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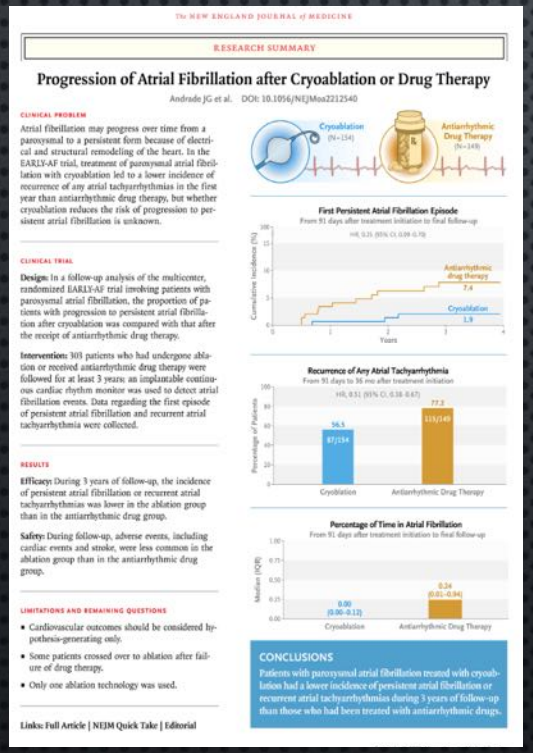


The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Progression of Atrial Fibrillation after Cryoablation or Drug Therapy

Andrade JG et al. DOI: 10.1056/NEJMoa2212540

CLINICAL PROBLEM

Atrial fibrillation may progress over time from a paroxysmal to a persistent form because of electrical and structural remodeling of the heart. In the EARLY-AF trial, treatment of paroxysmal atrial fibrillation with cryoablation led to a lower incidence of recurrence of any atrial tachyarrhythmias in the first year than antiarrhythmic drug therapy, but whether cryoablation reduces the risk of progression to persistent atrial fibrillation is unknown.

CLINICAL TRIAL

Design: In a follow-up analysis of the multicenter, randomized EARLY-AF trial involving patients with paroxysmal atrial fibrillation, the proportion of patients with progression to persistent atrial fibrillation after cryoablation was compared with that after the receipt of antiarrhythmic drug therapy.

Interventions: 303 patients who had undergone ablation or received antiarrhythmic drug therapy were followed for at least 3 years; an implantable continuous cardiac rhythm monitor was used to detect atrial fibrillation events. Data regarding the first episode of persistent atrial fibrillation and recurrent atrial tachyarrhythmia were collected.

RESULTS

Efficacy: During 3 years of follow-up, the incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias was lower in the ablation group than in the antiarrhythmic drug group.

Safety: During follow-up, adverse events, including cardiac events and stroke, were less common in the ablation group than in the antiarrhythmic drug group.

LIMITATIONS AND REMAINING QUESTIONS

- Cardiovascular outcomes should be considered hypothesis-generating only.
- Some patients crossed over to ablation after failure of drug therapy.
- Only one ablation technology was used.

Links: Full Article | NEJM Quick Take | Editorial

First Persistent Atrial Fibrillation Episode

From 91 days after treatment initiation to final follow-up

Recurrence of Any Atrial Tachyarrhythmia

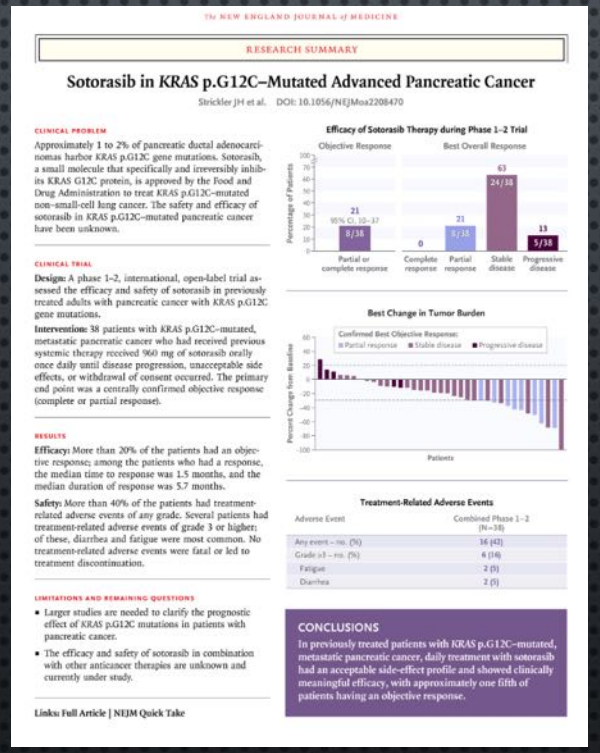
From 91 days to 36 mo after treatment initiation

Percentage of Time in Atrial Fibrillation

From 91 days after treatment initiation to final follow-up

CONCLUSIONS

Patients with paroxysmal atrial fibrillation treated with cryoablation had a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias during 3 years of follow-up than those who had been treated with antiarrhythmic drugs.



The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

Strickler JH et al. DOI: 10.1056/NEJMoa2208470

CLINICAL PROBLEM

Approximately 1 to 2% of pancreatic ductal adenocarcinomas harbor *KRAS* p.G12C gene mutations. Sotorasib, a small molecule that specifically and irreversibly inhibits KRAS G12C protein, is approved by the Food and Drug Administration to treat *KRAS* p.G12C–mutated non–small-cell lung cancer. The safety and efficacy of sotorasib in *KRAS* p.G12C–mutated pancreatic cancer have been unknown.

CLINICAL TRIAL

Design: A phase 1–2, international, open-label trial assessed the efficacy and safety of sotorasib in previously treated adults with pancreatic cancer with *KRAS* p.G12C gene mutations.

Interventions: 38 patients with *KRAS* p.G12C–mutated, metastatic pancreatic cancer who had received previous systemic therapy received 960 mg of sotorasib orally once daily until disease progression, unacceptable side effects, or withdrawal of consent occurred. The primary end point was a centrally confirmed objective response (complete or partial response).

RESULTS

Efficacy: More than 20% of the patients had an objective response; among the patients who had a response, the median time to response was 1.5 months, and the median duration of response was 5.7 months.

Safety: More than 40% of the patients had treatment-related adverse events of any grade. Several patients had treatment-related adverse events of grade 3 or higher; of these, diarrhea and fatigue were most common. No treatment-related adverse events were fatal or led to treatment discontinuation.

LIMITATIONS AND REMAINING QUESTIONS

- Larger studies are needed to clarify the prognostic effect of *KRAS* p.G12C mutations in patients with pancreatic cancer.
- The efficacy and safety of sotorasib in combination with other anticancer therapies are unknown and currently under study.

Links: Full Article | NEJM Quick Take

Efficacy of Sotorasib Therapy during Phase 1–2 Trial

Best Change in Tumor Burden

Treatment-Related Adverse Events

Adverse Event	Combined Phase 1–2 (N=38)
Any event — no. (%)	16 (42)
Grade ≥3 — no. (%)	6 (16)
Fatigue	2 (5)
Diarrhea	2 (5)

CONCLUSIONS

In previously treated patients with *KRAS* p.G12C–mutated, metastatic pancreatic cancer, daily treatment with sotorasib had an acceptable side-effect profile and showed clinically meaningful efficacy, with approximately one fifth of patients having an objective response.

DRA. SUSANA GARCIA ESCUDERO

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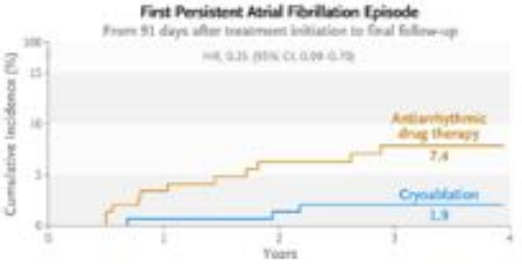

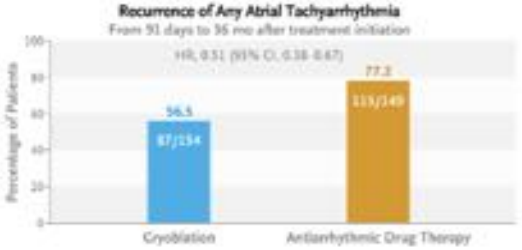

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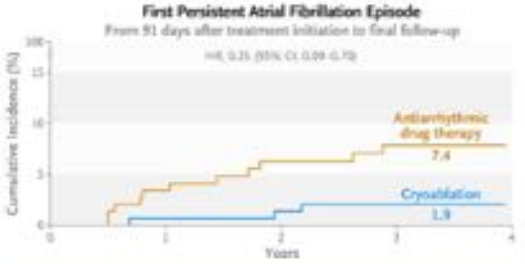

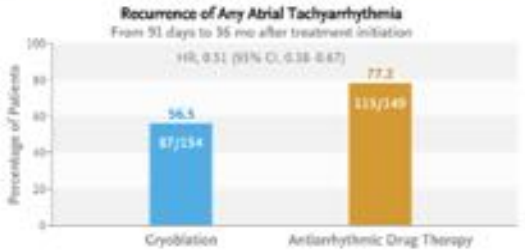

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Patients with paroxysmal atrial fibrillation treated with cryoablation had a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias during 3 years of follow-up than those who had been treated with antiarrhythmic drugs.

- Fibrilación auricular es un trastorno crónico y progresivo
- La progresión de fibrilación auricular paroxística (episodios de fibrilación auricular que duran <7 días continuos) a fibrilación auricular persistente (episodios de fibrilación auricular que duran ≥7 días continuos) ocurre en el 8% al 15% de los pacientes durante los 12 meses de seguimiento
- El objetivo principal del análisis de seguimiento actual fue evaluar el efecto del control del ritmo inicial sobre la progresión a la fibrilación auricular persistente según lo evaluado por un monitor de ritmo continuo implantable.

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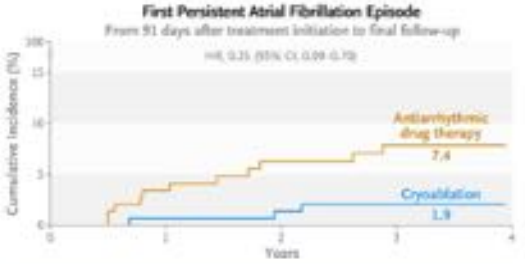

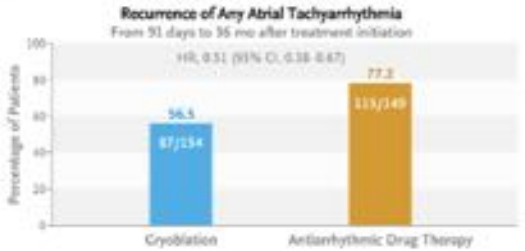

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Patients with paroxysmal atrial fibrillation treated with cryoablation had a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias during 3 years of follow-up than those who had been treated with antiarrhythmic drugs.

MÉTODO: ensayo aleatorizado (ensayo EARLY-AF), abierto, multicéntrico, 18 centros de Canadá

PARTICIPANTES:

- Mayores de 18 años
- Fibrilación auricular paroxística sintomática
- Al menos un episodio de fibrilación auricular documentado electrocardiográficamente dentro de los 24 meses anteriores a la aleatorización.
- Exclusión:
  antecedentes de uso diario de un fármaco antiarrítmico de clase I o clase III a dosis terapéuticas.
- Todos los pacientes dieron su consentimiento informado por escrito

PROCEDIMIENTO

- Inserción de un monitor cardíaco implantable (Reveal LINQ, Medtronic).
- Determinar el tiempo de aparición de la arritmia y cuantificar el porcentaje de tiempo en fibrilación.
- Se implantó en las primeras 24 horas tras inicio de la terapia con antiarrítmicos o del procedimiento de ablación con catéter.
- Anticoagulación oral : >65 años o CHADS $_2$ ≥1
- Grupo de ablación recibieron anticoagulación oral durante un mínimo de 3 meses después de la ablación, independientemente del riesgo de accidente cerebrovascular.

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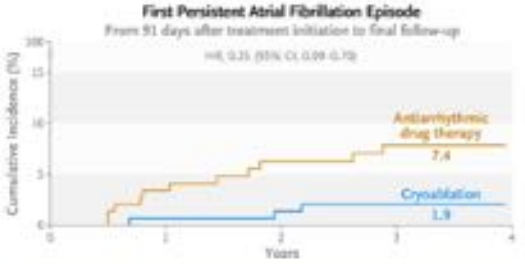

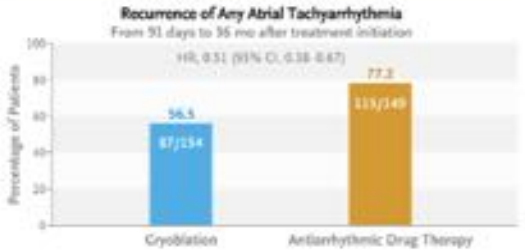

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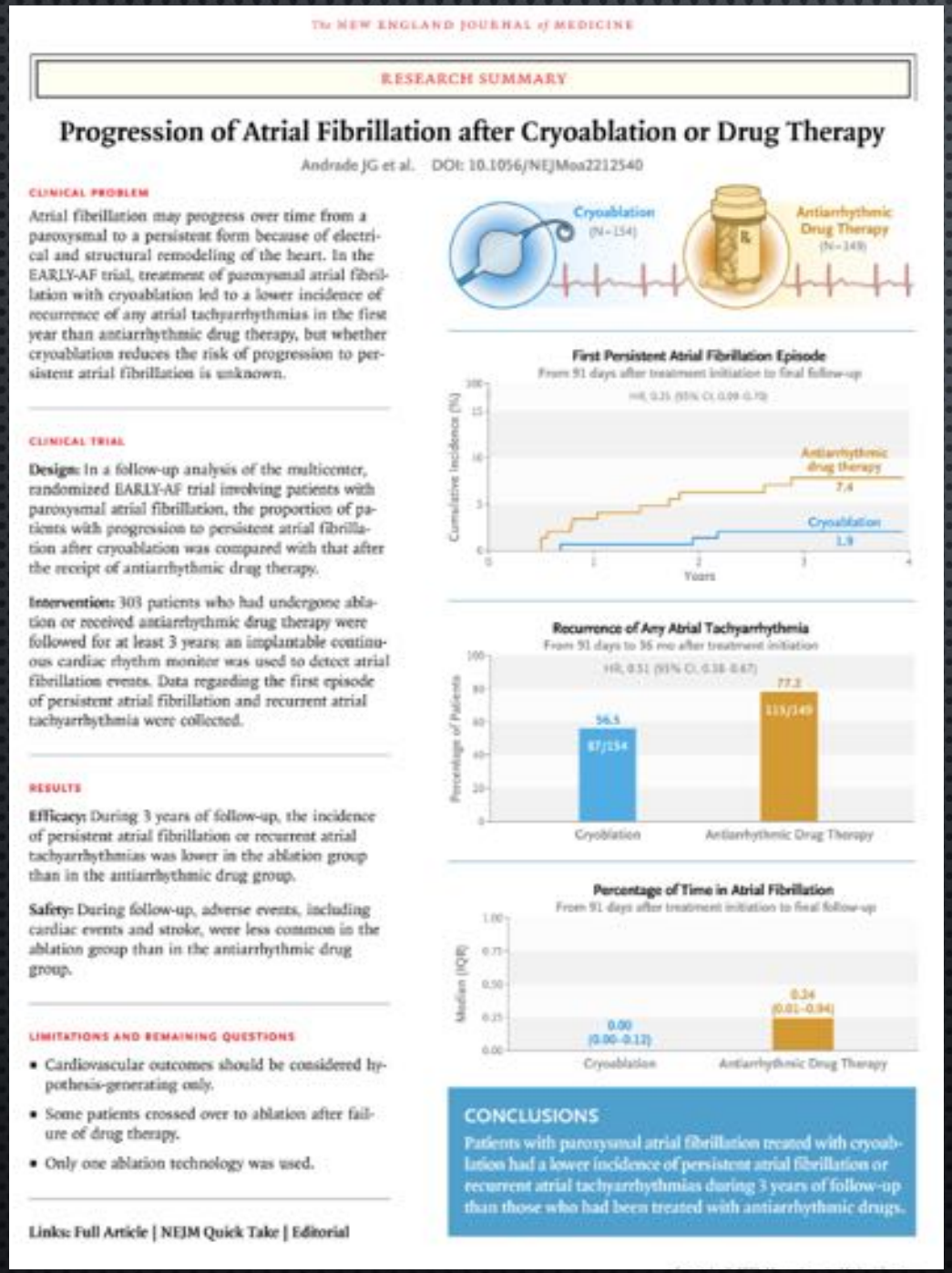
Patients with paroxysmal atrial fibrillation treated with cryoablation had a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias during 3 years of follow-up than those who had been treated with antiarrhythmic drugs.

MÉTODO: ensayo aleatorizado, abierto, multicéntrico, iniciado por el investigador, con adjudicación cegada del criterio de valoración en 18 centros de Canadá

PROCEDIMIENTO

- Los pacientes fueron seguidos durante al menos 3 años después del inicio del tratamiento (telefónica a los 7 días, visitas en persona a los 3, 6 y 12 meses y luego cada 6 meses)
- Las transmisiones automáticas del monitor cardíaco implantable se obtuvieron diariamente, y las transmisiones manuales se obtuvieron semanalmente.
- A los pacientes se les permitió cambiar de estrategia tras evaluación por comité:
  - Episodio de taquiarritmia auricular de 30 segundos o más que se produjera después del "período de cegamiento" (los primeros 90 días después del inicio del tratamiento)
  - Pacientes del grupo de fármacos antiarrítmicos, la recurrencia había ocurrido a pesar de recibir una dosis terapéutica de un fármaco antiarrítmico (definida como >100 mg por día de flecainida, >160 mg por día de sotalol, >300 mg por día de propafenona, o 800 mg por día de dronedarona)
  - Recurrencia de suficiente gravedad clínica para justificar un cambio en la terapia de acuerdo con la práctica clínica.



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MÉTODO: ensayo aleatorizado, abierto, multicéntrico, iniciado por el investigador, con adjudicación cegada del criterio de valoración en 18 centros de Canadá

PUNTOS FINALES

- **CRITERIO PRINCIPAL**: primera aparición de cualquier taquiarritmia auricular (fibrilación auricular, aleteo auricular o taquicardia auricular) con una duración de 30 segundos o más, entre 91 y 365 días después del inicio de un fármaco antiarrítmico o del procedimiento de ablación con catéter.
- **OBJETIVO PRINCIPAL**: evaluar la aparición de fibrilación auricular persistente (taquiarritmia auricular continua que dura ≥ 7 días o dura 48 horas a 7 días pero necesitando cardioversión)
- **PUNTOS SECUNDARIOS**:
  - Carga de arritmia (porcentaje de tiempo en FA)
  - Calidad de vida (encuensta)
  - Utilización de la atención médica: visitas a urgencias, hospitalizaciones, cardioversión o ablación (fuera de protocolo)y
  - Eventos adversos graves

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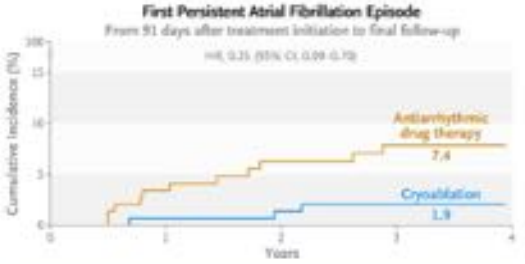

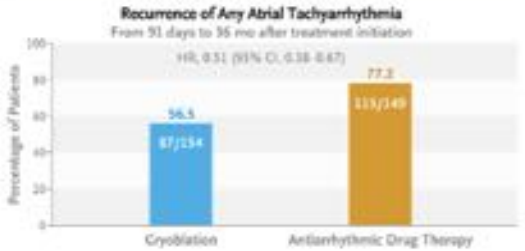

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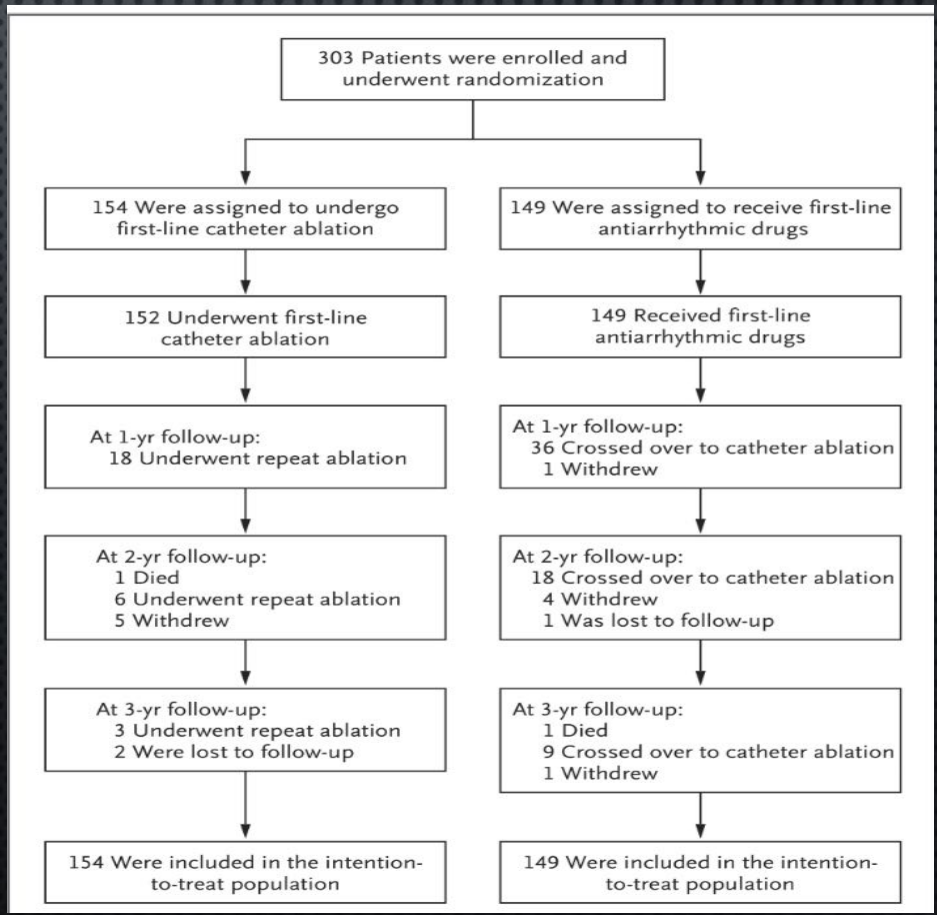
MÉTODO

- Entre el 17 de enero de 2017 y el 21 de diciembre de 2018: 303
- Asignaron al azar
- 3 años de seguimiento:
  - 63 de grupo fármacos se sometieron a ablación (recurrencia)
  - 27 de grupo de ablación se sometieron a ablación repetida
  - 2 (1 en cada grupo) murieron
  - 14 pacientes (7 en cada grupo) se retiraron del ensayo o se perdieron durante el seguimiento



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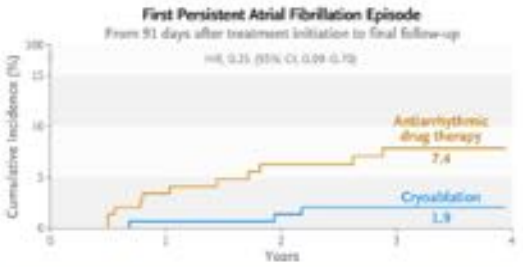

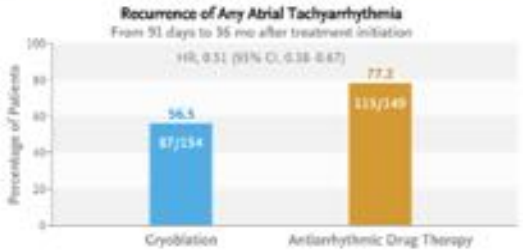

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Patients with paroxysmal atrial fibrillation treated with cryoablation had a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias during 3 years of follow-up than those who had been treated with antiarrhythmic drugs.

MÉTODO

- Características homogéneas en ambos grupos

SUPPLEMENTARY TABLE S1: Baseline Patient Characteristics, Stratified by The Entire Study Cohort at Enrollment and Those Completing 36 Months of Follow-Up*

Baseline Characteristics	Antiarrhythmic Group		Ablation Group	
	Entire cohort n=149	Completed 36 months follow-up n=141	Entire cohort n=154	Completed 36 months follow-up n=146
Age — yr	59.5±10.6	59.6±10.7	57.7±12.3	58.2±11.2
Male sex — no. (%)	102 (68.5)	97 (68.8)	112 (72.7)	105 (71.9)
BMI — kg/m^2	29.7±9.3	29.8±9.4	30.9±14.2	29.9±8.9
Obesity (BMI >30) — no. (%)	53 (35.6)	49 (34.8)	56 (36.6)	53 (36.3)
Median AF duration — years from first diagnosis (IQR)	1 (0, 4)	1 (0, 4)	1 (0, 3)	1 (0, 3)
Median Symptomatic AF episodes per month (IQR)	3 (1, 10)	3 (1, 10)	3 (1, 10)	3 (1, 10)
Prior cardioversion — no. (%)	63 (42.3)	59 (41.8)	56 (36.4)	54 (37.0)
Median CHA_2DS_2-VASc Score** — (IQR)	1 (0,2)	1 (0,2)	1 (0,2)	1 (0,2)
Medications — no. (%)				
Beta-blocker	92 (61.7)	85 (60.3)	85 (55.2)	80 (54.8)
Non-dihydropyridine calcium-channel blocker	10 (6.7)	9 (13)	11 (7.1)	11 (15)
ACE-Inhibitor	21 (14.1)	20 (29)	24 (15.6)	23 (31)
Angiotensin II receptor blocker	18 (12.1)	18 (26)	20 (13.0)	20 (27)
Mineralocorticoid-receptor antagonist	1 (0.7)	1 (1)	1 (0.7)	1 (1)
Oral Anticoagulation use				
Warfarin	9 (6.0)	9 (7.8)	5 (3.3)	5 (4.3)
DOAC	87 (58.4)	84 (59.6)	98 (63.6)	96 (65.8)
Concomitant Cardiovascular Conditions — no. (%)				
• Hypertension	55 (36.9)	53 (37.6)	57 (37.0)	54 (37.0)
• Ischemic heart disease	7 (4.7)	6 (4.3)	12 (7.8)	12 (8.2)
• Sleep Apnea	32 (21.5)	30 (21.3)	32 (20.8)	30 (20.5)
• Prior stroke or transient ischemic attack	5 (3.4)	5 (3.5)	4 (2.6)	4 (2.7)
• Tobacco Use	10 (6.7)	9 (6.4)	8 (5.2)	8 (5.5)
• Stable Heart Failure†	14 (9.4)	12 (8.5)	14 (9.1)	13 (9.8)
Left atrial diameter — mm	38.1±6.5	38.0±6.7	39.5±5.0	39.4±4.9
Left atrial volume — mL/m^2	35.4±12.5	35.0±12.4	35.6±15.2	34.9±14.8
Left ventricular ejection fraction — %	59.8±7.6	59.8±7.7	59.6±7.0	59.8±7.1

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Efficacy: During 3 years of follow-up, the incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias was lower in the ablation group than in the antiarrhythmic drug group.

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LIMITATIONS AND REMAINING QUESTIONS

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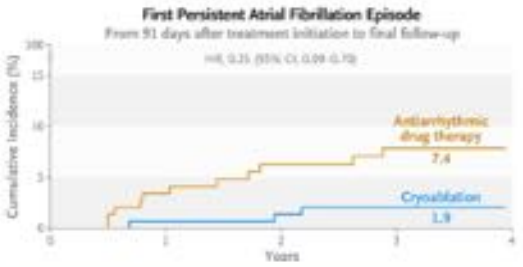

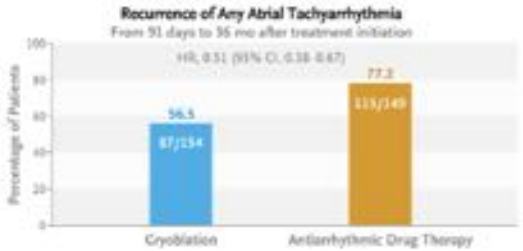

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MÉTODO

- La población inscrita reflejó las características demográficas esperadas de los pacientes con fibrilación auricular paroxística temprana

SUPPLEMENTARY TABLE S2. Representativeness of Study Participants

Category	
Disease, problem, or condition under investigation	Atrial Fibrillation (AF)
Special considerations related to:	
• Sex and Gender	Male sex is associated with a 1.5 to 2-fold risk of AF, even after adjusting for age and predisposing conditions.[12]
• Age	AF prevalence increases steeply with age; doubling with each decade of age.[12]
• Race or Ethnic Group	AF affects persons of White ethnicity disproportionately, with non-White ethnicities having a lower likelihood of developing AF (e.g., 0.49 for Blacks, 0.58 for Hispanics, 0.68 for Asians) despite having more comorbidities.[13]
• Geography	Geographical variations in AF incidence and prevalence exist, even after adjusting for socioeconomic status. These differences have been observed on a global (e.g., highest North America, lowest Africa), continental (e.g., highest Poland, lowest Serbia), and regional level (e.g., northern municipalities of Zealand vs. the rest of Denmark).[14]
Overall representativeness of this trial	The trial was designed to evaluate the effect of initial rhythm control treatment for patients with symptomatic treatment-naïve AF. By design, the study aimed to recruit patients who were at an early stage of their disease. As a result, the included patients were younger and relatively healthier (i.e., less comorbidities) than the overall population affected by AF. The participants in the present trial demonstrated the expected ratio based on self-identified sex (2:1 male:female) and were enrolled across Canada (7 of 10 Canadian Provinces). The enrolled population was predominantly of White ethnicity; however, the present trial demonstrated the expected ratios based on a combination of Canadian population demographics and the expected age-related prevalence of AF.

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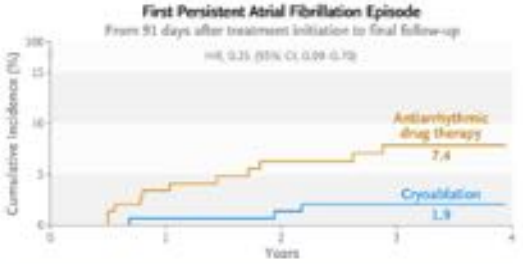

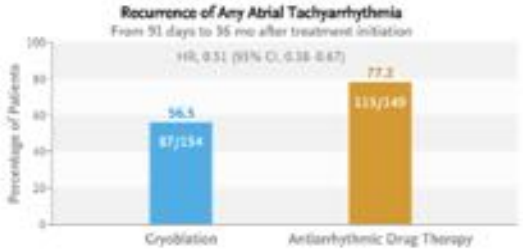

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MÉTODO

SUPPLEMENTARY TABLE S3: Antiarrhythmic Drug Dosing at Beginning and End of Follow-Up

	Beginning of Outcome Assessment Period		Final Follow-Up	
	Antiarrhythmic Drug N (%)	Median daily dose in mg/day (IQR)	Antiarrhythmic Drug N (%)	Median daily dose in mg/day (IQR)
Flecainide	98	200 (200, 300)	73	200 (150, 200)
Propafenone	12	600 (450, 600)	6	525 (412.5, 731.3)
Sotalol	19	240 (160, 320)	13	240 (160, 320)
Dronedarone	10	800 (800, 800)	5	800 (800, 800)
Amiodarone	10	200 (200, 200)	6	200 (200, 200)
None	--		46*	
Total	**149 (100%)**		**149 (100%)**	

IQR denotes interquartile range.

The outcome ascertainment period began on day 91 post treatment initiation. Recurrences of atrial tachyarrhythmia during these first 90 days were not counted in the determination of the first clinical failure for the primary end point to allow for medication optimization. During the first 90 days antiarrhythmic-drug therapy was progressively adjusted to the maximum tolerated doses according to standardized protocols, with the goal of complete suppression of atrial fibrillation as detected by the implanted monitor. In the event of inefficacy or intolerable side effects, a change to a second or third agent was specified during the first 90 days.

* The median number of antiarrhythmic drugs employed by the 46 patients that discontinued antiarrhythmic drug therapy during the follow-up period was 1.5 (IQR 1.0 to 2.0, range 1.0-4.0). Of the 46 patients, 43 discontinued following recurrence of any atrial tachyarrhythmia (inefficacy), one of which discontinued antiarrhythmic drugs following progression to persistent atrial tachyarrhythmia. Three patients discontinued antiarrhythmic drugs after prolonged periods of sinus rhythm maintenance (all of which had no documented recurrence over the entire follow-up period). Of the 43 patients that discontinued antiarrhythmic drug therapy after arrhythmia recurrence, 32 discontinued following a percutaneous catheter ablation procedure, and one patient discontinued following open-heart surgery (valve replacement and a concomitant surgical MAZE procedure). The remaining 10 patients discontinued antiarrhythmic drug therapy secondary to inefficacy combined with patient preference or side-effects.

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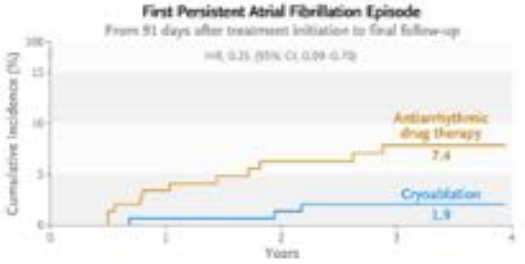

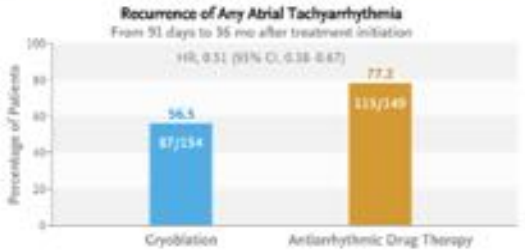

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MÉTODO

- La mediana de la puntuación de CHA_2DS_2-VASc al inicio del estudio fue 1 (rango intercuartílico, 0 a 2); las puntuaciones varían de 0 a 9
- Todos los pacientes con indicación de tratamiento preventivo del ictus recibieron anticoagulación oral (65,7% de los pacientes al inicio y 67,7% de los del seguimiento final)

SUPPLEMENTARY TABLE S4: Antithrombotic Therapy During the Study Period

	Baseline	Beginning of outcome assessment period*	Final follow-up
Warfarin — no.	14	14	14
Direct non-vitamin K oral anticoagulant — no.			
• Apixaban	65	97	69
• Dabigatran	15	15	16
• Edoxaban	4	10	4
• Rivaroxaban	101	118	102
Total	**199 (65.7%)**	**254† (83.8%)**	**205 (67.7%)**

For the antiarrhythmic group, the decision to initiate oral anticoagulation was based the Canadian Cardiovascular Society algorithm.[15-17] For those >65 years of age, or with a CHADS score of 1 or more, OAC with oral vitamin K antagonists (target INR between 2-3), low molecular weight heparin, or direct-acting non-VKA oral anticoagulant medications (DOACs) was strongly recommended. In patients <65 years of age and with a CHADS‡ score of 0, aspirin alone or no specific antithrombotic therapy may be considered at treating physician discretion.

For the ablation group, pre-procedure oral anticoagulation with oral vitamin K antagonists (target INR between 2-3), low molecular weight heparin, or direct-acting non-VKA oral anticoagulant medications (DOACs) was administered for at least one month prior to ablation (and/or the exclusion of a LA thrombus by a transesophageal echocardiogram within 48 hours of ablation). Intra-procedural anticoagulation was given as intravenous boluses and/or infusion of heparin, targeting an activated clotting time (ACT) of > 300 seconds. Post-procedure oral anticoagulation was re-administered within 4-6 hours of the procedure. Oral anticoagulation was continued for a minimum of 3 months post-ablation as catheter ablation damages the LA endothelium, creating a transient prothrombotic state, which may occur even in patients considered to have a low risk of stroke/systemic embolism by traditional risk schema. The decision to continue oral anticoagulation following the 3-month peri-procedural anticoagulation period was based the CCS algorithm.[15-17] Of note, AF ablation was not considered as an alternative to OAC.

Discontinuation of oral anticoagulation during the study period was strongly discouraged (except for patients <65 years of age and with a CHADS score of 0, in whom aspirin alone may be considered at treating physician discretion).

* The outcome ascertainment period began on day 91 post treatment initiation.

† Includes patients receiving peri-procedural oral anticoagulation therapy.

‡ The $CHADS_2$ score is a clinical estimation of the risk of stroke in patients with atrial fibrillation, where congestive heart failure, hypertension, age ≥75, and diabetes are given 1 point and history of stroke or transient ischemic attack are given 2 points.

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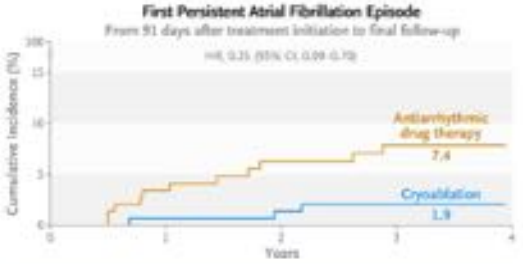

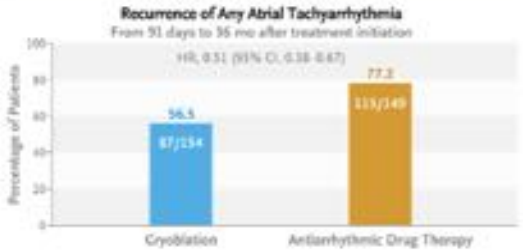

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RESULTADOS

FIBRILACIÓN AURICULAR PERSISTENTE

SUPPLEMENTARY TABLE S5: Occurrence of Persistent Atrial Fibrillation

Main Outcome:	Antiarrhythmic Group n=149	Ablation Group n=154	Treatment Effect
Progression to persistent atrial fibrillation — no. (%)	11 (7.4)	3 (1.9)	0.25 (0.09,0.70)*
Subcomponents of the Main Outcome			
Persistent atrial fibrillation lasting more than 7 days in duration — no. (%)	9 (6.0)	3 (1.9)	0.30 (0.10, 0.93)*
Cardioversion for atrial fibrillation lasting between 2 and 7 days in duration — no. (%)	7 (4.7)	1 (0.6)	0.14 (0.02, 0.85)†

* The treatment effect is expressed as the hazard ratio and 95% confidence interval.
† The treatment effect is expressed as the relative risk and 95% confidence interval.
The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

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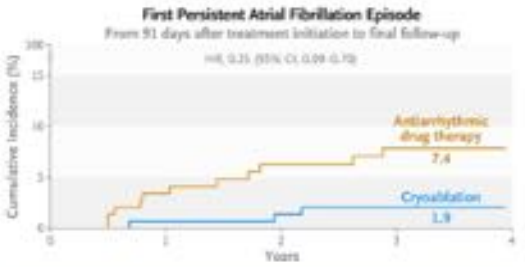

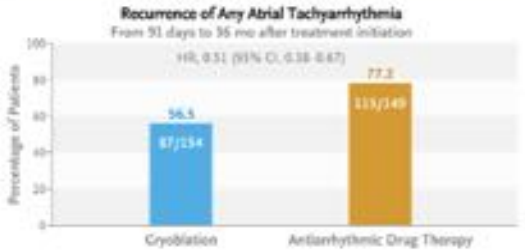

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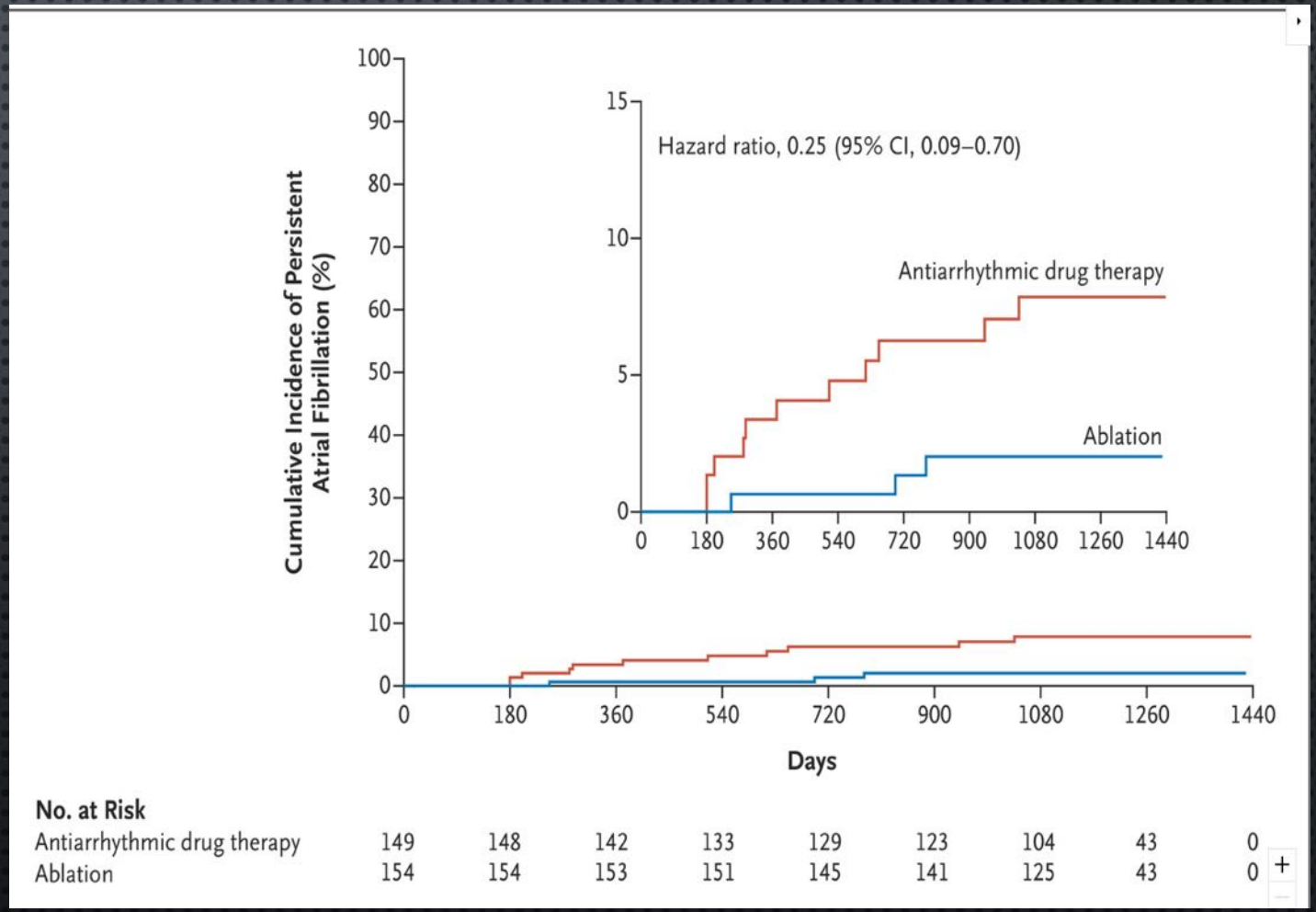

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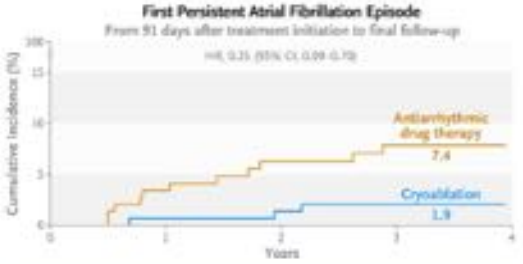

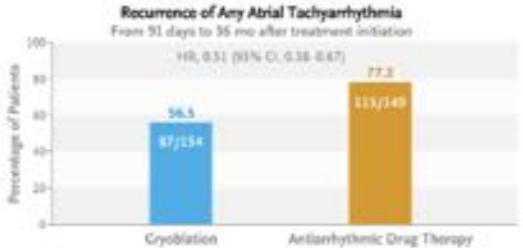

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FIBRILACIÓN AURICULAR PERSISTENTE - RECURRENCIA

Tabla 1. Puntos Finales Principales de Interés. *

punto final	Grupo de ablación (N=154)	Grupo de fármacos antiarrítmicos (N=149)	Cociente de riesgos instantáneos (IC del 95 %)
	número (porcentaje)		
Progresión a fibrilación auricular persistente desde 91 días después del inicio del tratamiento hasta el seguimiento final	3 (1,9)	11 (7,4)	0,25 (0,09–0,70)
Recurrencia de cualquier taquiarritmia auricular			
De 91 días a 12 meses después del inicio del tratamiento †	66 (42,9)	101 (67,8)	0,48 (0,35–0,66)
De 91 días a 36 meses después del inicio del tratamiento	87 (56,5)	115 (77,2)	0,51 (0,38–0,67)

* Los datos observados se muestran en las columnas del grupo de prueba. La razón de riesgo es una estimación del efecto basada en un modelo y se calculó con un análisis de regresión de Cox. Debido a que el plan de análisis estadístico no incluyó una disposición para corregir la multiplicidad al realizar pruebas para resultados secundarios u otros, los resultados se informan como estimaciones puntuales e intervalos de confianza del 95 %. Los anchos de los intervalos de confianza no se han ajustado por multiplicidad, por lo que los intervalos no deben usarse para inferir efectos de tratamiento definitivos para resultados secundarios.

† Los datos fueron informados previamente por Andrade et al. [11]

RESULTADOS

CARGA DE LA ARRITIMIA

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RESEARCH SUMMARY

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Andrade JG et al. DOI: 10.1056/NEJMoa2212540

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Atrial fibrillation may progress over time from a paroxysmal to a persistent form because of electrical and structural remodeling of the heart. In the EARLY-AF trial, treatment of paroxysmal atrial fibrillation with cryoablation led to a lower incidence of recurrence of any atrial tachyarrhythmias in the first year than antiarrhythmic drug therapy, but whether cryoablation reduces the risk of progression to persistent atrial fibrillation is unknown.

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Efficacy: During 3 years of follow-up, the incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias was lower in the ablation group than in the antiarrhythmic drug group.

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- Cardiovascular outcomes should be considered hypothesis-generating only.
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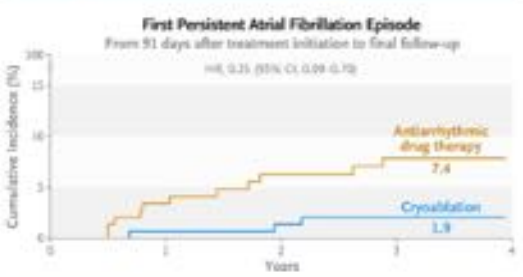
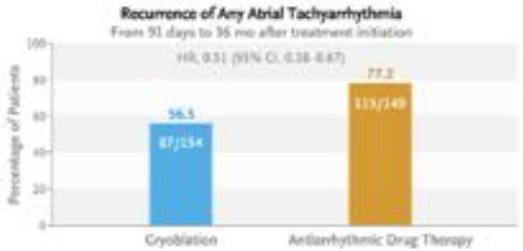
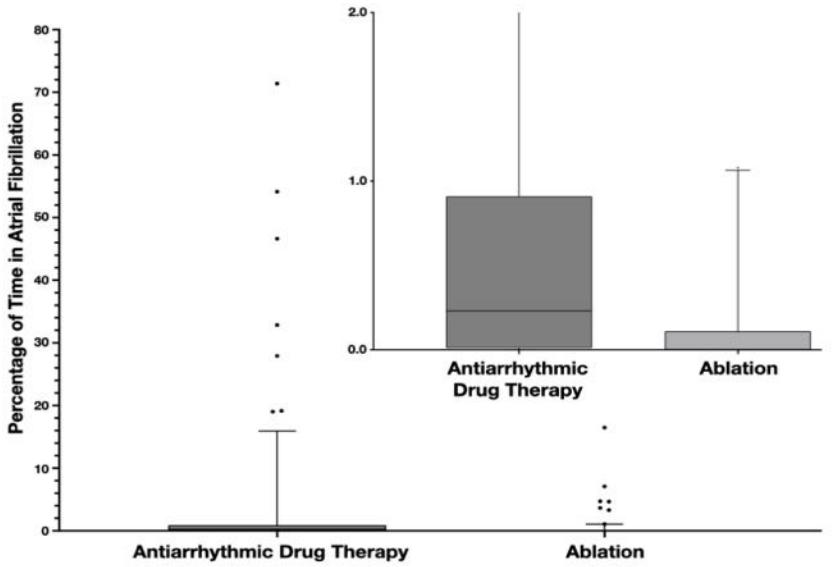




CONCLUSIONS

Patients with paroxysmal atrial fibrillation treated with cryoablation had a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias during 3 years of follow-up than those who had been treated with antiarrhythmic drugs.

SUPPLEMENTARY FIGURE S2. Atrial Fibrillation Burden in the Ablation and Antiarrhythmic Drug Groups



Shown are box-and-whisker plot of atrial fibrillation burden expressed as the percent time in atrial fibrillation (y axis). The inset demonstrates the whisker plots expressed on a y axis of 0.0% to 2.0%. The top T bar represents the 95th percentile, the top of the shaded box represents the 75th percentile, the middle line within the shaded box represents the 50th percentile, and the bottom of the shaded box represents the 25th percentile. The bottom whisker is meant to represent the 5th percentile. The circles beyond the upper whisker are data points for individual patients and are the outliers (beyond the 95th percentile).

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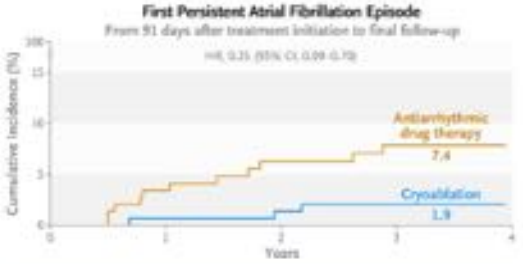

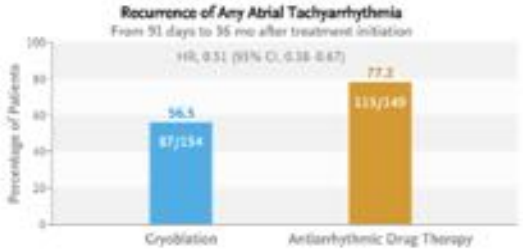

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SEGURIDAD

Table 3. Adverse Events.

Event	Ablation Group (N=154)	Antiarrhythmic Drug Group (N=149)
Any safety end-point event		
No. of patients with event	17	35
No. of events	20	41
Death — no.	1*	1†
Cardiac event — no.		
Pericardial effusion or tamponade	0	1‡
Pericarditis	0	0
Exacerbation of heart failure	0	2
Syncope	1	3
Wide-complex tachycardia or proarrhythmic event	0	2
Bradycardia or arteriovenous block for which pacemaker insertion was warranted	2	4
Acute coronary syndrome	0	3
Neurologic event — no.¶		
Stroke	0	2
Transient ischemic attack	0	1
Vascular event — no.		
Arteriovenous fistula	0	0
Hematoma for which intervention was not warranted	1	0
Pseudoaneurysm for which intervention was warranted	0	0
Deep-vein thrombosis	1	0
Pulmonary event — no.		
Persistent phrenic nerve palsy§	3	0
Pneumonia	1	0
Self-limited hemoptysis	1	1
Gastrointestinal event — no.		
Esophageal injury or perforation	0	0
Gastrointestinal upset such as indigestion or diarrhea	2	2
Acute pancreatitis	1	0
Bleeding in lower gastrointestinal tract	0	1
Adverse drug reaction leading to dose modification or discontinuation — no.		
Prolongation of QT interval	0	1
Presyncope	0	5
Tremor	0	1
Visual disturbance	0	1
Mild cognitive impairment	0	1
Insomnia	0	1
Angioedema	1	0
Other event — no.		
Erectile dysfunction	0	1
Rash	0	1
Epistaxis	2	0
Joint pain	0	2
Migraine	1	0
Sepsis	0	1
Mood disorder	2	0
Urinary retention	0	1
Arteritis	0	1
Nephrolithiasis	0	1

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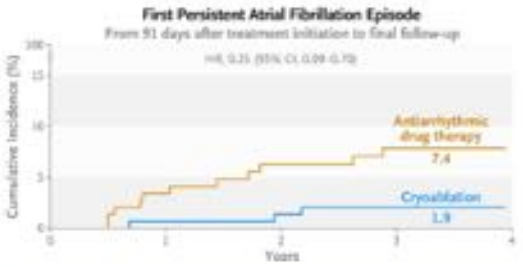

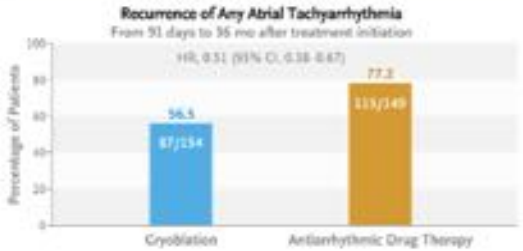

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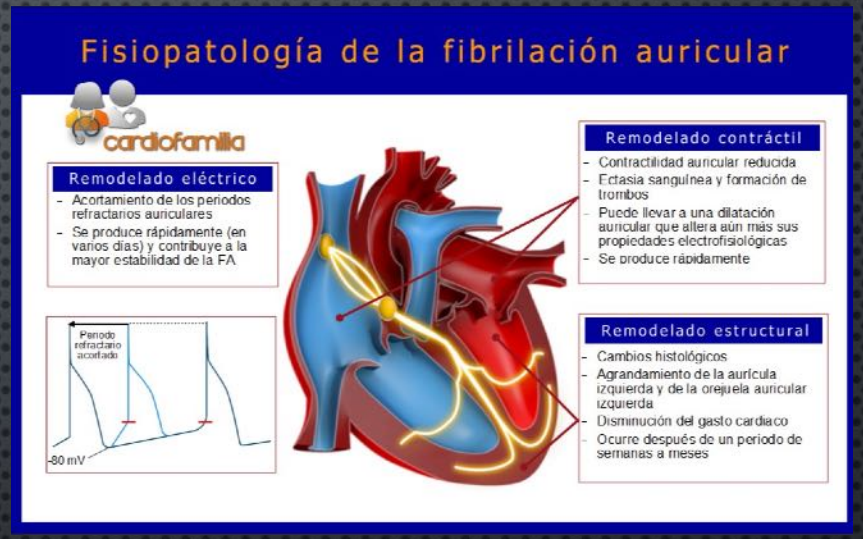
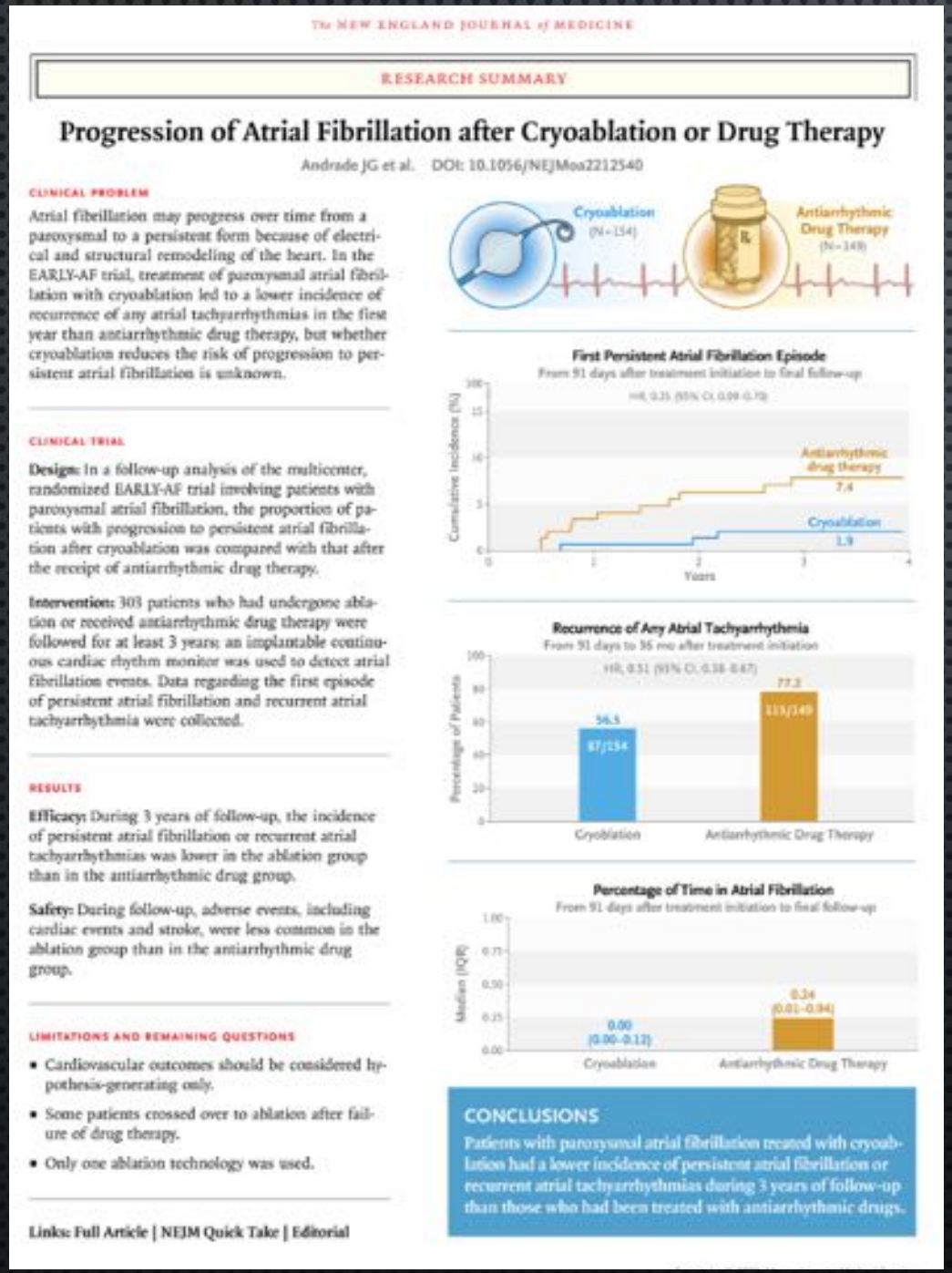
CONCLUSIÓN

- La ablación con catéter se asoció
  - ❑ Menor incidencia de fibrilación auricular persistente
  - ❑ Menor carga de arritmia



- La ablación con catéter se asocia con una reversión sustancial de la remodelación estructural
- La intervención temprana en la historia natural de la fibrilación auricular puede afectar la progresión de la enfermedad.
- **El seguimiento a largo plazo del ensayo EARLY-AF se basa en estas observaciones al mostrar que la ablación inicial con catéter fue potencialmente modificadora de la enfermedad**

- Ningún ensayo prospectivo o aleatorizado respalda la interrupción de la anticoagulación después de la ablación, por lo que la ablación con catéter no se considera una alternativa a la terapia de anticoagulación oral en pacientes con riesgo elevado de accidente cerebrovascular



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CONCLUSIONS

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LIMITACIONES

- Varios pacientes pasaron de la terapia con medicamentos antiarrítmicos a la ablación con catéter después del fracaso de la terapia médica para controlar los síntomas relacionados con la arritmia, aunque es posible que los pacientes no hayan recibido tratamiento suficiente
- Los resultados cardiovasculares solo pueden ser generadores de hipótesis
- Debido a que el ensayo se realizó con una sola tecnología de ablación, es posible que los resultados observados no se puedan generalizar a otras fuentes de energía de ablación

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RESEARCH SUMMARY

Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

Strickler JH et al. DOI: 10.1056/NEJMoa2208470

CLINICAL PROBLEM

Approximately 1 to 2% of pancreatic ductal adenocarcinomas harbor *KRAS* p.G12C gene mutations. Sotorasib, a small molecule that specifically and irreversibly inhibits its KRAS G12C protein, is approved by the Food and Drug Administration to treat *KRAS* p.G12C–mutated non–small-cell lung cancer. The safety and efficacy of sotorasib in *KRAS* p.G12C–mutated pancreatic cancer have been unknown.

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Design: A phase 1–2, international, open-label trial assessed the efficacy and safety of sotorasib in previously treated adults with pancreatic cancer with *KRAS* p.G12C gene mutations.

Intervention: 38 patients with *KRAS* p.G12C–mutated, metastatic pancreatic cancer who had received previous systemic therapy received 960 mg of sotorasib orally once daily until disease progression, unacceptable side effects, or withdrawal of consent occurred. The primary end point was a centrally confirmed objective response (complete or partial response).

RESULTS

Efficacy: More than 20% of the patients had an objective response; among the patients who had a response, the median time to response was 1.5 months, and the median duration of response was 5.7 months.

Safety: More than 40% of the patients had treatment-related adverse events of any grade. Several patients had treatment-related adverse events of grade 3 or higher; of these, diarrhea and fatigue were most common. No treatment-related adverse events were fatal or led to treatment discontinuation.

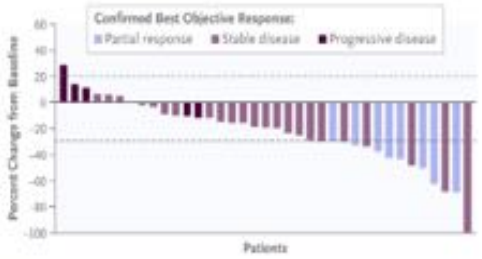
LIMITATIONS AND REMAINING QUESTIONS

- Larger studies are needed to clarify the prognostic effect of *KRAS* p.G12C mutations in patients with pancreatic cancer.
- The efficacy and safety of sotorasib in combination with other anticancer therapies are unknown and currently under study.

Links: Full Article | NEJM Quick Take

Efficacy of Sotorasib Therapy during Phase 1–2 Trial

Best Change in Tumor Burden

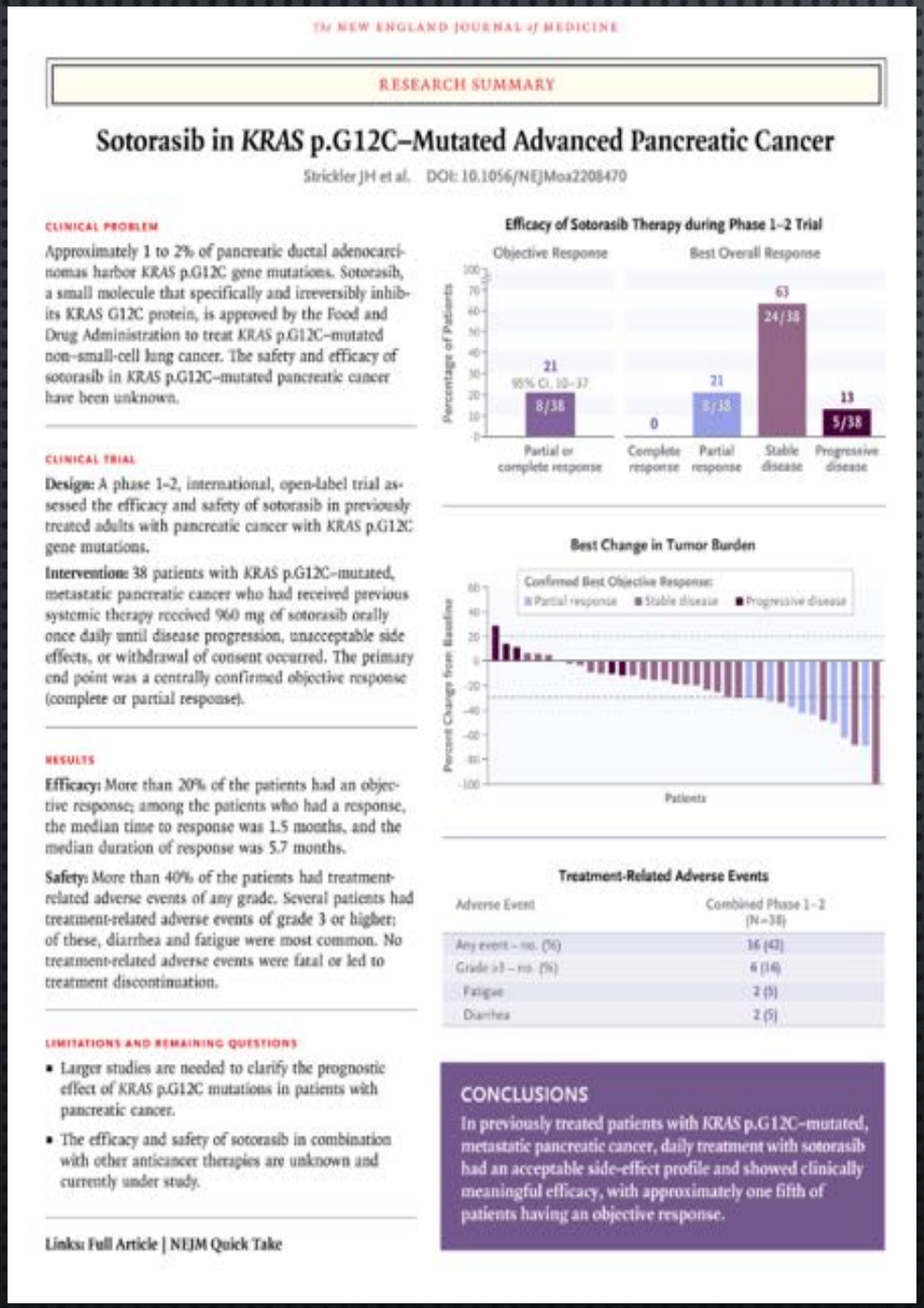


Treatment-Related Adverse Events

Adverse Event	Combined Phase 1–2 (N=38)
Any event – no. (%)	16 (42)
Grade ≥3 – no. (%)	6 (16)
Fatigue	2 (5)
Diarrhea	2 (5)

CONCLUSIONS

In previously treated patients with *KRAS* p.G12C–mutated, metastatic pancreatic cancer, daily treatment with sotorasib had an acceptable side-effect profile and showed clinically meaningful efficacy, with approximately one fifth of patients having an objective response.



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- En 2020, el cáncer de páncreas representó 495 773 nuevos casos de cáncer y 466 003 muertes relacionadas con el cáncer en todo el mundo.
- Tratamiento: cirugía + QT
- Aunque estos regímenes de quimioterapia ofrecen modestos beneficios de supervivencia y calidad de vida, causan efectos tóxicos y no son adecuados para muchos pacientes debido a la edad, el estado funcional o la fragilidad relacionada con la enfermedad

- **OLAPARIB**: inhibidor de la poli(adenosina difosfato-ribosa) polimerasa (PARP), ha sido aprobado como tratamiento de mantenimiento para el adenocarcinoma ductal pancreático metastásico pretratado que alberga una línea germinal *BRCA*mutación, que ocurre en 4 a 7% de los pacientes

- **PEMBROLIZUMAB** ha sido aprobado para tratar tumores sólidos irresecables o metastásicos, con inestabilidad de microsatélites alta o reparación defectuosa del ADN (en 1 a 2% de los adenocarcinomas ductales pancreáticos)

- **LAROTRECTINIB Y ENTRECTINIB** son inhibidores de la quinasa del receptor de tropomiosina aprobados para tratar tumores sólidos con una fusión del gen *NTRK*

Actualmente se están explorando terapias adicionales dirigidas a diversas mutaciones genéticas en el cáncer de páncreas

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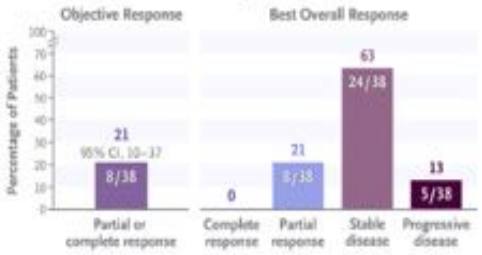

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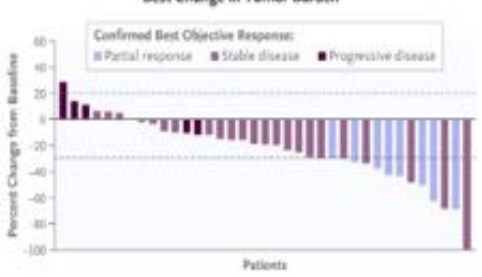

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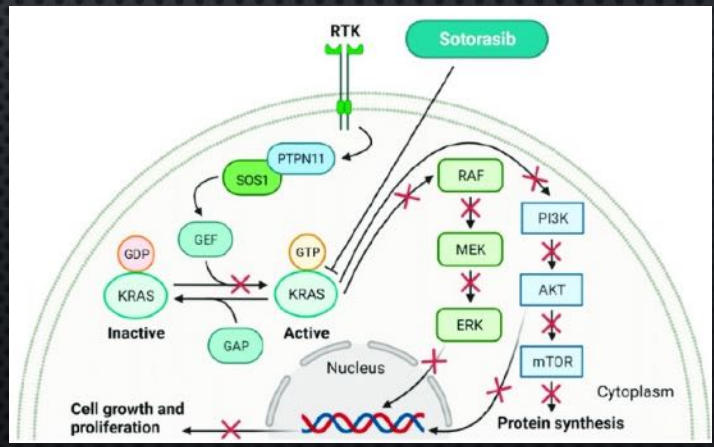
- Las mutaciones en el gen homólogo del oncogén viral del sarcoma de rata Kirsten (***KRAS***) se encuentran en aproximadamente el 90 % de los adenocarcinomas ductales pancreáticos, que es el tipo histológico más prevalente de cáncer de páncreas
- ***KRAS* p.G12C** mutación ocurre en aproximadamente 1 a 2% de los pacientes

SOTORASIB es una pequeña molécula que inhibe específica e irreversiblemente KRAS pG12C



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RESULTS

Efficacy: More than 20% of the patients had an objective response; among the patients who had a response, the median time to response was 1.5 months, and the median duration of response was 5.7 months.

Safety: More than 40% of the patients had treatment-related adverse events of any grade. Several patients had treatment-related adverse events of grade 3 or higher; of these, diarrhea and fatigue were most common. No treatment-related adverse events were fatal or led to treatment discontinuation.

LIMITATIONS AND REMAINING QUESTIONS

- Larger studies are needed to clarify the prognostic effect of *KRAS* p.G12C mutations in patients with pancreatic cancer.
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Links: Full Article | NEJM Quick Take

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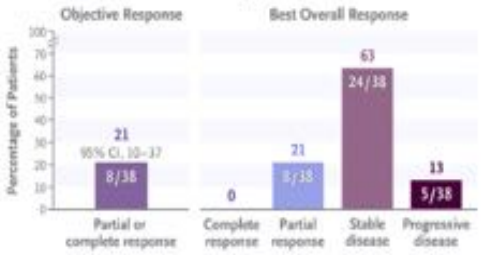

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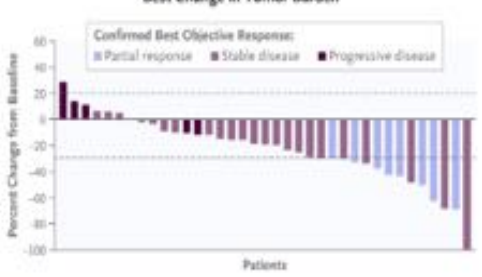

Treatment-Related Adverse Events

Adverse Event	Combined Phase 1–2 (N=38)
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Diarrhea	2 (5)

CONCLUSIONS

In previously treated patients with *KRAS* p.G12C–mutated, metastatic pancreatic cancer, daily treatment with sotorasib had an acceptable side-effect profile and showed clinically meaningful efficacy, with approximately one fifth of patients having an objective response.

METODO

Ensayo de fase 1-2, internacional, abierto

Evaluar la seguridad y la eficacia del tratamiento con sotorasib en pacientes con cáncer de páncreas con mutación *KRAS* p.G12C que habían recibido al menos una terapia sistémica previa.

El **OBJETIVO PRINCIPAL FASE 1** fue evaluar la seguridad e identificar la dosis recomendada para la fase 2

En la fase 2, los pacientes recibieron sotorasib en una dosis de 960 mg por vía oral una vez al día.

PUNTO FINAL PRIMARIO FASE 2 respuesta objetiva confirmada (definida como una respuesta completa o parcial)

Los puntos finales de eficacia se evaluaron en la población agrupada de ambas fases e incluyeron la respuesta objetiva, la duración de la respuesta, el tiempo hasta la respuesta objetiva, el control de la enfermedad (definido como una respuesta objetiva o enfermedad estable), la supervivencia sin progresión y la supervivencia general.

También se evaluó la seguridad

The NEW ENGLAND JOURNAL of MEDICINE

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Strickler JH et al. DOI: 10.1056/NEJMoa2208470

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Desde el 3 de julio de 2019 hasta el 25 de enero de 2021, los investigadores de 25 centros en siete países reclutaron un total de 38 pacientes con cáncer de páncreas con mutación *KRAS* p.G12C previamente tratados

Se inscribieron 12 pacientes en la fase 1 y 26 pacientes en la fase 2

Los 38 pacientes recibieron sotorasib oral a una dosis de 960 mg al día y se incluyeron en el análisis

La mediana de duración del tratamiento fue de 18 semanas (rango, 1 a 48)

- 25 pacientes (66%) recibieron tratamiento durante 3 meses o más
- 8 (21%) recibieron tratamiento durante 6 meses o más
- 2 pacientes (5 %) continuaron recibiendo tratamiento después de la progresión de la enfermedad según la evaluación del investigador de que habría un beneficio clínico continuado

Fecha de corte de los datos (1 de noviembre de 2021), 36 pacientes (95 %) habían interrumpido el tratamiento, siendo la progresión de la enfermedad el motivo más frecuente

- 26 (72 %) fallecieron o se retiraron del ensayo y no recibieron terapia contra el cáncer posterior.
- La mayoría de los 10 pacientes restantes fueron tratados con quimioterapia

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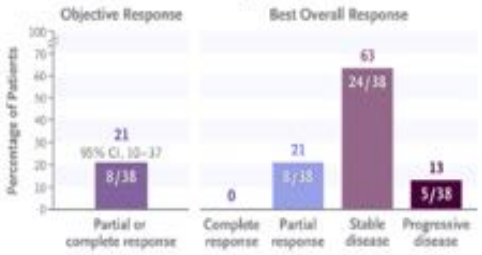

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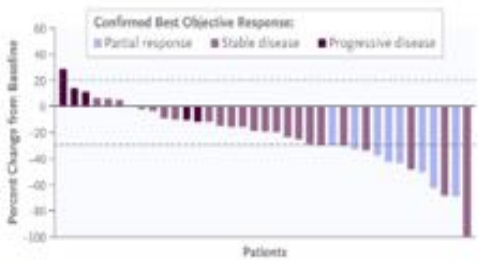

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CARACTERISTICAS PACIENTES

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Phase 1 (N=12)	Phase 2 (N=26)	Combined Phase 1–2 (N=38)
Sex — no. (%)			
Male	9 (75)	20 (77)	29 (76)
Female	3 (25)	6 (23)	9 (24)
Median age (range) — yr	62.5 (45–75)	67 (53–81)	65.5 (45–81)
ECOG performance-status score — no. (%)†			
0	1 (8)	11 (42)	12 (32)
1	7 (58)	15 (58)	22 (58)
2	4 (33)	0	4 (11)
Disease stage at initial diagnosis — no. (%)			
I	2 (17)	1 (4)	3 (8)
II	4 (33)	7 (27)	11 (29)
III	1 (8)	2 (8)	3 (8)
IV	5 (42)	16 (62)	21 (55)
Stage IV disease at screening — no. (%)	12 (100)	26 (100)	38 (100)
Histopathological subtype — no. (%)			
Adenocarcinoma	11 (92)	26 (100)	37 (97)
Other or unknown	1 (8)	0	1 (3)
No. of sites of metastatic disease — no. (%)			
1	4 (33)	13 (50)	17 (45)
2	5 (42)	10 (38)	15 (39)
≥3	3 (25)	3 (12)	6 (16)
Site of metastases — no. (%)			
Liver	9 (75)	22 (85)	31 (82)
Lung	5 (42)	11 (42)	16 (42)
Brain	0	1 (4)	1 (3)
Bone	3 (25)	1 (4)	4 (11)
Previous lines of anticancer therapy — no. (%)			
1	2 (17)	6 (23)	8 (21)
2	3 (25)	10 (38)	13 (34)
3	2 (17)	7 (27)	9 (24)
≥4	5 (42)	3 (12)	8 (21)
Median lines of previous anticancer therapy (range) — no.	3 (1–5)	2 (1–8)	2 (1–8)
Type of previous anticancer therapy — no. (%)			
Chemotherapy	12 (100)	26 (100)	38 (100)
Fluoropyrimidine	11 (92)	23 (88)	34 (89)
Irinotecan	11 (92)	22 (85)	33 (87)
Oxaliplatin or cisplatin	11 (92)	21 (81)	32 (84)
Gemcitabine	7 (58)	21 (81)	28 (74)
Nab-paclitaxel	7 (58)	18 (69)	25 (66)
Liposomal irinotecan	2 (17)	3 (12)	5 (13)
Erlotinib	1 (8)	0	1 (3)
Select regimens			
FOLFIRINOX	11 (92)	18 (69)	29 (76)
Gemcitabine + nab-paclitaxel	7 (58)	18 (69)	25 (66)
Fluorouracil + liposomal irinotecan	2 (17)	3 (12)	5 (13)

* Percentages may not total 100 because of rounding. FOLFIRINOX denotes fluorouracil, leucovorin, irinotecan, and oxaliplatin, and nab-paclitaxel nanoparticle albumin–bound paclitaxel.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

- Características iniciales de los pacientes inscritos en la fase 1 y la fase 2 fueron similares
- Mayoría de los pacientes eran hombres
- 55 % tenían enfermedad en estadio IV en el momento del diagnóstico inicial
- Todos los pacientes tenían enfermedad metastásica en el momento de la inscripción
- Habían recibido una mediana de 2 líneas (rango, 1 a 8) de terapia previamente
- Mutaciones comunes al inicio
  - ✓ *TP53* (en el 75 % de los pacientes)
  - ✓ *CDKN2A* (en el 18 %)
  - ✓ *BRCA2* (en el 18 %)
  - ✓ *SMAD4* (en 11 %)

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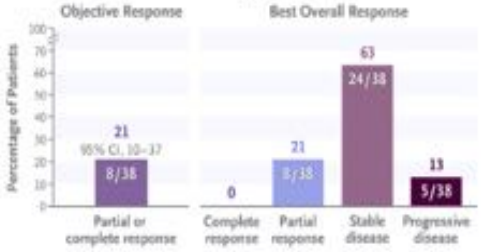

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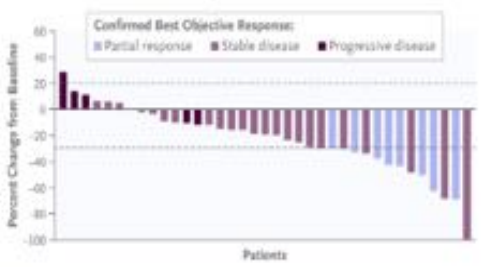

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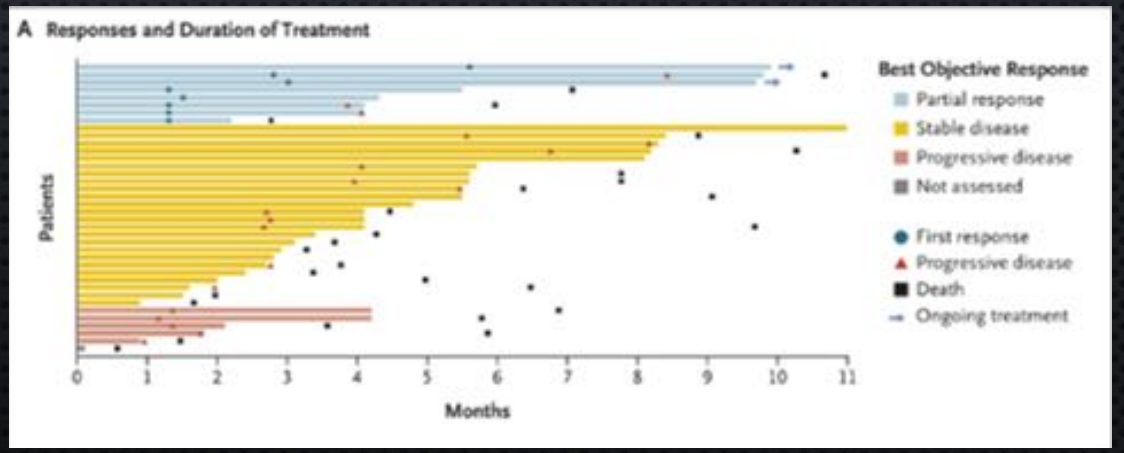
EFICACIA

Table 2. Efficacy of Sotorasib Therapy.*

Variable	Phase 1 (N=12)	Phase 2 (N=26)	Combined Phase 1–2 (N=38)
Best overall response — no. (%)†			
Confirmed complete response	0	0	0
Confirmed partial response	3 (25)	5 (19)	8 (21)
Stable disease	6 (50)	18 (69)	24 (63)
Progressive disease	2 (17)	3 (12)	5 (13)
Could not be evaluated	0	0	0
Not assessed	1 (8)	0	1 (3)
Percentage of patients with objective response (95% CI) — %	25 (6–57)	19 (7–39)	21 (10–37)
Percentage of patients with disease control (95% CI) — %‡	75 (43–95)	89 (70–98)	84 (69–94)
Median time to objective response (range) — mo§	1.4 (1.3–1.5)	2.8 (1.3–5.6)	1.5 (1.3–5.6)
Median duration of response (95% CI) — mo§¶	—	—	5.7 (1.6–NE)

* An objective response was defined as a complete or partial response. NE denotes could not be evaluated.
† The best overall response was determined by blinded independent central review.
‡ Disease control was defined as an objective response or stable disease.
§ The median time to objective response and the median duration of response were calculated for the patients who had a confirmed objective response.
¶ The median duration of response (Kaplan–Meier estimates) is not provided for individual phases because of the small number of patients.

- 8 pacientes (21 %) tuvieron una respuesta parcial confirmada
  - mediana del tiempo hasta la respuesta fue de 1,5 meses (rango, 1,3 a 5,6), y la duración de la respuesta fue de 5,7 meses
- Ningún paciente tuvo una respuesta completa



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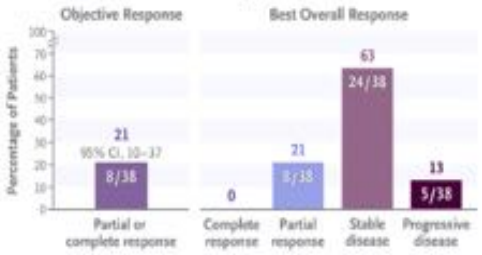

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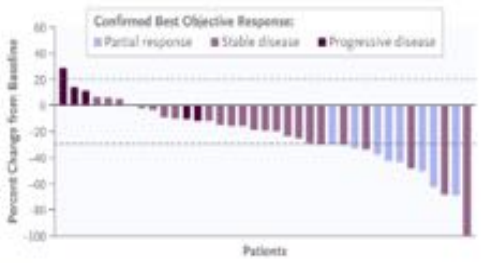

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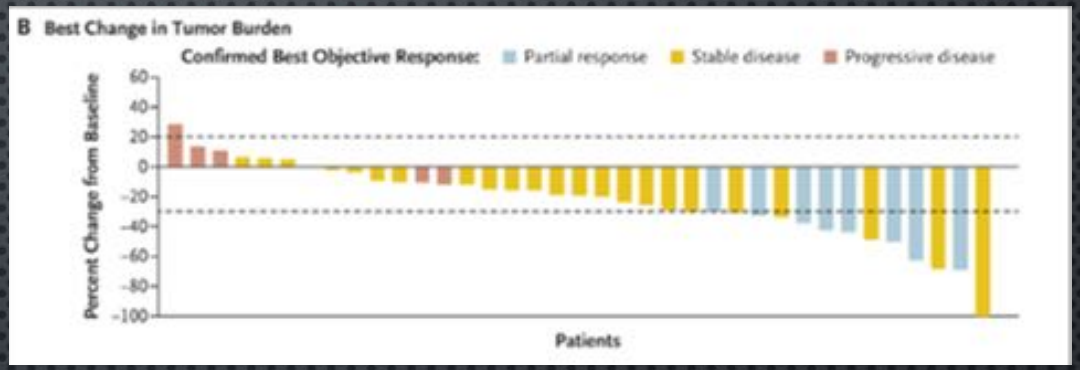

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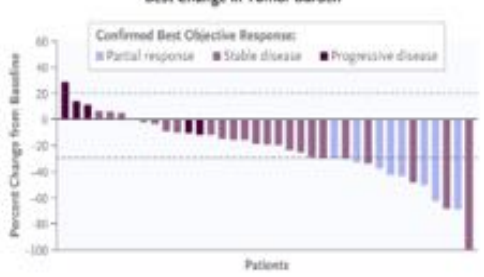

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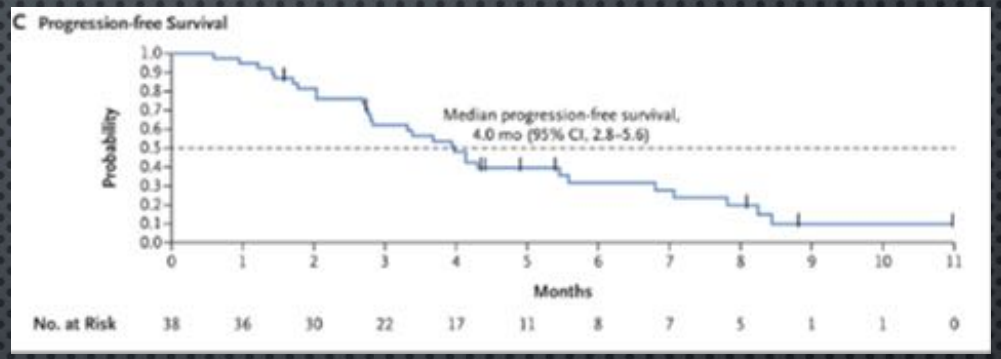
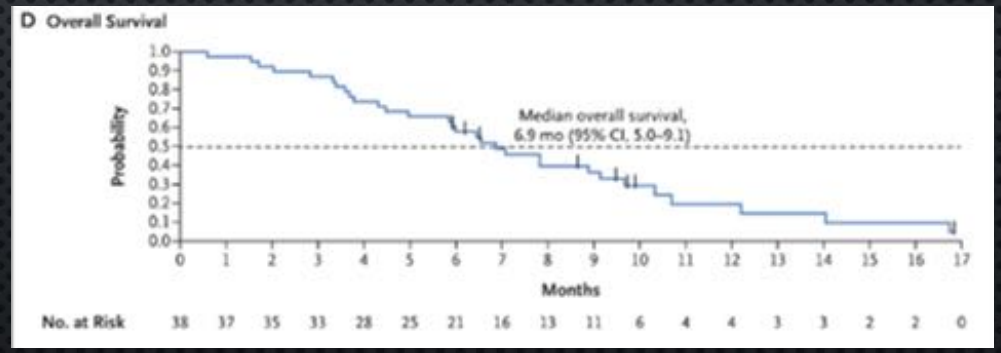
La mediana de supervivencia libre de progresión fue de 4 meses (IC del 95 %, 2,8 a 5,6)



La mediana de supervivencia general fue de 6,9 meses (IC del 95 %, de 5,0 a 9,1)



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Intervention: 38 patients with *KRAS* p.G12C–mutated, metastatic pancreatic cancer who had received previous systemic therapy received 960 mg of sotorasib orally once daily until disease progression, unacceptable side effects, or withdrawal of consent occurred. The primary end point was a centrally confirmed objective response (complete or partial response).

RESULTS

Efficacy: More than 20% of the patients had an objective response; among the patients who had a response, the median time to response was 1.5 months, and the median duration of response was 5.7 months.

Safety: More than 40% of the patients had treatment-related adverse events of any grade. Several patients had treatment-related adverse events of grade 3 or higher; of these, diarrhea and fatigue were most common. No treatment-related adverse events were fatal or led to treatment discontinuation.

LIMITATIONS AND REMAINING QUESTIONS

- Larger studies are needed to clarify the prognostic effect of *KRAS* p.G12C mutations in patients with pancreatic cancer.
- The efficacy and safety of sotorasib in combination with other anticancer therapies are unknown and currently under study.

Links: Full Article | NEJM Quick Take

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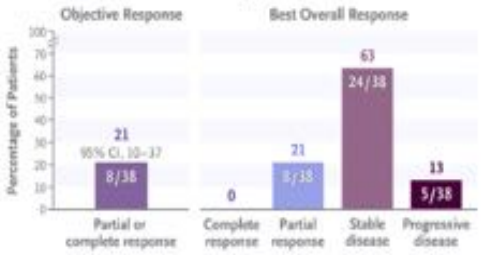
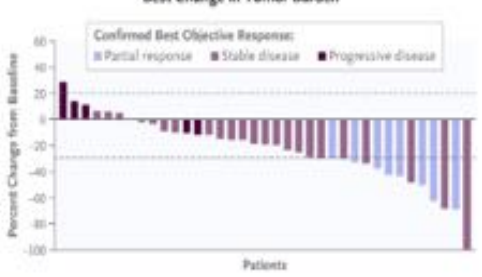


Best Change in Tumor Burden



Treatment-Related Adverse Events

Adverse Event	Combined Phase 1–2 (N=38)
Any event – no. (%)	16 (42)
Grade ≥3 – no. (%)	6 (16)
Fatigue	2 (5)
Diarrhea	2 (5)

CONCLUSIONS

In previously treated patients with *KRAS* p.G12C–mutated, metastatic pancreatic cancer, daily treatment with sotorasib had an acceptable side-effect profile and showed clinically meaningful efficacy, with approximately one fifth of patients having an objective response.

SEGURIDAD

Table 3. Adverse Events.*

Adverse Event	Adverse Events Reported during Treatment			Treatment-Related Adverse Events		
	Phase 1 (N=12)	Phase 2 (N=26)	Combined Phase 1–2 (N=38)	Phase 1 (N=12)	Phase 2 (N=26)	Combined Phase 1–2 (N=38)
	number of patients (percent)					
Any adverse event	12 (100)	26 (100)	38 (100)	5 (42)	11 (42)	16 (42)
Grade ≥2	12 (100)	23 (89)	35 (92)	3 (25)	9 (35)	12 (32)
Grade ≥3	9 (75)	15 (58)	24 (63)	0	6 (23)	6 (16)
Grade ≥4	7 (58)	7 (27)	14 (37)	0	0	0
Serious adverse event	9 (75)	15 (58)	24 (63)	0	3 (12)	3 (8)
Adverse event leading to dose reduction or interruption of therapy	5 (42)	9 (35)	14 (37)	0	5 (19)	5 (13)
Adverse event leading to discontinuation of therapy	1 (8)	1 (4)	2 (5)	0	0	0
Fatal adverse event	7 (58)	7 (27)	14 (37)	0	0	0

* Shown are adverse events that occurred during treatment and those that occurred within 30 days after the last dose of sotorasib or the end of the trial, whichever occurred earlier. Relatedness to treatment was determined by the investigators. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Diarrea
Dolor abdominal
Nauseas
Vómitos
Fiebre

Diarrea
Fatiga

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

Strickler JH et al. DOI: 10.1056/NEJMoa2208470

CLINICAL PROBLEM

Approximately 1 to 2% of pancreatic ductal adenocarcinomas harbor *KRAS* p.G12C gene mutations. Sotorasib, a small molecule that specifically and irreversibly inhibits its KRAS G12C protein, is approved by the Food and Drug Administration to treat *KRAS* p.G12C–mutated non–small-cell lung cancer. The safety and efficacy of sotorasib in *KRAS* p.G12C–mutated pancreatic cancer have been unknown.

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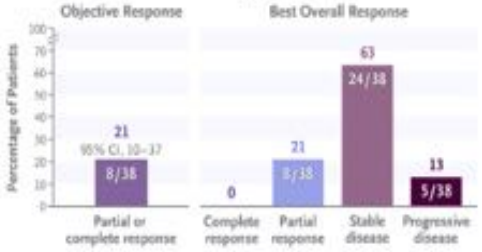

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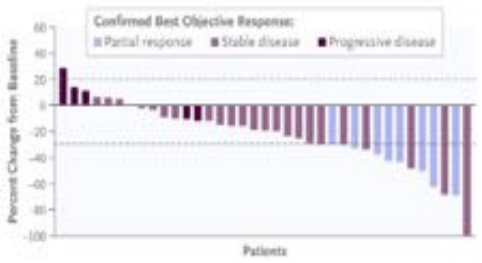

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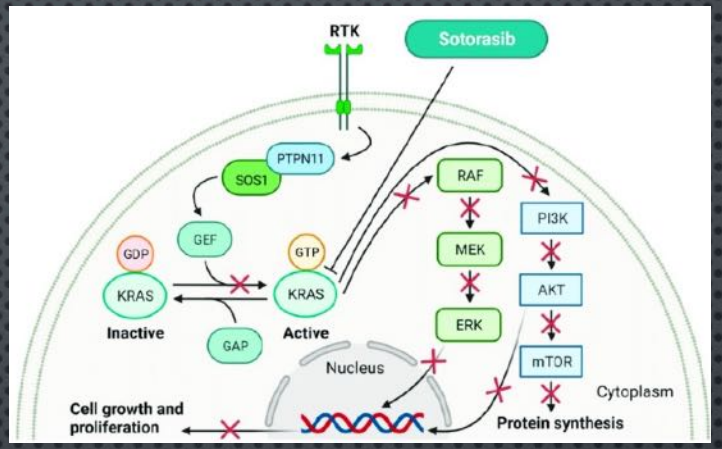
DISCUSIÓN



KRAS es la isoforma mutada con mayor frecuencia en el cáncer de páncreas
Sotorasib se une de forma irreversible y selectiva a este bolsillo, que está presente en el mutante KRAS G12C, y lo bloquea en el estado inactivo unido a GDP, inhibiendo así la señalización oncogénica

- En este ensayo, la terapia con sotorasib tuvo una eficacia clínicamente significativa y un perfil de seguridad aceptable en pacientes con *KRAS*Cáncer de páncreas metastásico con mutación p.G12C.
- Los resultados de este ensayo son prometedores en el contexto de los resultados observados con regímenes aprobados de tratamiento de segunda línea para el cáncer de páncreas avanzado
- Sotorasib se asoció principalmente con efectos tóxicos de bajo grado
  La diarrea y la fatiga fueron los eventos adversos relacionados con el tratamiento que ocurrieron con mayor frecuencia

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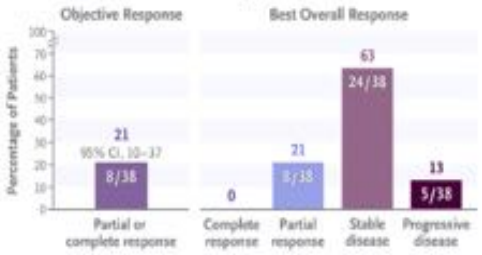

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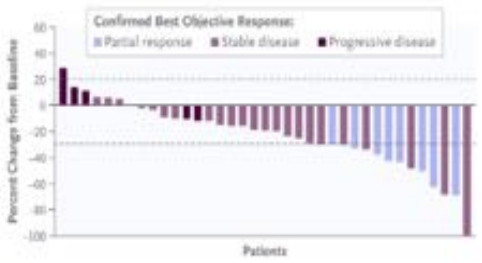

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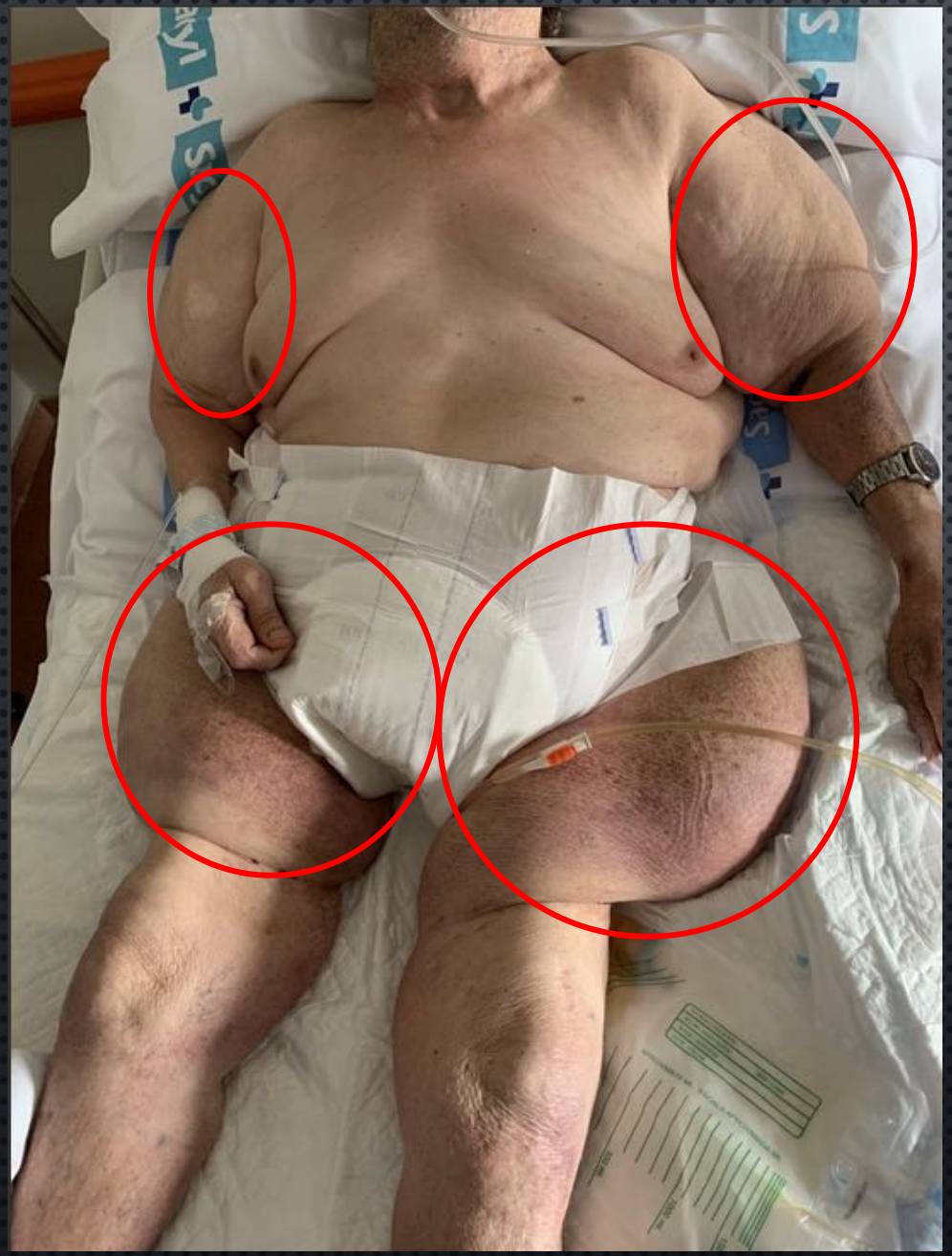
LIMITACIONES

- Aunque estos datos son alentadores, se necesitan análisis adicionales en pacientes con cáncer de páncreas mutado en *KRAS* p.G12C para evaluar la eficacia de estas combinaciones
- Se necesitan estudios con cohortes más grandes para aclarar el efecto pronóstico de la mutación *KRAS* p.G12C en pacientes con cáncer de páncreas.


CASO
CLÍNICO



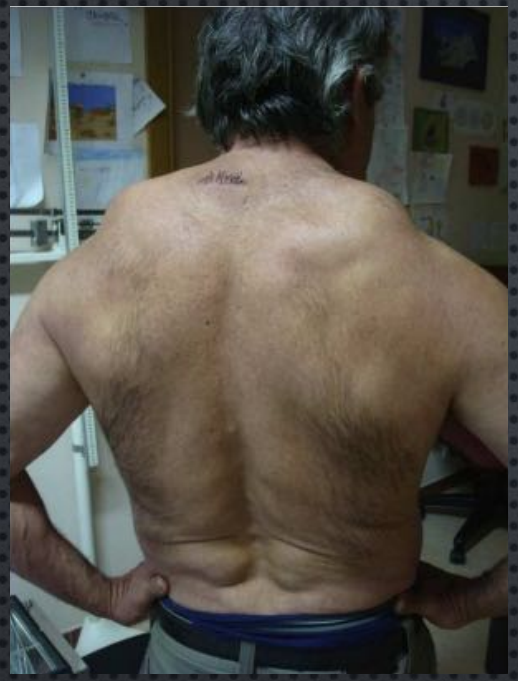
MOTIVO INGRESO: Varón 76 años que ingresa por disnea

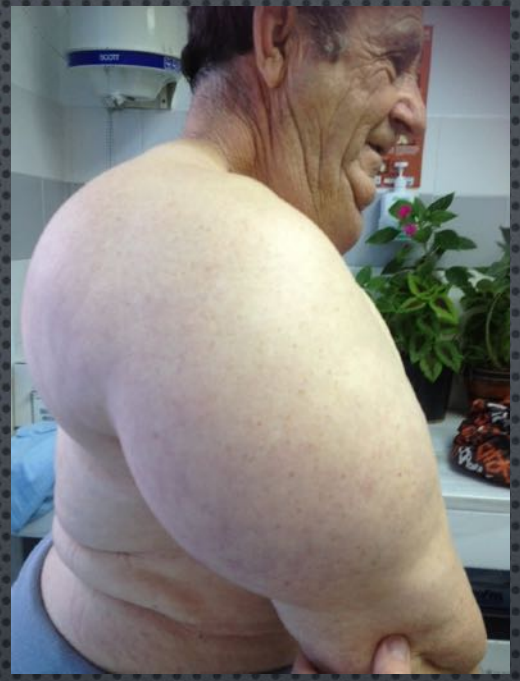
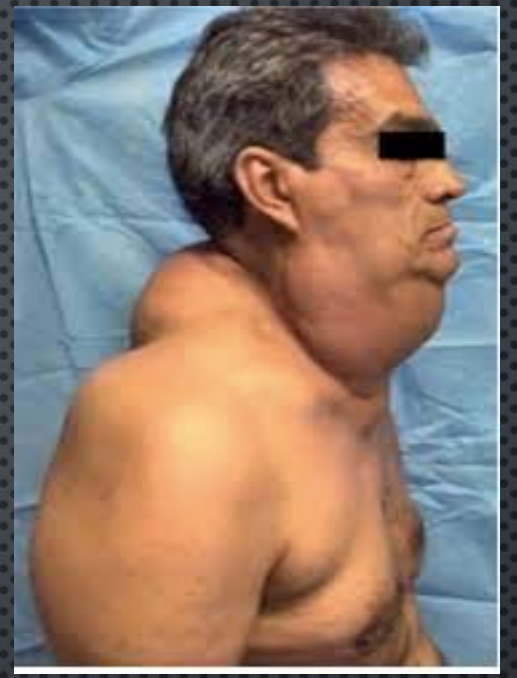
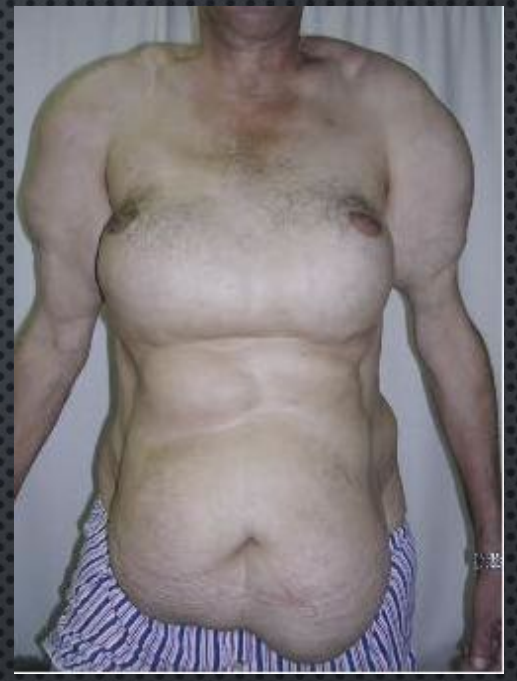
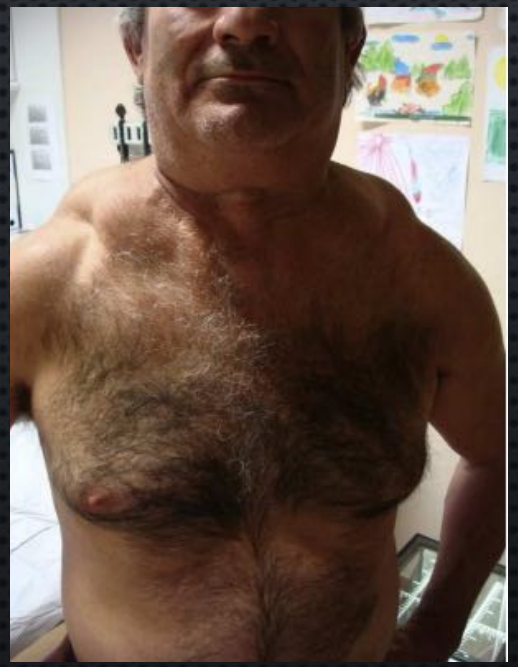
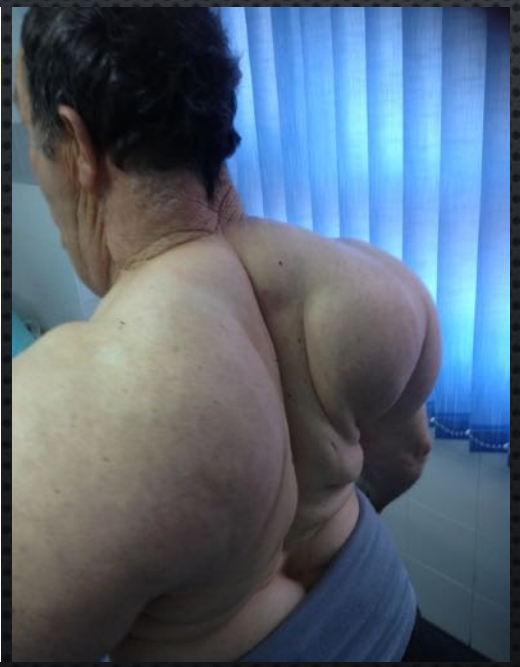
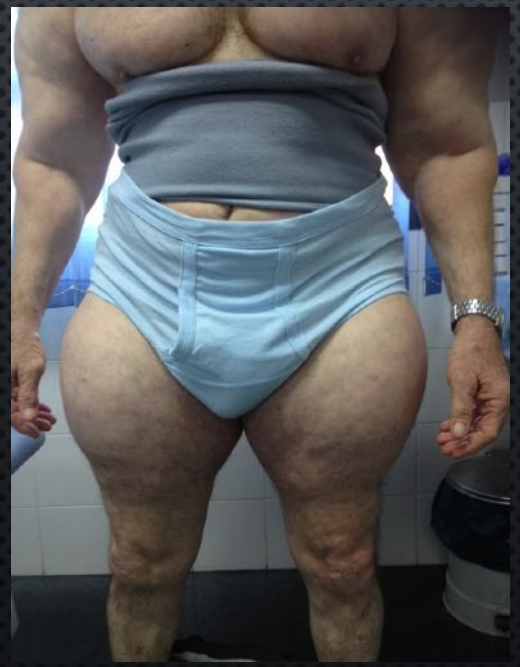
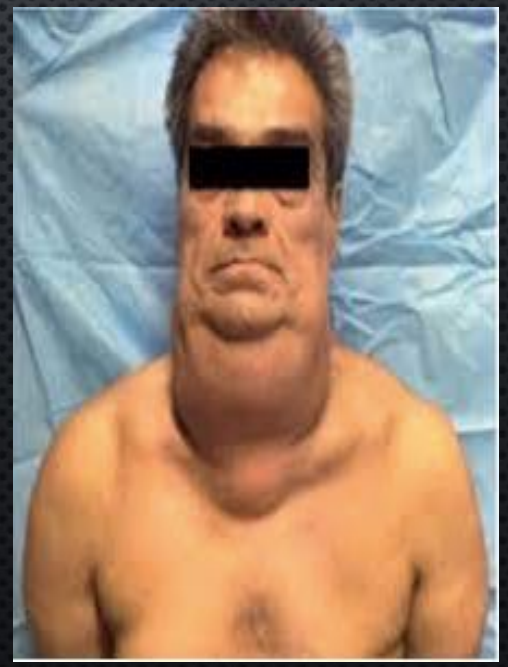
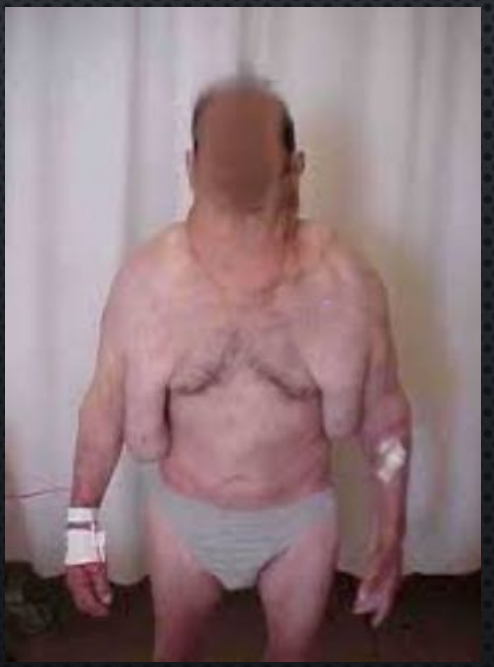
ANTECEDENTES PERSONALES
NAMC. Institucionalizado
Enolismo crónico (60 gr/día)
HTA
Dislipemia
Cardiopatia mixta: hipertensiva y dilatada con Fe 25%. NYHA IV.
Hepatopatía crónica
Anemia multifatorial
SASH en tratamiento con CPAP
Carcinoma epidermoide de origen desconocido con masa laterocervical derecha + metástasis pulmonares: RT paliativa

ENFERMEDAD ACTUAL: presenta 5 días de evolución de aumento de disnea habitual con edemas en EEII. No clínica infecciosa.

APROX-DX:- INSUFICIENCIA CARDIACA CONGESTIVA en paciente con cardiopatía dilatada e hipertensiva y disfunción severa de FEVI.

EVOLUCIÓN: evolución tórpida a pesar de tratamiento siendo éxitus



LIPOMATOSIS SIMÉTRICA MÚLTIPLE
ENFERMEDAD DE MADELUNG

Semergen. 2012;38(4):211-213

Medicina de Familia
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ORIGINAL

Enfermedad de Madelung

M. Garín Alegre[a,*], M. de Grado Molinero[b] y L. Argueta Ruano[c]

[a] Medicina de Familia y Comunitaria, Hospital Universitario Marqués de Valdecilla, Santander, España
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Recibido el 8 de septiembre de 2011; aceptado el 18 de octubre de 2011
Disponible en Internet el 20 de diciembre de 2011

PALABRAS CLAVE
Etilismo;
Enfermedad de Madelung;
Cirugía ambulatoria;
Anatomía patológica

Resumen La enfermedad de Madelung o lipomatosis simétrica múltiple es una enfermedad rara caracterizada por la presencia de masas de tejido adiposo, distribuidas de forma simétrica en cuello, nuca, tronco, hombros y parte proximal de los miembros. Afecta fundamentalmente a hombres entre los 30 y 60 años con historia de etilismo crónico, siendo la resección quirúrgica el único tratamiento efectivo.

KEYWORDS
Alcoholism;
Madelung's disease;
Ambulatory surgery;
Histopathology

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Enfermedad de Madelung
Enfermedad de Launois-Bensaude
Lipomatosis cefalotorácica
Lipomatosis cervical benigna familiar
Lipomatosis simétrica benigna
Lipomatosis simétrica múltiple
Lipomatosis simétrica difusa
Adenolipomatosis simétrica
Lipomatosis simétrica indolente

- Múltiples **depósitos de tejido adiposo** (no encapsulados), distribuidos en forma simétrica, ubicados característicamente en el cuello, la nuca, los hombros, el tronco y la parte proximal de los miembros
- Respetando cara, antebrazos, piernas, manos y pies.

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- Primera descripción fue de Benjamín Brodie en 1846
- Debe su nombre al cirujano Otto Wilhelm Madelung que presentó una serie de 35 casos en 1888
- Launois y Bensaude presenta otras serie de 30 casos en 1898

- Enfermedad rara
- Más frecuencia en países mediterraneos (Italia => uno de cada 25.000 varones *) y Europa del Este
- Mas rara en mujeres. Proporción 15:1
- Edad comienzo: 20-60 años
- Casos familiares. La mayoría esporádicos

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- Desconocida
- Relación importante con el alcoholismo crónico (60-90%)
- Asociación frecuente con neuropatía periférica de tipo desmielinizante.
- Incremento de la actividad de la lipoproteinlipasa en el tejido adiposo

HIPOTESIS

- Defecto en la movilización de triglicéridos limitado a las zonas afectadas
- Neoplasia, con origen en adipocitos de la grasa parda
- Acumulación de triglicéridos en áreas de residuos embrionarios de tejido adiposo pardo
- Hiperplasia celular de adipocitos
- Disfunción mitocondrial

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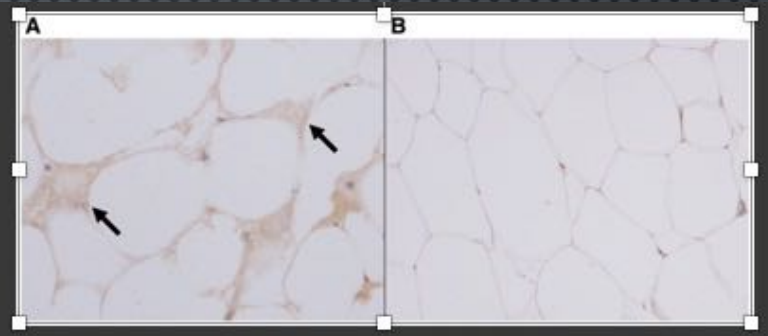
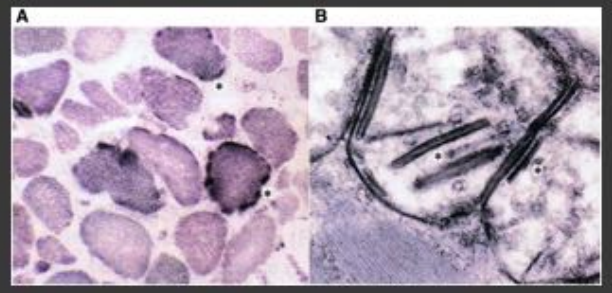


Biopsia lipomas



Biopsia muscular con agregados de mitocondrias anormales

LIPOMATOSIS SIMÉTRICA MÚLTIPLE
ENFERMEDAD DE MADELUNG

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ORIGINAL

Enfermedad de Madelung

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Recibido el 8 de septiembre de 2011; aceptado el 18 de octubre de 2011
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PALABRAS CLAVE
Etilismo;
Enfermedad de Madelung;
Cirugía ambulatoria;
Anatomía patológica

Resumen La enfermedad de Madelung o lipomatosis simétrica múltiple es una enfermedad rara caracterizada por la presencia de masas de tejido adiposo, distribuidas de forma simétrica en cuello, nuca, tronco, hombros y parte proximal de los miembros. Afecta fundamentalmente a hombres entre los 30 y 60 años con historia de etilismo crónico, siendo la resección quirúrgica el único tratamiento efectivo.

KEYWORDS
Alcoholism;
Madelung's disease;
Ambulatory surgery;
Histopathology

Madelung's disease

Abstract Madelung's disease or Benign Symmetric Lipomatosis is a rare disease characterised by masses of adipose tissue spread symmetrically along the neck, trunk, shoulders and upper arms. It affects men from 30 to 60 years old with a previous history of alcoholism. Surgery is the only effective treatment.

SUBTIPO 1: varones con IMC normal o bajo.
Masas circunscriptas de tejido graso con atrofia progresiva del tejido graso no involucrado.

SUBTIPO 2: ambos sexos con IMC alto.
Infiltración grasa es más difusa.

EVOLUCIÓN

- 1-2 años de crecimiento rápido de las masas lipomatosas
- Años de lenta progresión.
- Nuevos crecimientos rápidos inducidos por traumatismos o cirugías.

COMPLICACIONES

- Limitación de movilidad
- Disnea y la disfagia
- Degeneración maligna a liposarcoma mixoide rara

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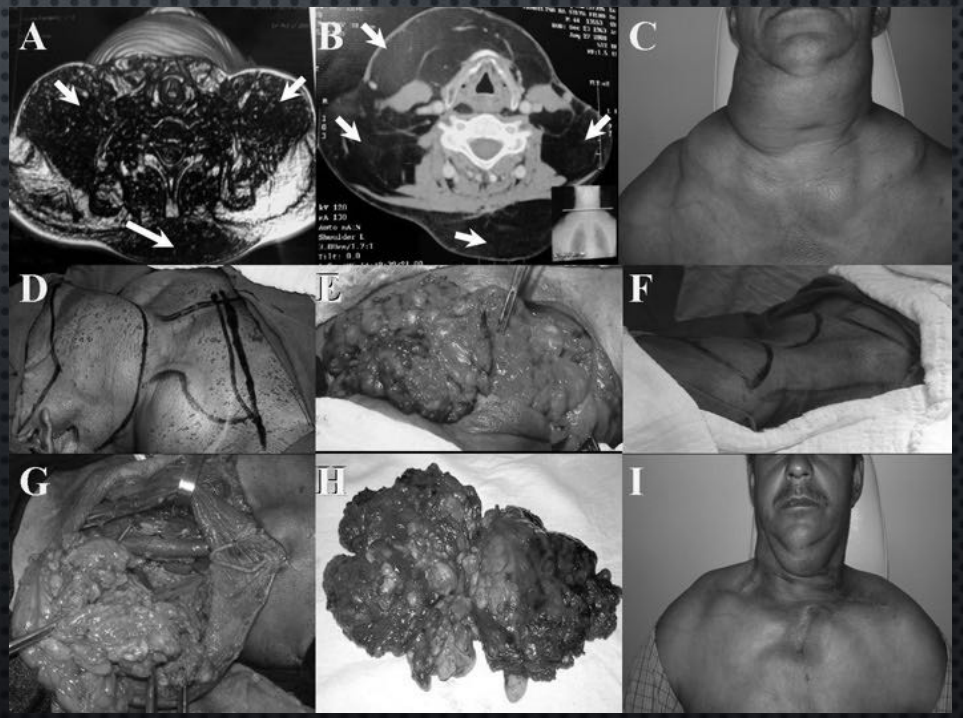
TRATAMIENTO

- Abstinencia alcohólica
- No fumar
- Cirugía o liposucción: si compromiso funcional o por razones estéticas.



Masas no encapsuladas cuya escisión completa es muy difícil, y frecuentemente recidivan.


coffee
break