# Hematopoyesis clonal de potencial indeterminado (CHIP): Un nuevo factor de riesgo vascular

Jose María Mostaza

Hospital La Paz-Carlos III

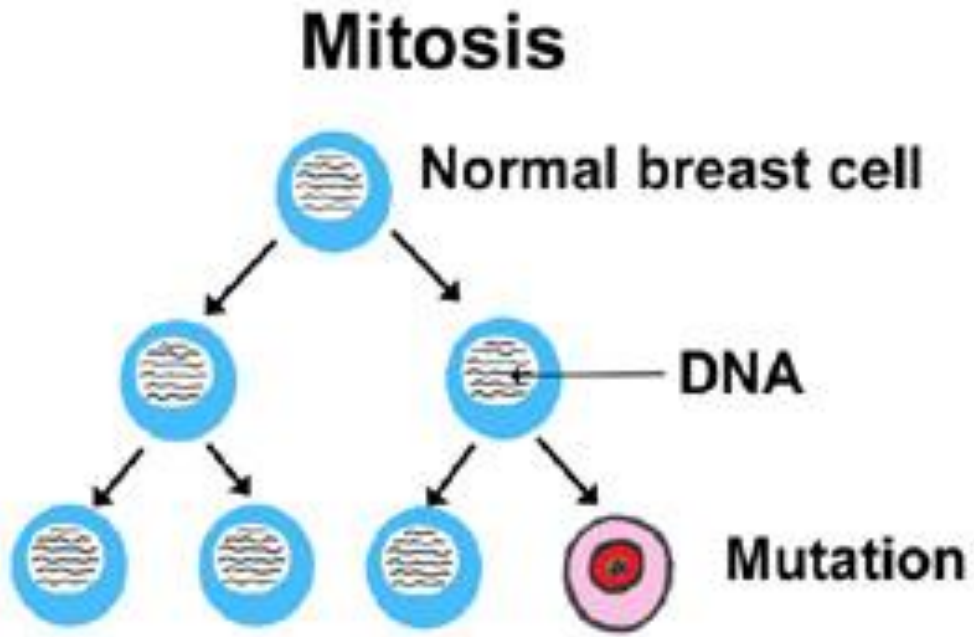
# Conflicto de intereses

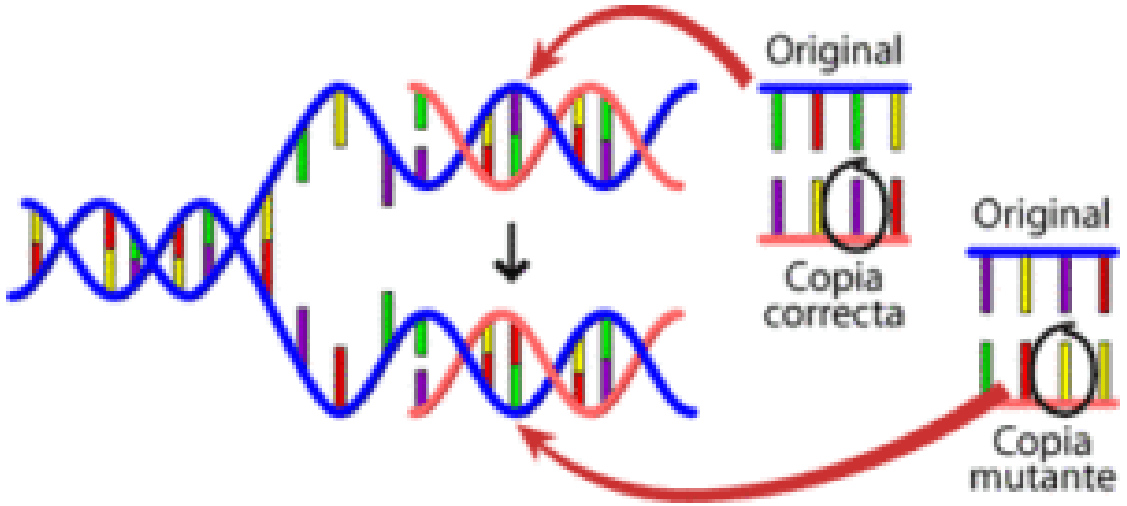
Ninguno

# Conflicto intelectual

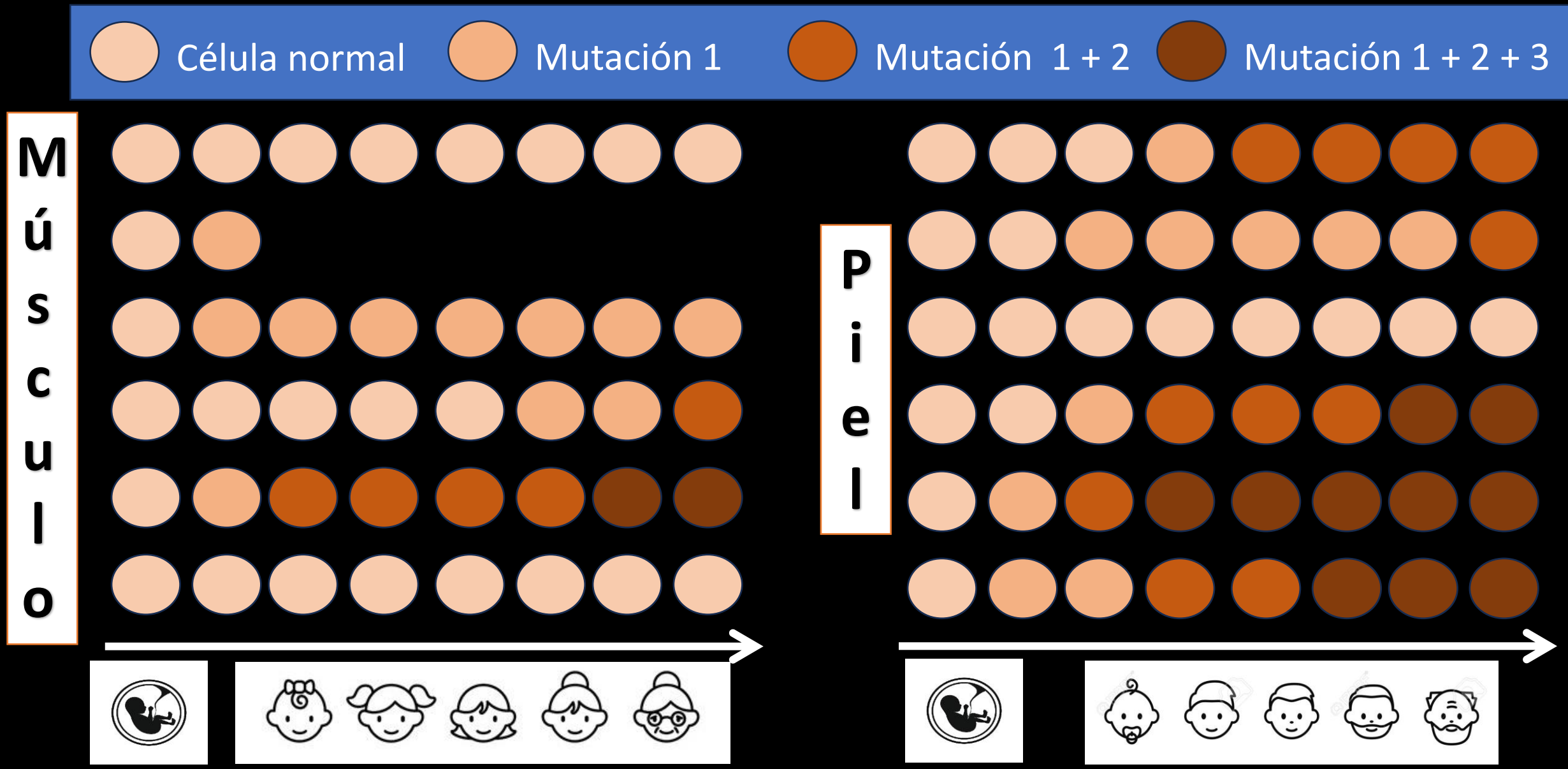
Todos

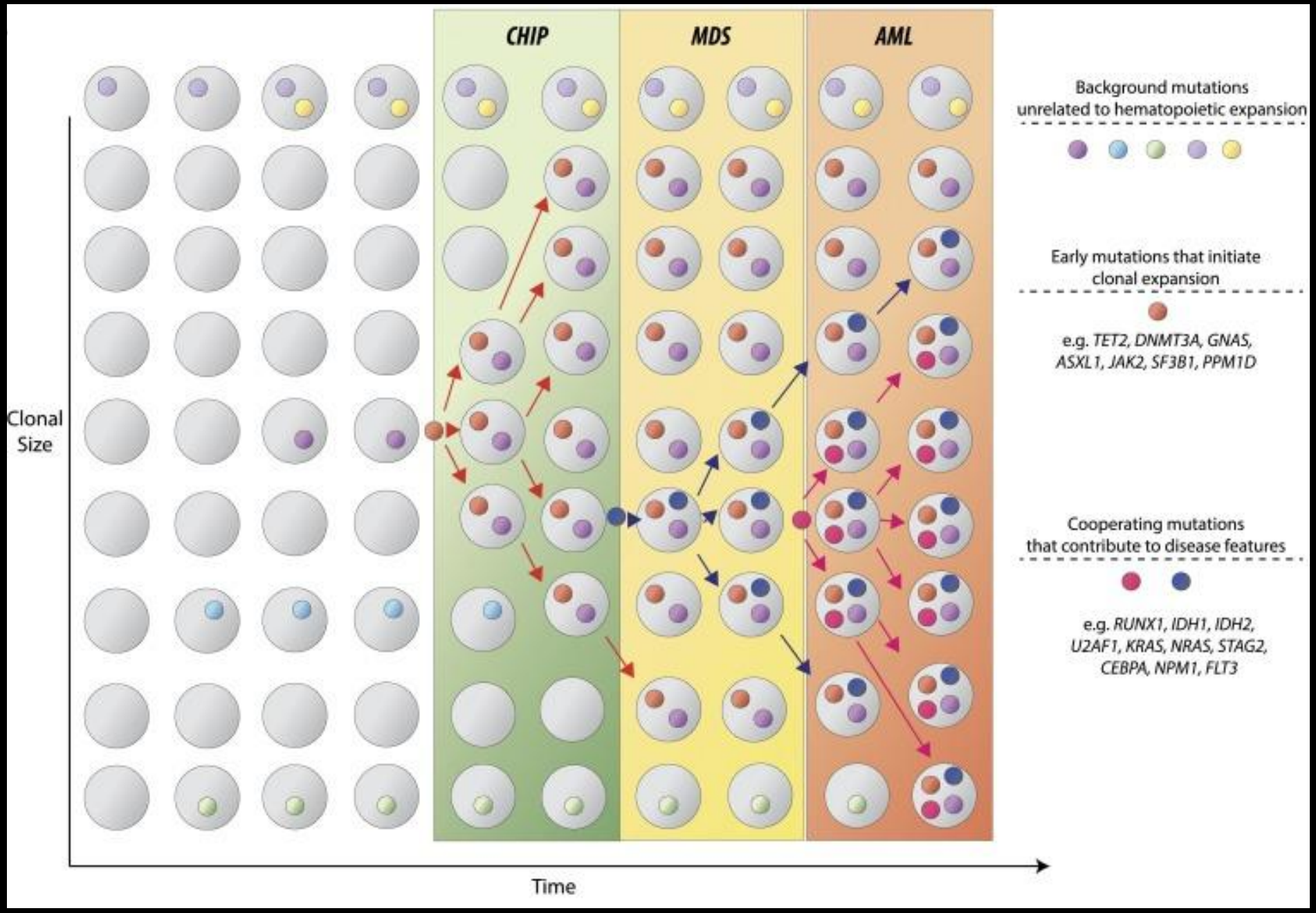
# MUTACIONES SOMATICAS



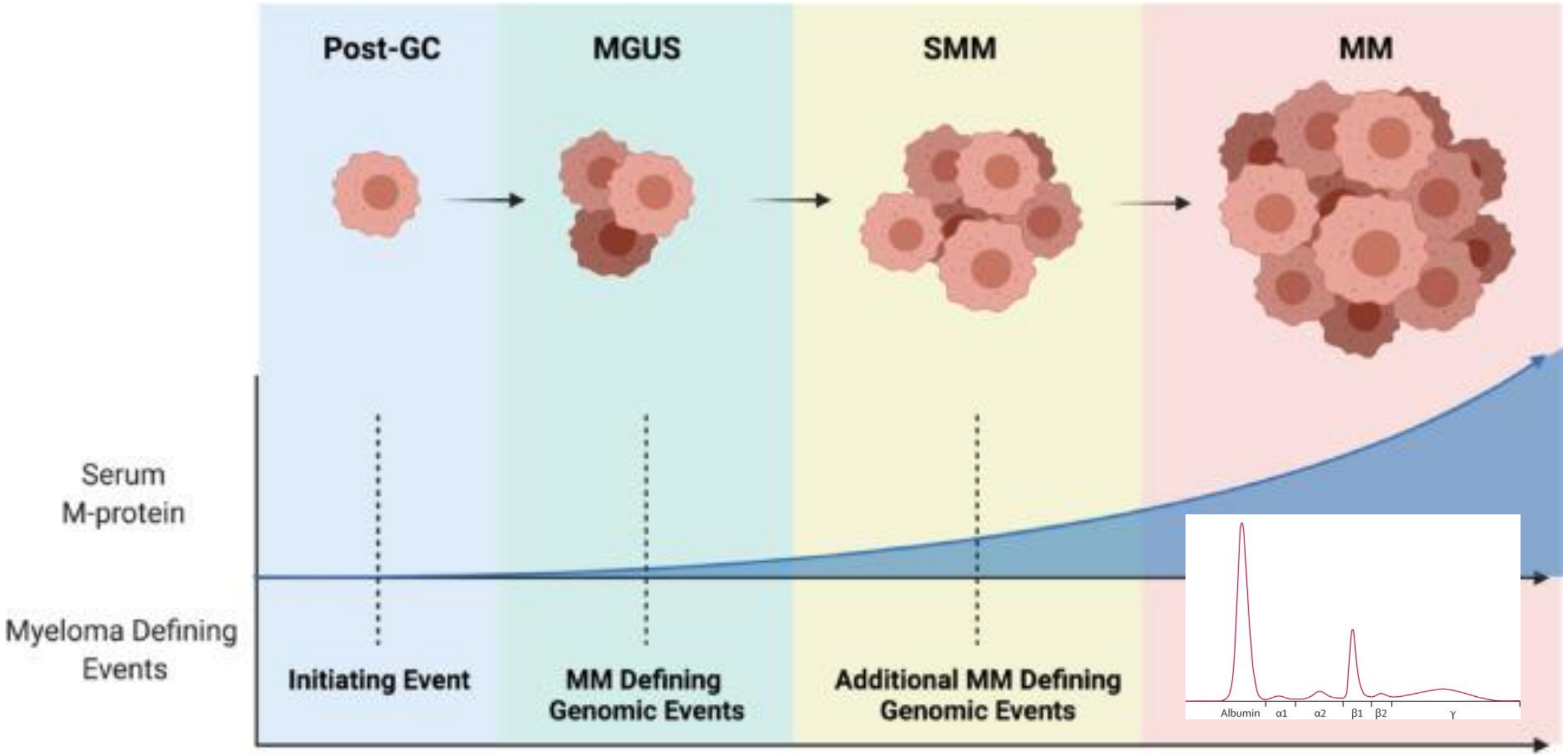



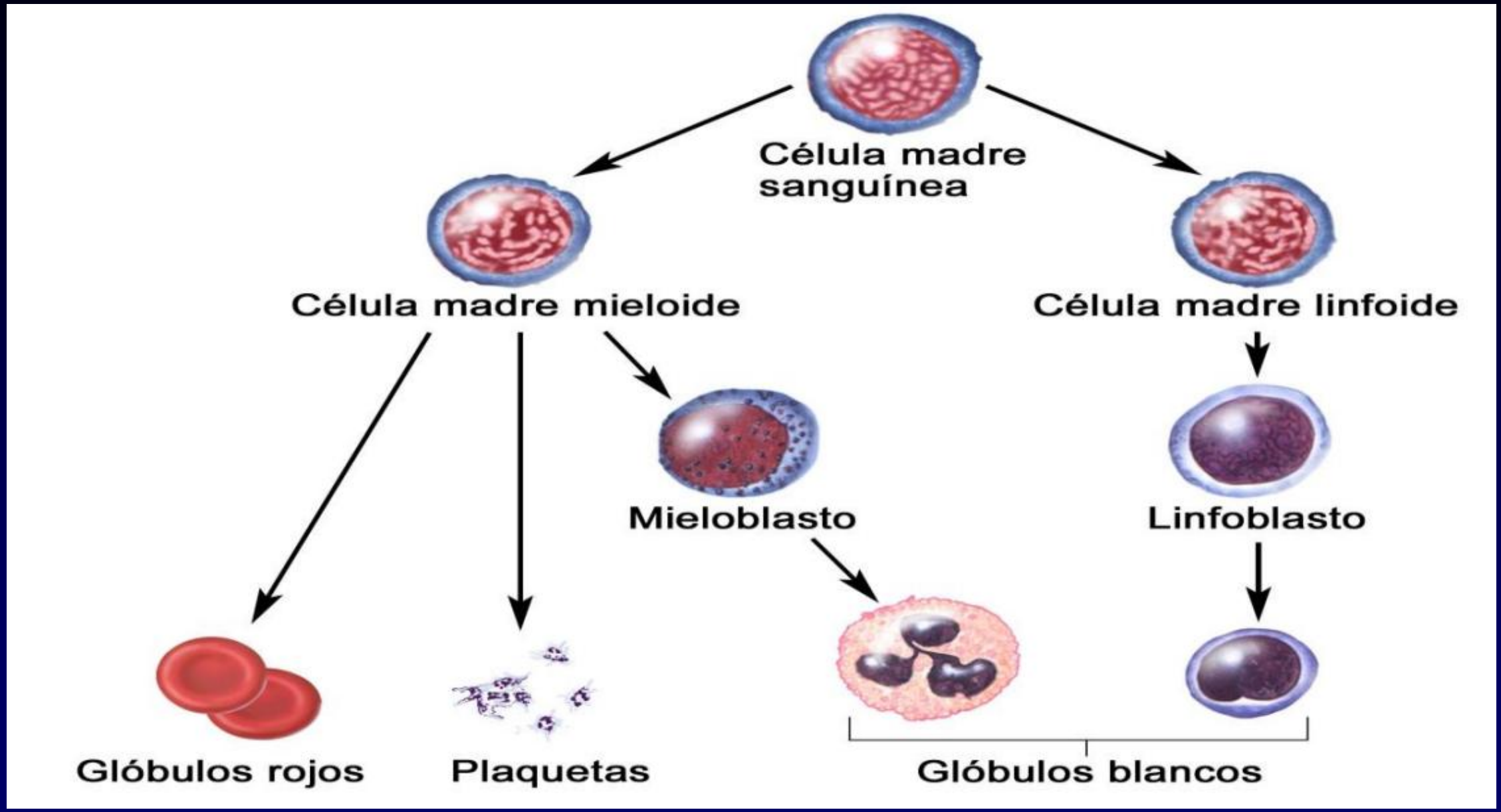
# Acúmulo de mutaciones somáticas y aparición de clones mutantes a lo largo de la vida

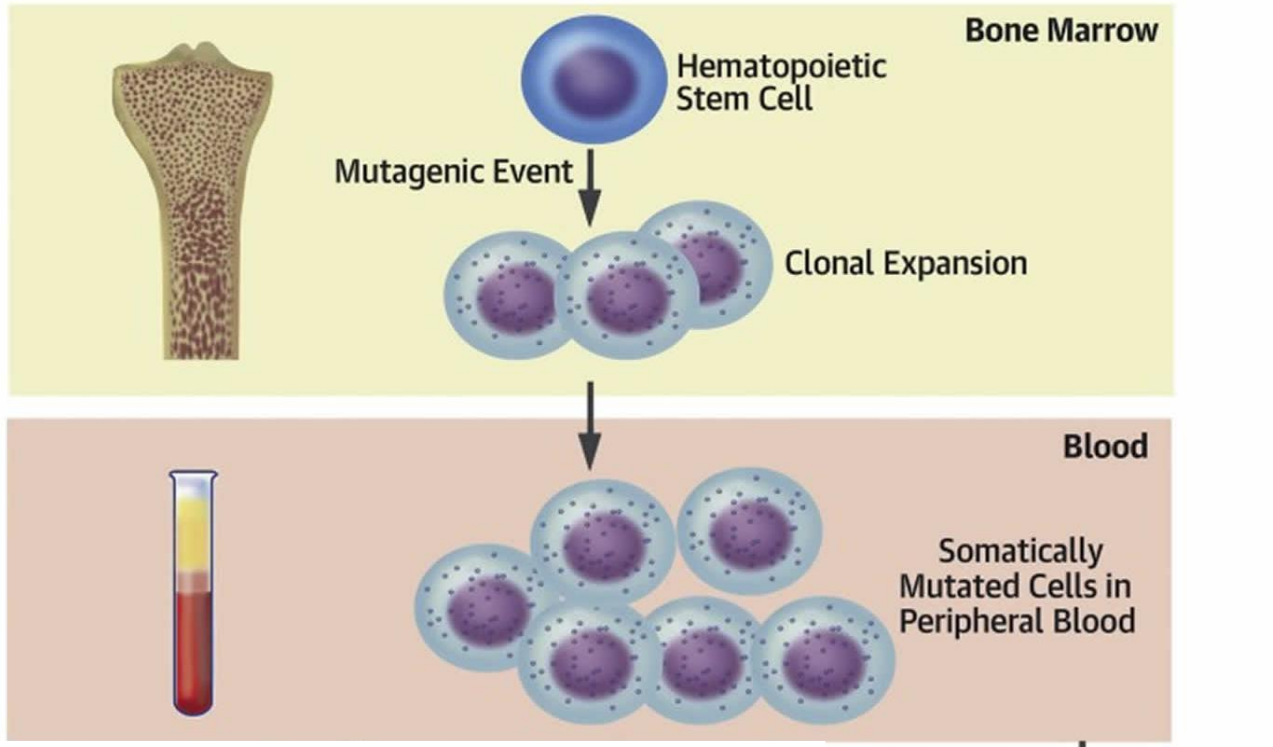





Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, Ebert BL. Blood. 2015 Jul 2;126(1):9-16. doi: 10.1182/blood-2015-03-631747.


Post-GC
MGUS
SMM
MM
Serum
M-protein
Myeloma Defining
Events
Initiating Event
MM Defining
Genomic Events
Additional MM Defining
Genomic Events
Albumin
α1
α2
β1
β2
γ


Célula madre sanguínea
Célula madre mieloide
Célula madre linfoide
Mieloblasto
Linfoblasto
Glóbulos rojos
Plaquetas
Glóbulos blancos




Khetarpal SA et al. JACC 2019; 74: 578-586.
Libby P et al. JACC 2019; 74: 567-77.

***CHIP (Hematopoyesis clonal de potencial indeterminado): Conjunto de células hematopoyéticas procedentes de un clon generado por una mutación inductora, cuya frecuencia alélica en sangre sea de al menos un 2%, en ausencia de neoplasia hematológica***

| Principales genes portadores de mutaciones somáticas asociadas a expansión clonal | |
|---|---|
| *DNMT3A* | Implicado en demetilación |
| *TET2* | Implicado en demetilación. Modificaciones epigenéticas |
| *ASKL1* | Represión transcripcional |
| *TP53* | Apoptosis y reparación del DNA |
| *JAK2* | Crecimiento, diferenciación y desarrollo |

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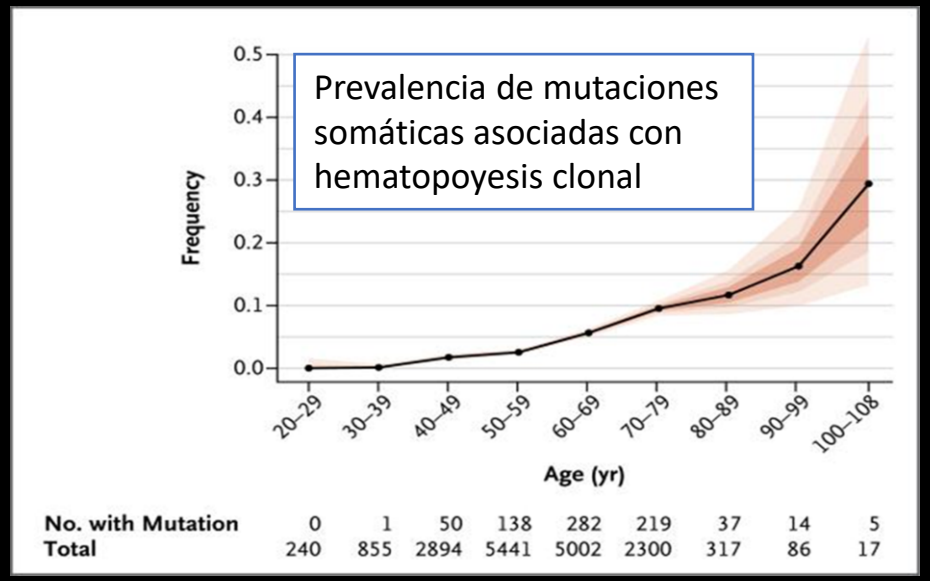
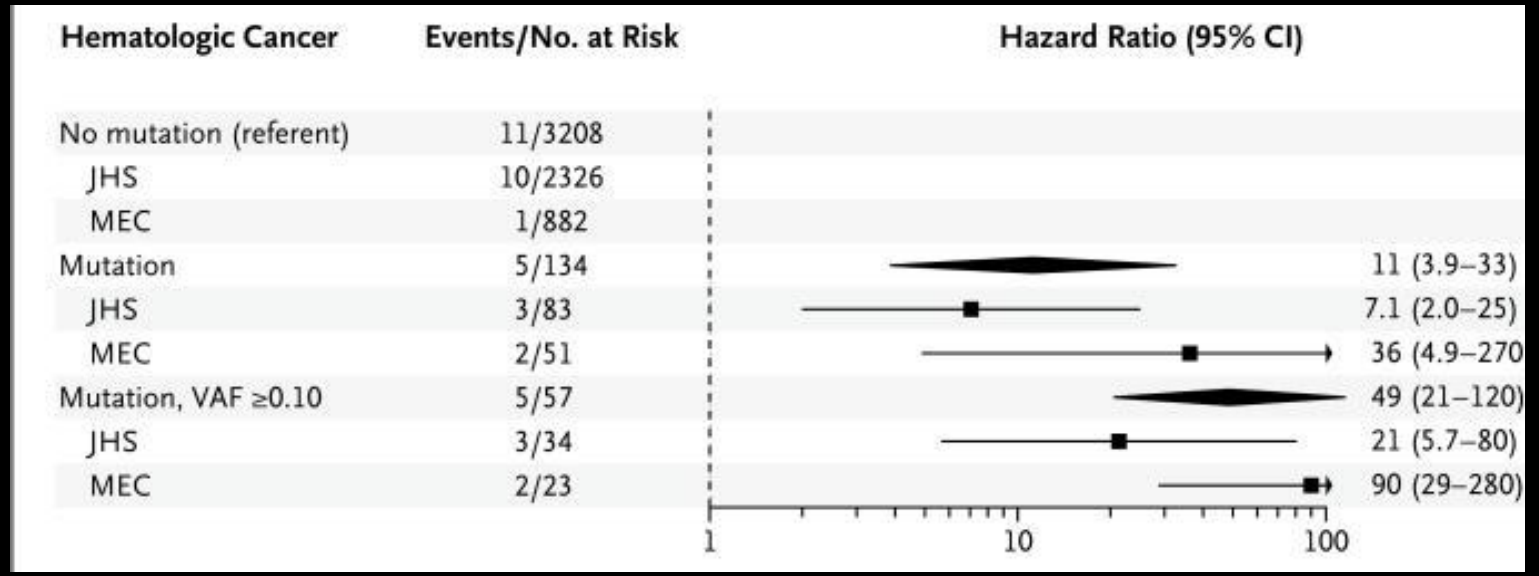
ORIGINAL ARTICLE

# Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes




*Jaiswal S et al. N Engl J Med. 2014;371:2488-98.*

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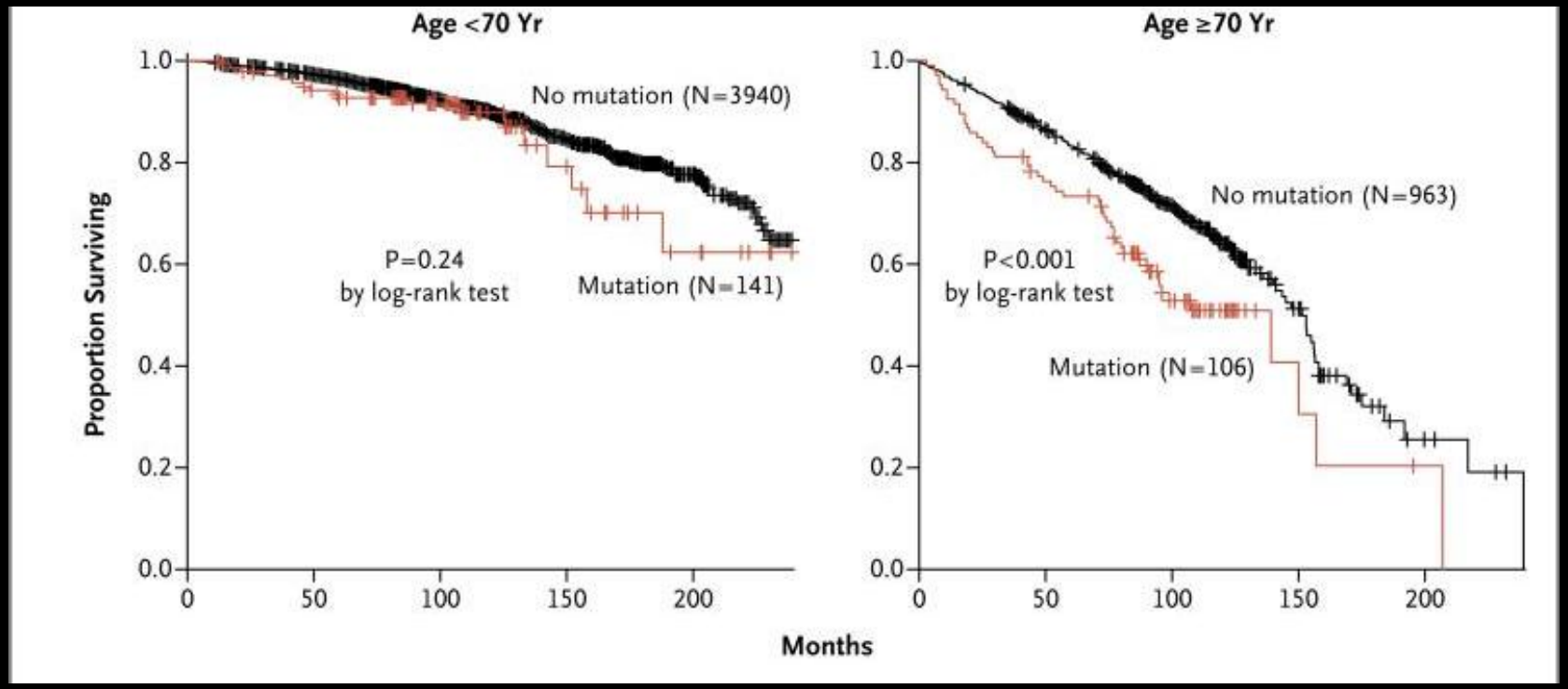
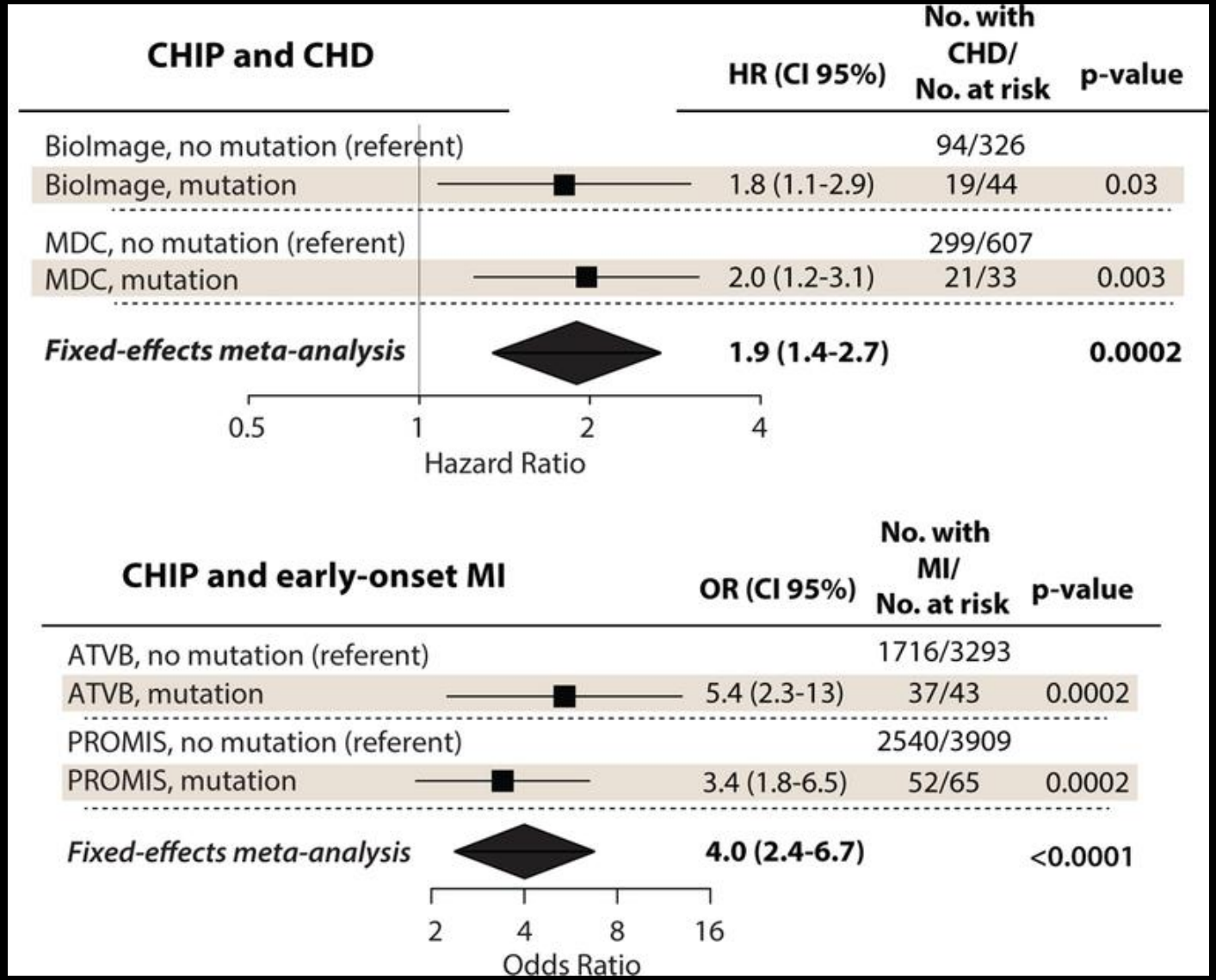


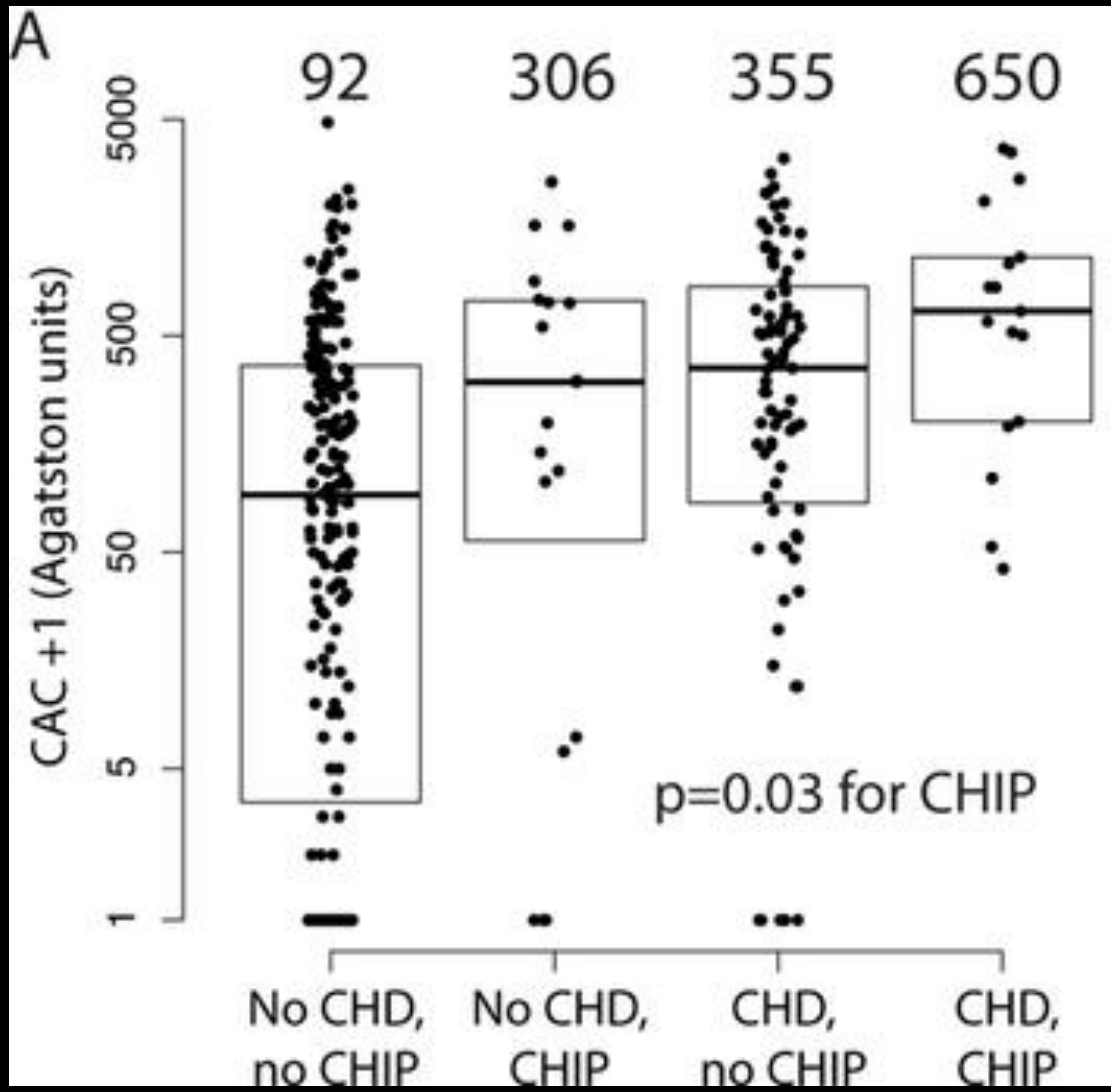

*Jaiswal S et al. N Engl J Med. 2014;371:2488-98.*

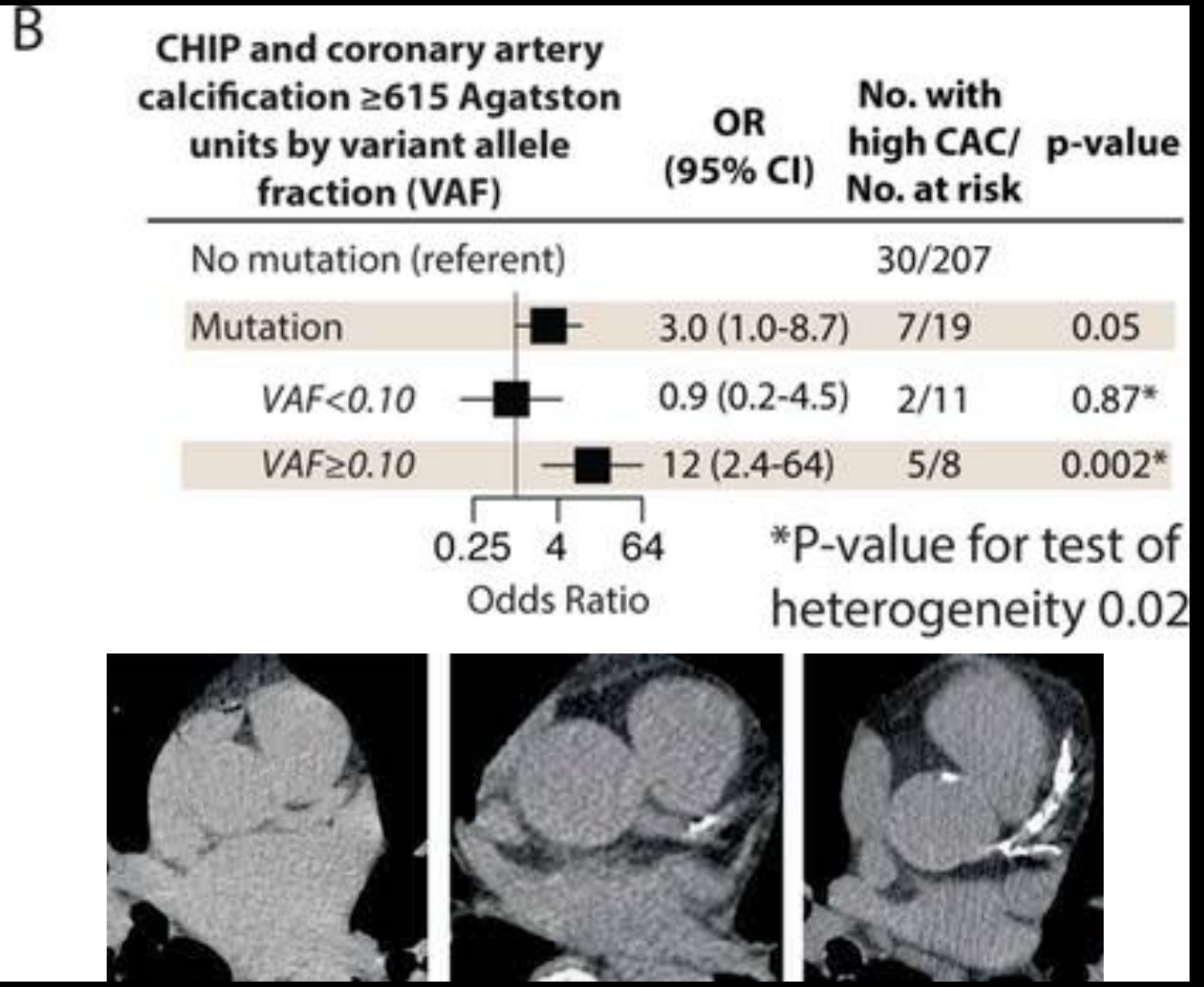
# Incidencia de enfermedad coronaria en función de CHIP en diferentes cohortes




Jaiswal S et al. N Engl J Med. 2017 13;377(2):111-121.

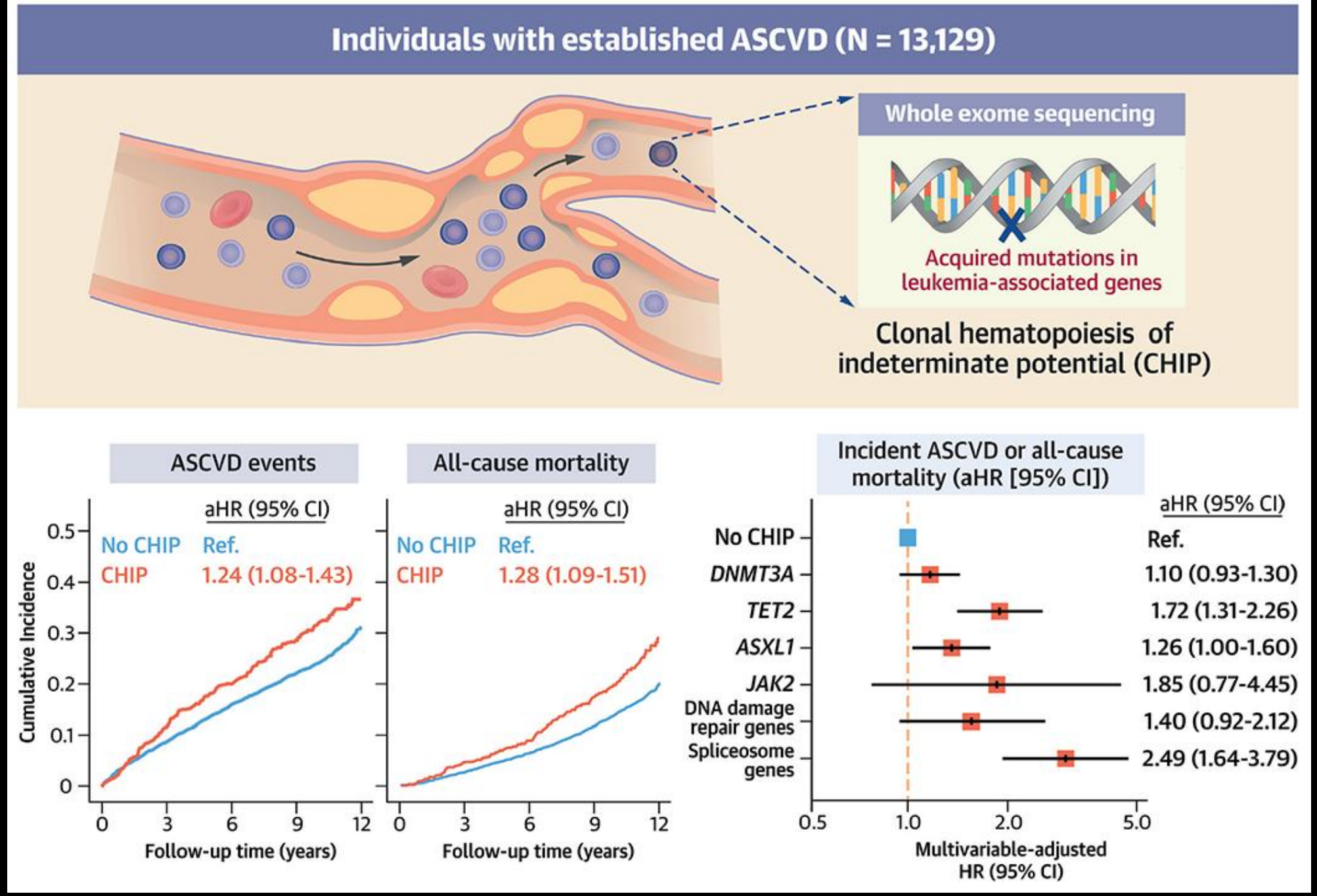
# Calcio coronario en función de la presencia y tamaño de CHIP



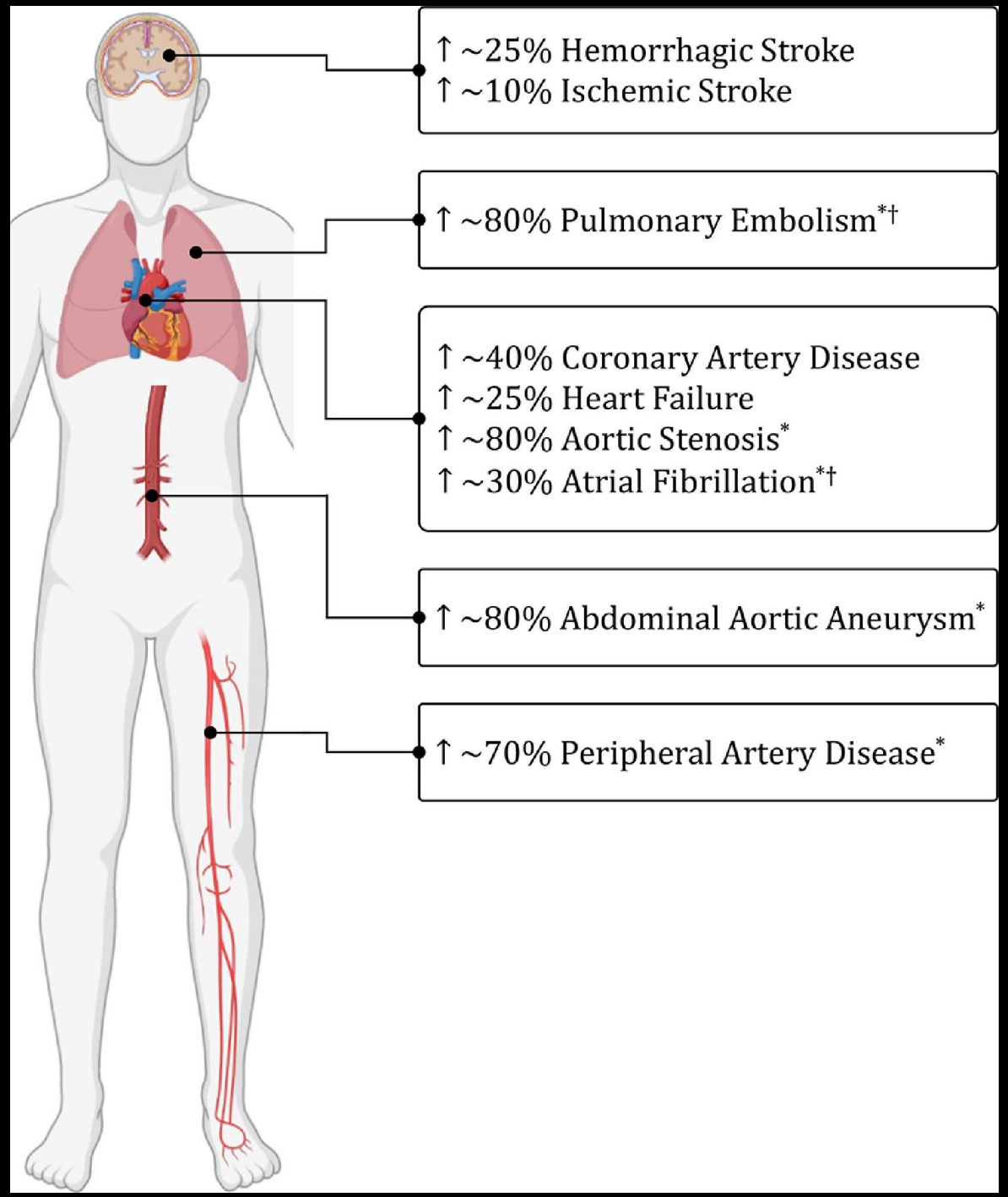






Jaiswal S et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. N Engl J Med. 2017 Jul 13;377(2):111-121.




Gumuser ED, et al. J Am Coll Cardiol. 2023 May 23;81(20):1996-2009.

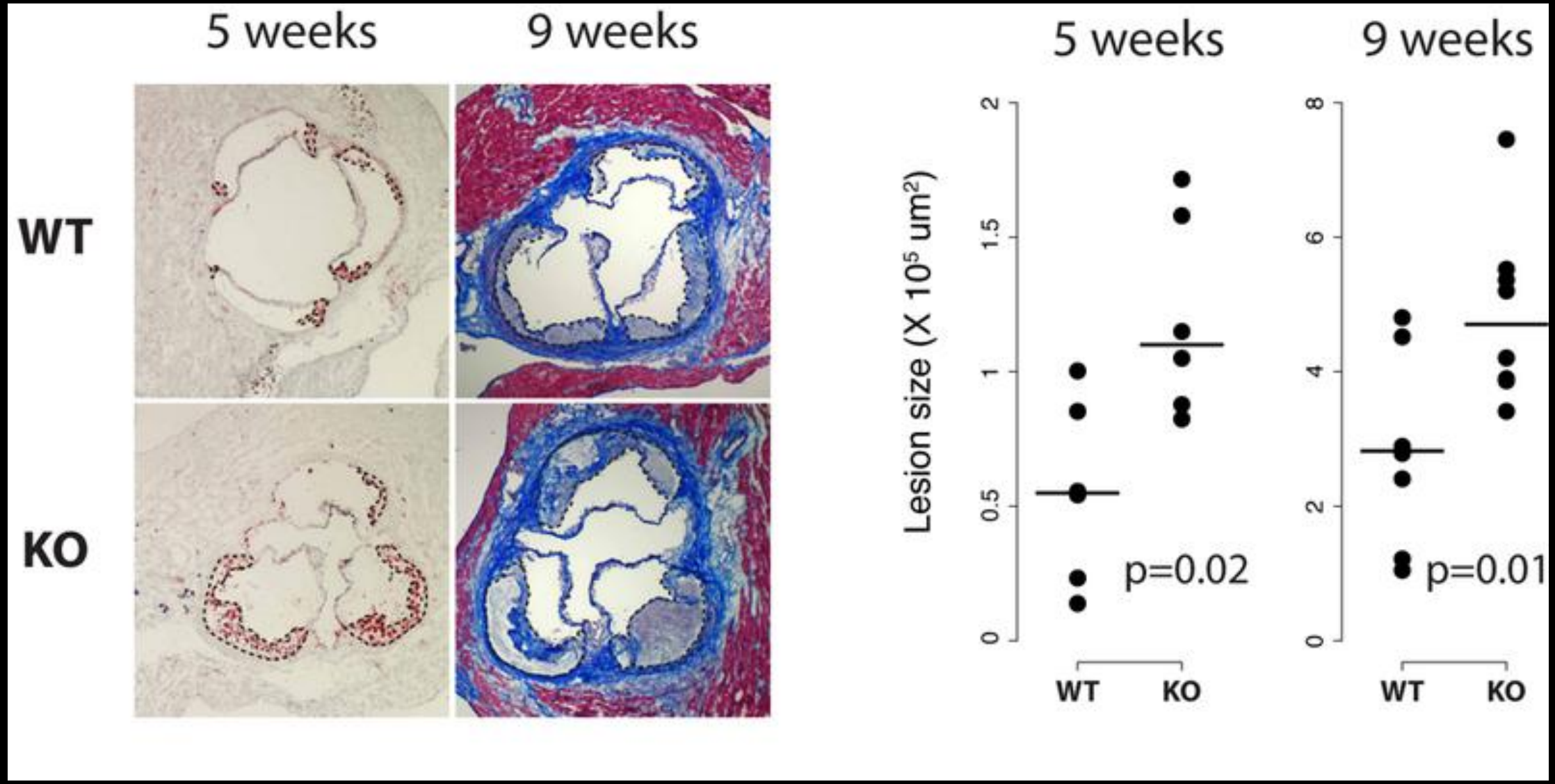



# Summary of association reported between CHIP and cardiovascular diseases.

* Not peer reviewed (preprint and preliminary analyses)
† The increased risk due to large CHIP (VAF ≥0.10)
Abbreviations: CHIP, clonal hematopoiesis of indeterminate potential; VAF, variant allele frequency.

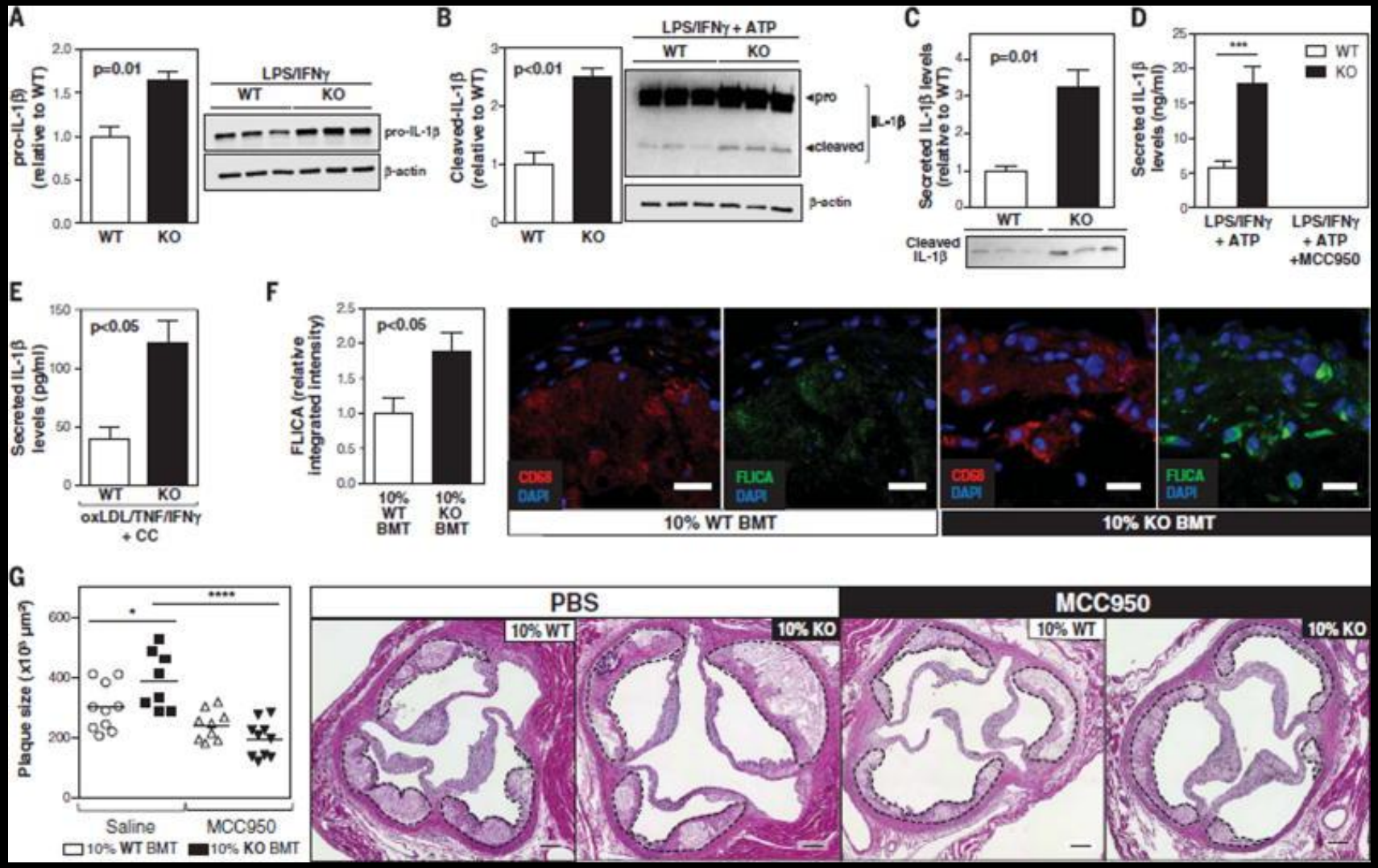
***Saadatagah S et al. Transl Res 2022:S1931-5244(22)00200-6. doi: 10.1016/j.trsl.2022.08.013***

# El trasplante de MO deficiente en TET2 aumenta la lesion aterosclerótica en un modelo de arteriosclerosis en ratón




Jaiswal S et al. N Engl J Med. 2017 Jul 13;377(2):111-121.

# El deficit de TET2 favorece una mayor expression de IL1β a través del inflamosoma NLRP3




Fuster JJ, et al. Science. 2017 Feb 24;355(6327):842-847.

# Mecanismos por lo que la expansión clonal se asocia con mayor riesgo de arteriosclerosis

- **Mayor actividad inflamatoria = activación del inflamosoma (NLRP3)**
- Mayor activación de los neutrófilos
- **Mayor interacción de monocitos/macrófagos clonales con el endotelio**
- Aumento de la formación de NET (Neutrophil Extracellular Trap)
- Cambios epigenéticos debido a la modulación de la metilación del ADN
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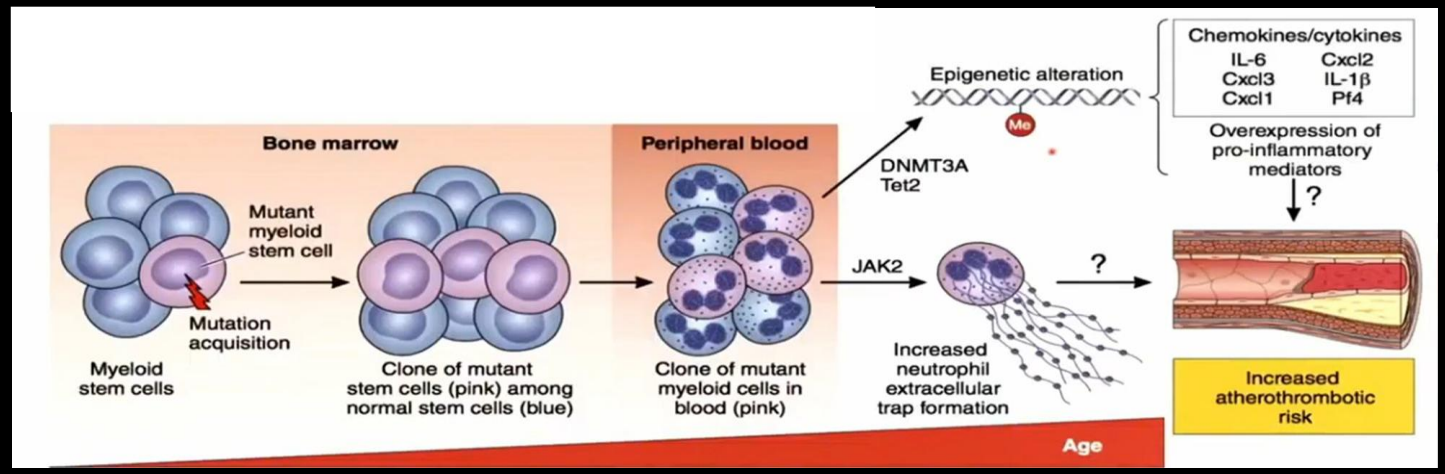


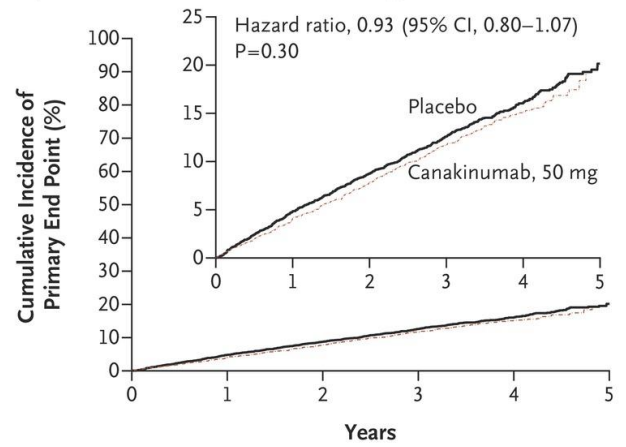
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2017 VOL. 377 NO. 12

# Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

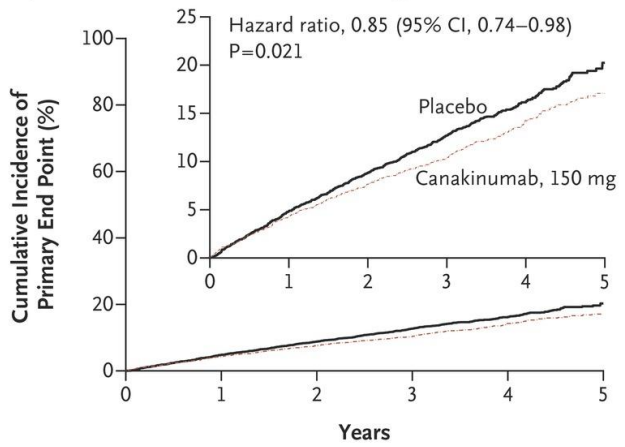
P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

**A Primary End Point with Canakinumab, 50 mg, vs. Placebo**



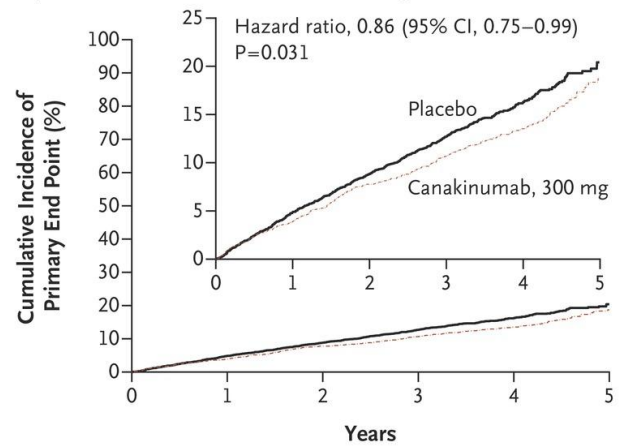

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 3344 | 3141 | 2973 | 2632 | 1266 | 210 |
| Canakinumab | 2170 | 2057 | 1950 | 1713 | 762 | 47 |

**B Primary End Point with Canakinumab, 150 mg, vs. Placebo**



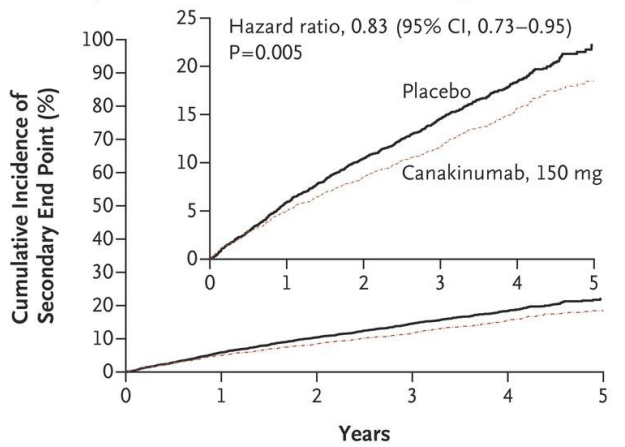

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 3344 | 3141 | 2973 | 2632 | 1266 | 210 |
| Canakinumab | 2284 | 2151 | 2057 | 1849 | 907 | 207 |

**C Primary End Point with Canakinumab, 300 mg, vs. Placebo**




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 3344 | 3141 | 2973 | 2632 | 1266 | 210 |
| Canakinumab | 2263 | 2149 | 2038 | 1819 | 938 | 199 |

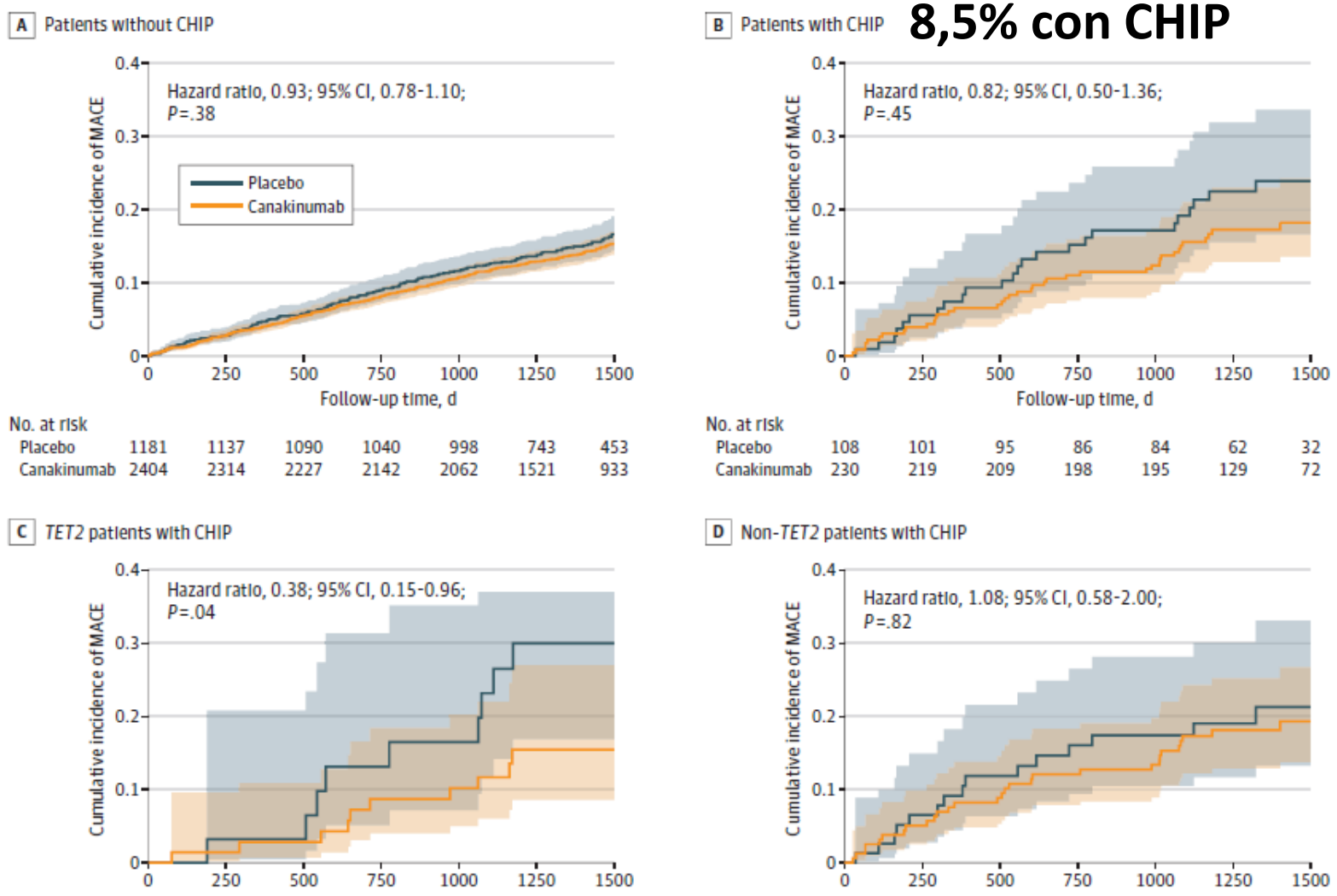
**D Key Secondary End Point with Canakinumab, 150 mg, vs. Placebo**




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 3344 | 3107 | 2921 | 2578 | 1238 | 206 |
| Canakinumab | 2284 | 2135 | 2039 | 1824 | 892 | 201 |

Figure 2. Association of Canakinumab and Placebo With Incident Major Adverse Cardiovascular Events (MACE) According to *TET2* Clonal Hematopoiesis of Indeterminate Potential (CHIP) Status

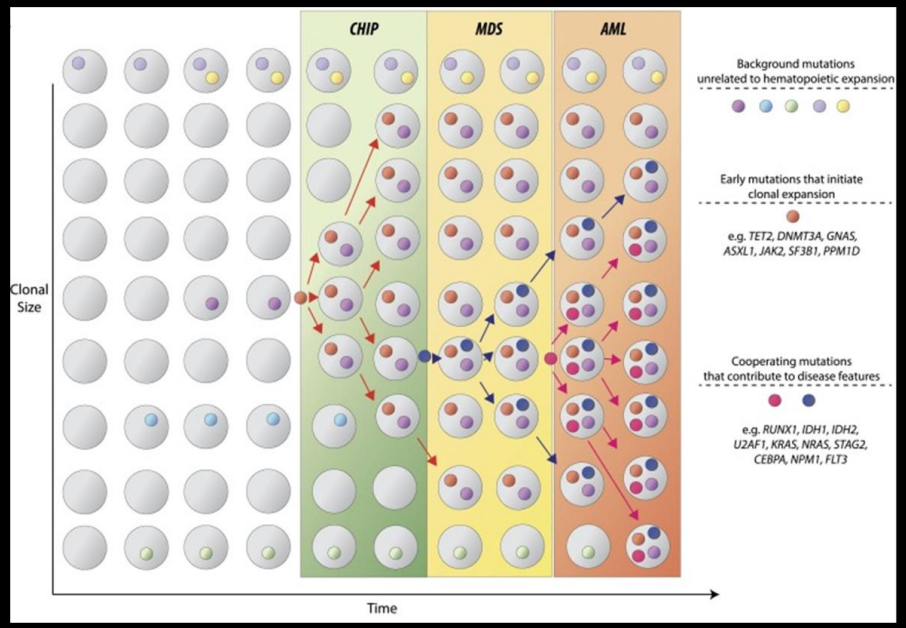
**8,5% con CHIP**



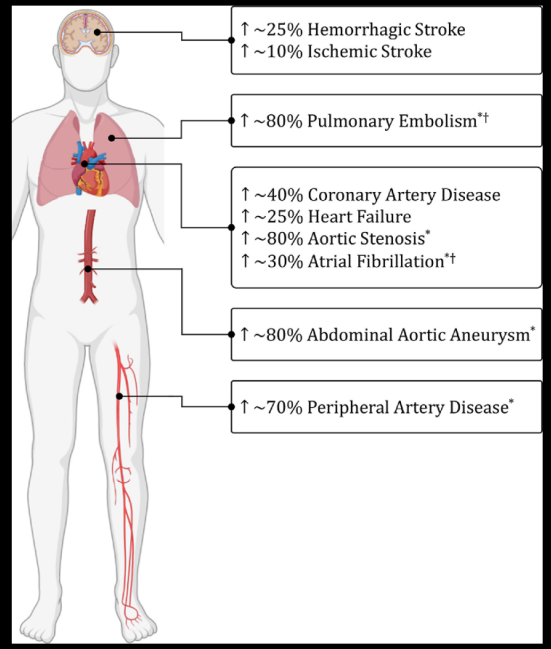

↓ MACE 7% sin CHIP

↓ MACE 18% con CHIP

↓ MACE 62% con CHIP secundario a mutaciones en *TET2*




Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, Ebert BL. Blood. 2015 Jul 2;126(1):9-16. doi: 10.1182/blood-2015-03-631747.

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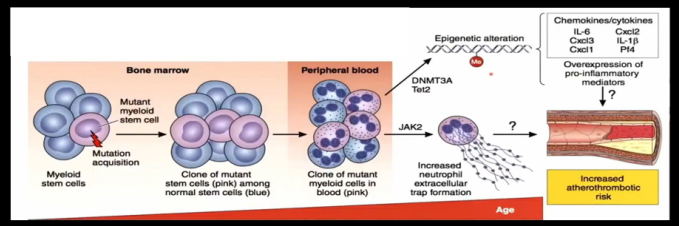


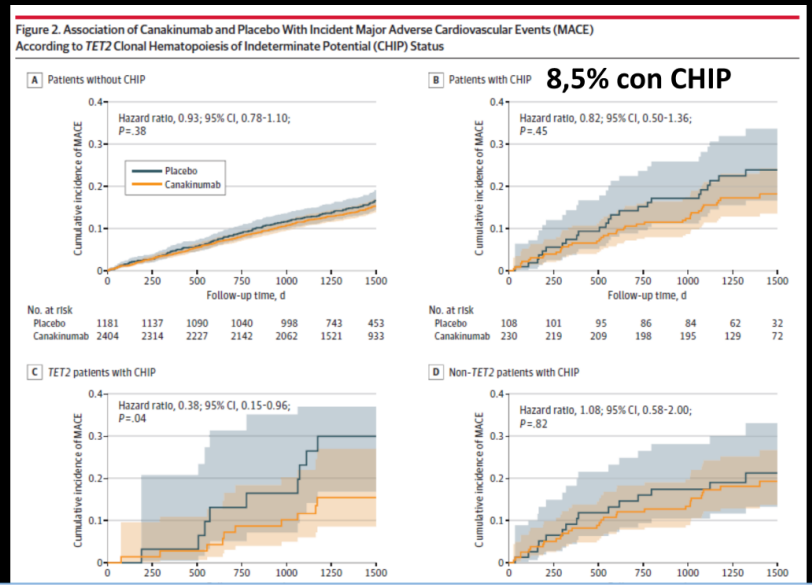


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