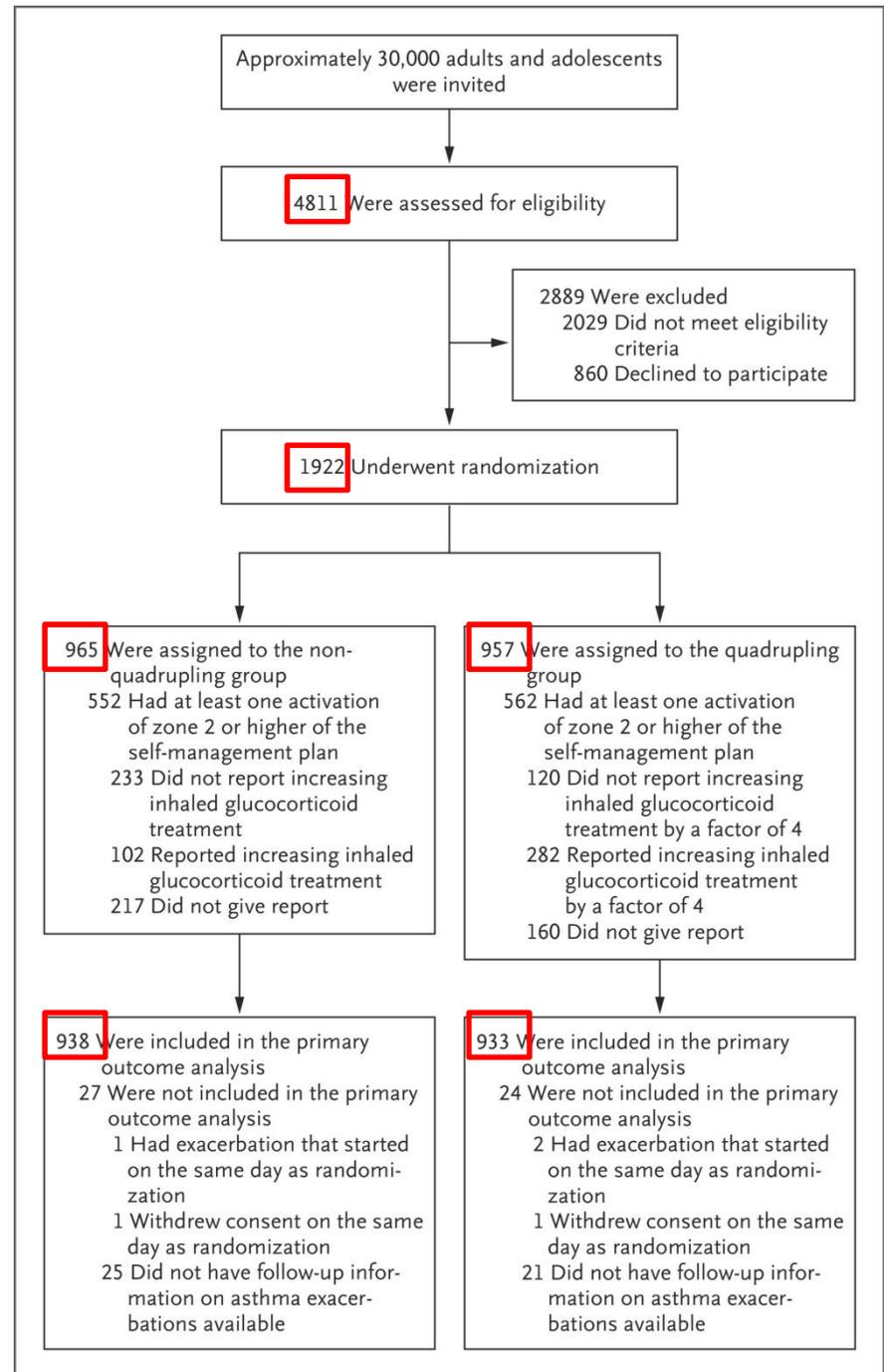
Critères :

Inclusion:

- >16 ans,
- asthmatique sous GCI,
- au moins 1 exacerbation dans l'année nécessitant cortico systémiques

Exclusion:

- BPCO >20 UPA
- Glucocorticoïdes oraux
- Grossesse (en cours ou planifiée), Allaitement
- Exacerbation <1 mois avant randomisation



Méthode

- Randomisation stratifiée par :
 - Région
 - Tabagisme
 - Dose habituelle de CSI

Table 2. Baseline Characteristics of the Participants.*

Characteristic	Non-Quadrupling Group (N=965)	Quadrupling Group (N=957)
Age — yr		
Mean	56.7±15.2	56.2±15.5
Range	19–94	16–91
Sex — no. (%)		
Male	316 (33)	301 (31)
Female	649 (67)	656 (69)
Source of recruitment — no. (%)		
Primary care	774 (80)	785 (82)
Secondary care	191 (20)	172 (18)
Mean peak expiratory flow at screening — liters/min	381.1±112.2	386.9±110.8
Type of inhaler — no. (%)		
Glucocorticoid	303 (31)	275 (29)
Combination	662 (69)	682 (71)
Smoking status — no. (%)		
Never smoked	552 (57)	564 (59)
Current smoker	66 (7)	59 (6)
Former smoker	347 (36)	334 (35)
Pack-years among current or former smokers		
No. of participants	413	393
Mean pack-yr	13.9±16.1	12.3±14.5

Intervention

Signes de moins bon contrôle de l'asthme:

- ↗ utilisation inhalateur
- ↗ troubles du sommeil liés à l'asthme
- Peak flow <80% de l'habituel

action



Quadrupling Group

- Inhalateur pour exacerbations + 4x la dose de CSI habituel
- Retour au traitement habituel après résolution des symptômes ou maximum après 14j

Non-Quadrupling Group

- Inhalateur pour exacerbations habituel

Plan d'autogestion du groupe **SANS** quadruplement

ZONE 1	ZONE 2	ZONE 3	ZONE 4
Your asthma is under control if: <ul style="list-style-type: none"> You have no or minimal symptoms during the day and night (wheezing, coughing, shortness of breath or tightness in the chest) You can do all of your normal activities without asthma symptoms Your peak flow reading is normal or near normal for you: _____ 	Your asthma is getting worse if you have ONE or MORE of the following: <ul style="list-style-type: none"> You need your reliever inhaler more than usual You have more difficulty sleeping because of your asthma Your peak flow is below _____ 	Your asthma is much more severe if you have ONE or MORE of the following: <ul style="list-style-type: none"> You need to take your reliever inhaler every four hours or more often You are unable to manage your normal activities You have symptoms during the day or night Your peak flow reading is below _____ 	It is an asthma emergency if any of the following happen: <ul style="list-style-type: none"> Your reliever inhaler (usually blue) does not help. One or more of your symptoms get worse (wheezing, coughing, shortness of breath or tightness in the chest) You are too breathless to speak Your peak flow reading is below _____
Action Take your preventer inhaler every day, even when you are feeling well. Your preventer inhaler is: _____ Take your reliever inhaler if you have symptoms. Your reliever inhaler is: _____	Action Use your reliever inhaler to relieve your symptoms and continue your preventer medication at your normal dose. If your symptoms get worse follow Zone 3 instructions	Action Continue taking your medicine as shown in Zone 2. Continue to take your reliever medicine when needed. If you have been prescribed steroid tablets, start taking them and let your doctor or asthma nurse know within 24 hours If you have not been prescribed steroid tablets see a doctor or asthma nurse urgently Take _____ 5mg Prednisolone tablets immediately and again every morning for _____ days or until your symptoms have improved and your peak flow is back to normal (as in Zone 1). For you this means _____ If you do not improve with these tablets go to Zone 4.	Action <ol style="list-style-type: none"> Take one to two puffs of your reliever inhaler (usually blue) Sit up and take slow steady breaths If you don't feel better, continue to take two puffs of your reliever inhaler every two minutes. You can take up to ten puffs If you do not feel better after taking your reliever inhaler as above or if you are worried at any time call 999 If an ambulance does not arrive within 15 minutes, and you do not feel any better, repeat step 3
If you are always in Zone 1, your doctor or asthma nurse may want to reduce your regular medicines.	Start to record your morning peak flow, symptoms and medication in the study diary.	If you are in Zone 3 ask your doctor or asthma nurse for an asthma review, even if you feel better.	If your symptoms improve and you do not need to call 999 you will need to see your doctor or asthma nurse within 24 hours Do not delay calling for help if your asthma is getting worse, day or night
If you have stopped your treatment for any reason you should restart it at the first sign of asthma	Phone you research nurse to arrange a study visit.	Do not ignore worsening asthma. Get medical help	This information does not apply to people using Symbicort SMART regime who should discuss their advice with their doctor or asthma nurse

- Même intervention dans les 2 groupes, avec explication du plan d'autogestion
- Seule différence dans les 2 groupes : zone 2, début de décompensation asthmatique

Plan d'autogestion du groupe **AVEC** quadrumplement

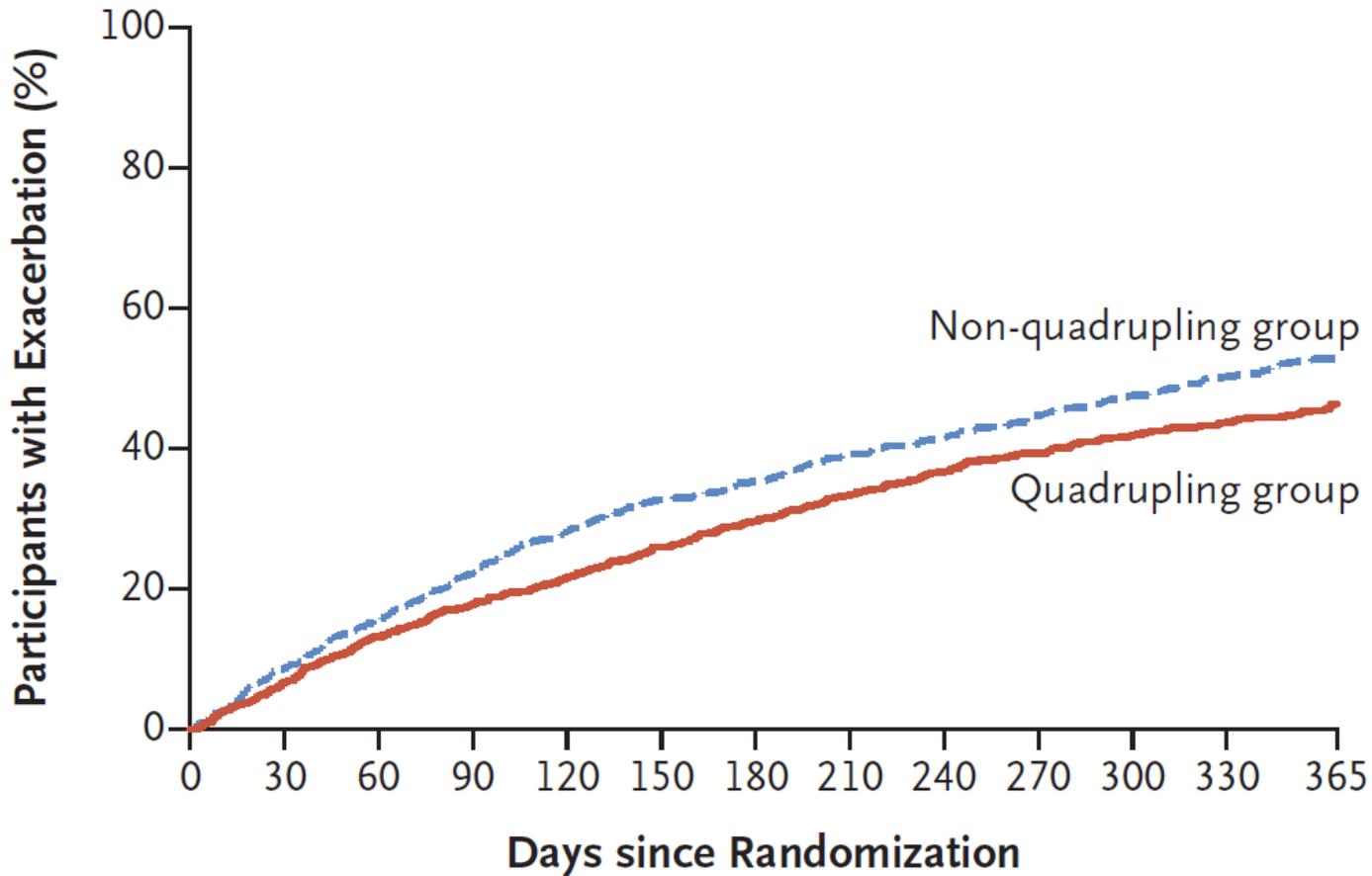
ZONE 1	ZONE 2	ZONE 3	ZONE 4
<p>Your asthma is under control if:</p> <ul style="list-style-type: none"> You have no or minimal symptoms during the day and night (wheezing, coughing, shortness of breath or tightness in the chest) You can do all of your normal activities without asthma symptoms <p>• Your peak flow reading is normal or near normal for you: _____</p>	<p>Your asthma is getting worse if you have ONE or MORE of the following:</p> <ul style="list-style-type: none"> You need your reliever inhaler more than usual You have more difficulty sleeping because of your asthma <p>• Your peak flow is below _____</p>	<p>Your asthma is much more severe if you have ONE or MORE of the following:</p> <ul style="list-style-type: none"> You need to take your reliever inhaler every four hours or more often You are unable to manage your normal activities You have symptoms during the day or night <p>• Your peak flow reading is below _____</p>	<p>It is an asthma emergency if any of the following happen:</p> <ul style="list-style-type: none"> Your reliever inhaler (usually blue) does not help. One or more of your symptoms get worse (wheezing, coughing, shortness of breath or tightness in the chest) You are too breathless to speak <p>• Your peak flow reading is below _____</p>
<p>Action</p> <p>Take your preventer inhaler every day, even when you are feeling well.</p> <p>Your preventer inhaler is: _____</p> <p>Take your reliever inhaler if you have symptoms.</p> <p>Your reliever inhaler is: _____</p>	<p>Action</p> <p>Use your reliever inhaler to relieve your symptoms and increase your preventer medication as described below:</p> <p>Write the plan here:</p> <div data-bbox="490 605 952 725" style="border: 1px solid black; height: 84px; width: 239px;"></div> <p>Once your symptoms or peak flow have returned to normal or after a maximum of 14 days return to your normal treatment.</p> <p>If your symptoms get worse follow Zone 3 instructions</p>	<p>Action</p> <p>Continue taking your medicine as shown in Zone 2.</p> <p>Continue to take your reliever medicine when needed.</p> <p>If you have been prescribed steroid tablets, start taking them and let your doctor or asthma nurse know within 24 hours</p> <p>If you have not been prescribed steroid tablets see a doctor or asthma nurse urgently</p> <p>Take _____ 5mg Prednisolone tablets immediately and again every morning for _____ days or until your symptoms have improved and your peak flow is back to normal (as in Zone 1). For you this means _____.</p>	<p>Action</p> <ol style="list-style-type: none"> 1. Take one to two puffs of your reliever inhaler (usually blue) 2. Sit up and take slow steady breaths 3. If you don't feel better, continue to take two puffs of your reliever inhaler every two minutes. You can take up to ten puffs 4. If you do not feel better after taking your reliever inhaler as above or if you are worried at any time call 999 5. If an ambulance does not arrive within 15 minutes, and you do not feel any better, repeat step 3
<p>If you are always in Zone 1, your doctor or asthma nurse may want to reduce your regular medicines.</p>	<p>Start to record your morning peak flow, symptoms and medication in the study diary.</p>	<p>If you are in Zone 3 ask your doctor or asthma nurse for an asthma review, even if you feel better.</p>	<p>If your symptoms improve and you do not need to call 999 you will need to see your doctor or asthma nurse within 24 hours</p> <p>Do not delay calling for help if your asthma is getting worse, day or night</p>
<p>If you have stopped your treatment for any reason you should restart it at the first sign of asthma</p>	<p>Phone you research nurse to arrange a study visit.</p>	<p>Do not ignore worsening asthma. Get medical help</p>	<p>This information does not apply to people using Symbicort SMART regime who should discuss their advice with their doctor or asthma nurse</p>

- Même intervention dans les 2 groupes, avec explication du plan d'autogestion
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Outcomes

- Primaire :
 - Temps avant 1^{ère} exacerbation sévère, définie comme :
 - consommation de glucocorticoïdes systémiques
 - consultation non planifiée pour l'asthme
- Secondaires:
 - Nombre de patients présentant une exacerbation sévère
 - Score qualité de vie
 - Peak Flow
 - Dose cumulée de corticoïdes inhalés et systémiques dans les 12 mois après la randomisation
- Sécurité:
 - Événements dans les 2 semaines après l'activation de la zone 2

Résultats: outcome 1^{er}



Résultats: outcomes 2nd

- 1114 (58%) ont atteint la zone 2 ou +

Exacerbation: use of systemic glucocorticoids and/or unscheduled healthcare consultation for asthma

Any exacerbations

No	445 (47%)	499 (53%)	Risk difference -6.7% (-11.2 to -2.3)	Risk ratio 0.87 (0.80 to 0.95)
Yes	485 (52%)	422 (45%)		
Not known ²	9 (1%)	14 (1%)		
	Non quadrupling group (n = 939)	Quadrupling group (n = 935)		

- PF et score de qualité de vie disponibles pour <50% des patients

Safety

Suivi des effets secondaires durant les 2 semaines après activation de la zone 2 :

- Événements indésirables **graves** (hospitalisations / pneumonies):
 - Groupe **dose quadruplée** : **2%** (**11** événements sérieux)
 - Groupe **dose non-quadruplée** : **4%** (**32** événements sérieux)

Dose quadruplée : moins d'effets indésirables graves (**p<0.001**)

- Événements indésirables **non-graves** (candidose orale / dysphonie):
 - Groupe **dose quadruplée** : **7%** (**36** événements)
 - Groupe **dose non-quadruplée** : **2%** (**13** événements)

Dose quadruplée : moins d'effets indésirables non-graves (**p<0.001**)

Discussion

- Points positifs
 - Peut être appliqué à notre pratique
 - Très peu de patients perdus de vue
 - Bénéfice de l'intervention démontrée lors analyses intention-to-treat et per protocol
- Limitations
 - Étude non aveuglée -> biais potentiels
 - Qualité des outcomes secondaires diminué par la nature pragmatique de l'étude
 - Magnitude du bénéfice limité? NNT 15

Merci



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