Ticagrelor and the inhibition of growth in small AAAs – results from a RCT

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A key limitation of contemporary treatment strategies of AAA is the lack of therapy directed at reducing expansion.

As a result, patients with small AAAs are simply monitored by regular repeat imaging → cost and reduced QoL.

∼70% of small AAAs eventually require surgical repair → risks of death and major complications as well as high cost.

Presently, about 15,000 men and women are being monitored for small AAAs in Sweden (population 10 million).
Platelet inhibitors

• Clinical data suggest a pathophysiological role for the intraluminal thrombus (ILT), and that platelet inhibitors may have a potential growth inhibitory effect


• Supported by morphological and experimental data

In an experimental rat model of AAA, treatment with AZD6140, a $\text{P}2\text{Y}_{12}$ receptor antagonist to inhibit platelet activation:

→ Significantly attenuated aneurysm formation

→ Reduction in inflammatory cell recruitment

→ Healing of aortic wall with preservation of elastin structure and enhanced SMC colonization
Ticagrelor (BriliqueTM, BrilintaTM)

- An Oral Reversible P2Y$_{12}$ Antagonist
- Potent antiplatelet drug
- Currently approved for Acute Coronary Syndrome (ACS)
- By blocking platelet aggregation, it is hypothesized that treatment with ticagrelor will reduce AAA progression by arresting expansion of the ILT and the recruitment of platelet:leukocyte aggregates
Multi-centre, randomized, double-blinded for Ticagrelor and placebo

**Inclusion criteria:** AAA diameter 35-49 mm, ASA-naïve

**Primary objective:** mean reduction in AAA volume growth rate (%) measured with MRI at baseline and 12 months

**Secondary objectives:** US/MRI-diameter growth rate, thrombus volume enlargement rate, need for surgery (≥55mm), aneurysm rupture

**Power:** 140 patients (70 patients per arm) provide 80% power to detect 20% reduction in growth rate
Enrolled (N=158)

Randomized (N=144)

Allocated to ticagrelor (n=72)
  Received ticagrelor (n=69)
  Discontinued intervention (n=14)
  Analyzed for ITT (N=69)
  Analyzed for PPA (N=55)

Allocated to placebo (n=72)
  Received placebo (n=70)
  Discontinued intervention (n=7)
  Analyzed for ITT (N=70)
  Analyzed for PPA (N=63)
AAA growth pattern

MRI volume (cm$^3$)  |  MRI diameter (cm)  |  US diameter (cm)

Days from baseline MRI

Days from baseline MRI

Days from baseline US
MRI Aortic volume change (%)

**Primary analysis (ITT)**

- **Ticagrelor**: 9.1%
- **Placebo**: 7.5%
- P = 0.205

**Supportive analysis (PPA)**

- **Ticagrelor**: 8.5%
- **Placebo**: 7.4%
- P = 0.372
Secondary endpoints

MRI Aortic diameter change

- Ticagrelor: 2.5 mm
- Placebo: 1.8 mm

p = 0.113

US Aortic diameter change

- Ticagrelor: 2.3 mm
- Placebo: 2.2 mm

p = 0.778

MRI Thrombus volume change

- Ticagrelor: 13.0%
- Placebo: 10.9%

p = 0.590
Adverse events

Dyspnea

Bradycardia

Bleeding

- Ticagrelor
- Placebo
Conclusion

- In this RCT the platelet inhibitor Ticagrelor did not inhibit growth of small AAA
  + RCT design
  + Strong platelet inhibitor with no non-responders
  + Highly reproducible and sensitive primary endpoint (volume)
  + Clear and robust results

- Platelet inhibition is not a viable therapeutic principle to reduce growth of small AAAs
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