Antiplatelet Therapy in Patients With Abdominal Aortic Aneurysm Without Symptomatic Atherosclerotic Disease

the benefits and risks associated with antiplatelet prophylaxis in those without symptomatic atherosclerotic disease are still not clear

- Abdominal aortic aneurysm (AAA) has been associated with a 2-fold increase in risk of cardiovascular ischemic events.
- Coexisting cardiovascular disease is one of the key determinants of prognosis during surveillance and post-AAA repair
- studies suggested higher survival among patients with AAA receiving antiplatelet therapy
- clinical guidelines recommend antiplatelet therapy for patients with symptomatic atherosclerosis disease

we designed a target trial using a target trial emulation framework12 with the purpose of estimating the effect of antiplatelet therapy vs no antiplatelet therapy on the risk of ischemic events (myocardial infarction [MI] and ischemic stroke) and bleeding in a cohort of patients with AAA without concomitant symptomatic atherosclerotic vascular disease

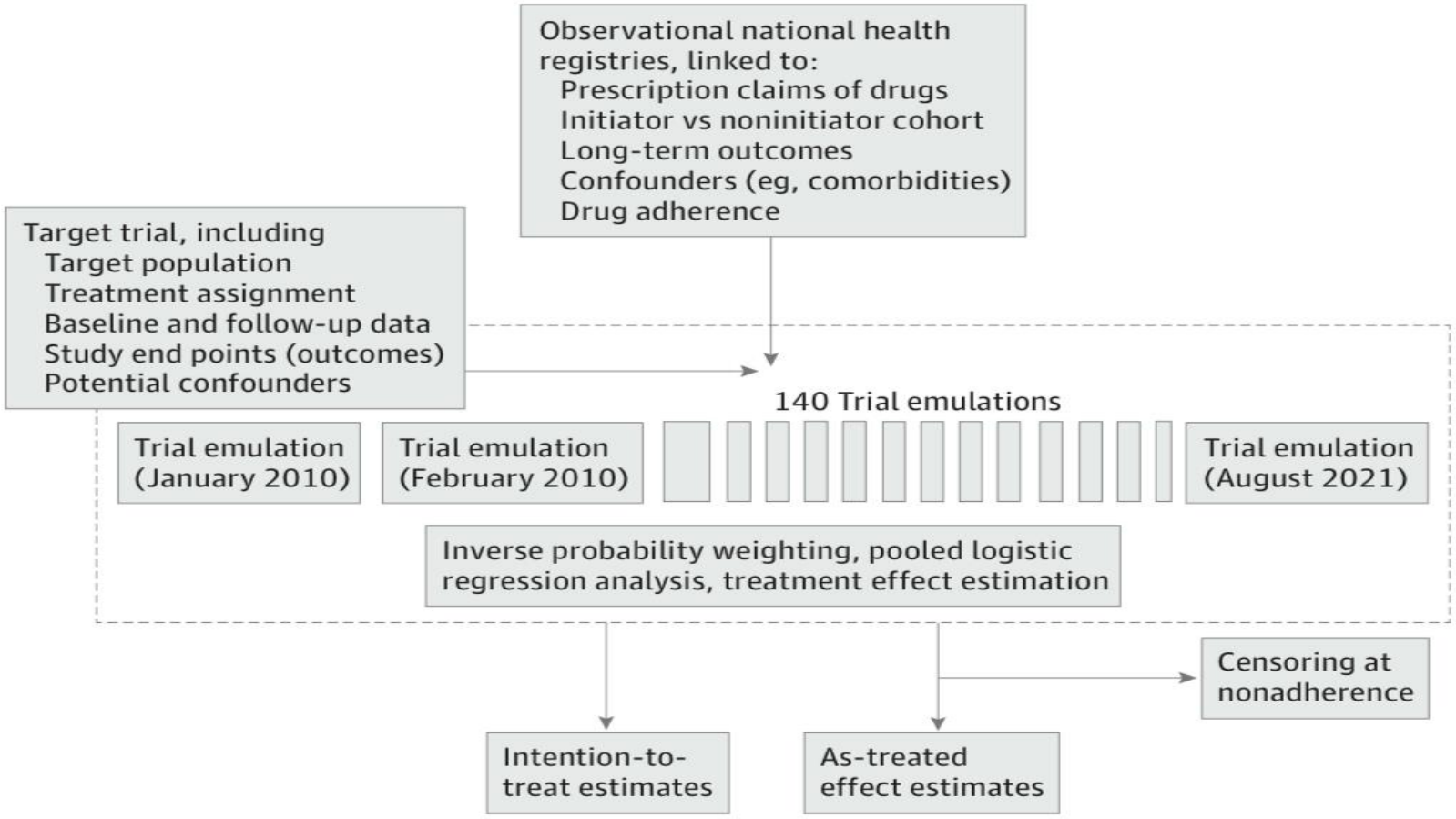
eligibility criteria (followed up for maximum of 5 years)

- Diagnosis of AAA
- Age 50-90
- No previous anti platelet therapy
- No other indication for anti platelet therapy(any history of atherosclerosis, ihd, ischemic stroke, peripheral arterial occlusive disease
- No contra indication for anti platelet therapy

- We retrieved information on diagnoses, hospitalizations, and outpatient visits from the Danish National Patient Registry (DNPR).
- The DNPR holds information on hospitalizations since 1977 and outpatient visits at all hospitals in Denmark since 1995
- Data include Civil Personal Registry numbers, dates of admission and discharge, primary and up to 20 secondary diagnoses

- We applied trial eligibility criteria to individuals registered in the DNPR between January 1, 2010, and August 21, 2021.
- To enable inclusion of patients eligible more than once, and to include noninitiators who later began antiplatelet therapy, we emulated the target trial as a sequence of trials, with a new trial starting each month, similar to previous study designs in other disease areas.
- , 140 trials were constructed

Figure 1. Study Design and Data Processing in Relation to Target Trial Specifications and Trial Emulation



Among patients with AAA who were antiplatelet-naive,

we compared 2 treatment strategies

(aspirin, 75-150 mg, or clopidogrel, 75 mg)

no initiation of antiplatelet therapy

Outcome Measures

- diagnosis of myocardial infarction (MI) and/or ischemic stroke.
- risk of MI and ischemic stroke separately and a safety outcome of major bleeding (defined as bleeding events leading to hospital contact)
- Follow-up started at the end of the baseline month of every sequential new trial and ended at the first outcome event, death, loss to follow-up, 5 years after baseline, or administrative end of data.

- the indicator for treatment was defined as initiation of antiplatelet therapy within the baseline month.

propensity score

- age (continuous and squared terms)
- Sex
- relevant comorbidity (hypertension, diabetes, atrial fibrillation, kidney disease, and heart failure)
- medical treatment with other cardioprotective agents (statins and antihypertensive therapy),
- proxy for smoking status (diagnosis of smoking-related chronic obstructive pulmonary disease, tobacco abuse/registered smoking status, smoking cessation advice, or prescription fill of medicine for smoking cessation).

- Briefly, individuals in the treatment arm were censored if they discontinued antiplatelet therapy
- individuals in the non treatment arm were censored if they initiated antiplatelet therapy
- Discontinuation; maximum gap between daily doses of 60 days (grace period)

Post baseline (time-varying) covariates

- , hypertension,
- diabetes,
- atrial fibrillation,
- kidney disease,
- heart failure,
- medical treatment with other cardioprotective agents (statins and antihypertensive therapy), and smoking.

Subgroup and Sensitivity Analyses

- , we selected clinically relevant subgroups for whom estimated treatment effect could potentially be different and performed:
- with or without concomitant statin therapy
- restricting the analyses to include only aspirin as exposure((as opposed to the main analysis including aspirin or clopidogrel)
- patients aged 80 years or older
- patients with a cancer diagnosis within the past 5 years.

We also conducted sensitivity analyses by prolonging the discontinuation gap between daily doses of prescription fills to 90 days only for the as-treated analyses. We then conducted analyses in a cohort restricted to patients with a maximum of 6 months between AAA diagnosis and study inclusion

- A total of 25 326 individuals(diagnosis of AAA)
- 6344 individuals(25.0%; 65.2% men; 34.8% women; median age, 72 [IQR, 64-78] years) met eligibility criteria)
- for multiple sequential trials, the patients contributed a total of 131 047 individual trial cases, of which 3363 initiated antiplatelet therapy and 127 684 did not
- g initiators of antiplatelet therapy, 3166 participants (94.1%) initiated aspirin, while 197 individuals (5.9%) initiated clopidogrel.

- the median age was 72.0 (IQR, 64.0- 78.0) years,
- 34.7% were women
- , 19.0% were registered smokers,
- 7.4% had a history of diabetes,
- 34.6% received concomitant statin therapy,
- 51.1% received concomitant antihypertensive therapy

- total of 5 011 227 person
- 182 ischemic events were observed among antiplatelet initiators,
- 5602 ischemic events were observed among those who did not initiate antiplatelet therapy.
- Median follow-up duration was 24 (IQR, 11-40) months for initiators and 23 months (IQR, 11-38) months for noninitiators

- , 114 ischemic events were observed among antiplatelet initiators and 4331 ischemic events were observed among noninitiators during a median follow-up of 18 (IQR, 8-34) months for initiators and 20 (IQR, 9-35) months for noninitiators.

Table 1. Baseline Characteristics of the Trial Population After IPTW

Characteristic	No. (%)			Standardized difference[a]
	Total (N = 131 047)	Noninitiators (n = 127 684)	Initiators (n = 3363)	
Sex				
Female	45 403 (34.6)	44 215 (34.6)	1188 (35.3)	0.003
Male	85 644 (65.4)	83 469 (65.4)	2175 (64.7)	
Age, median (IQR), y	72.0 (64.0-78.0)	72.0 (64.0-78.0)	72.0 (66.0-77.0)	0.072
Time since AAA diagnosis, mean (SD), d	1117 (1054)	1137 (1054)	356 (771)	0.846
Smoking[b]	24 350 (18.6)	23 701 (18.6)	648 (19.3)	0.010
Comorbidity				
Hypertension	31 590 (24.1)	30 739 (24.1)	851 (25.3)	0.019
Diabetes	5847 (4.5)	9385 (7.3)	252 (7.5)	<0.001
COPD	20 273 (15.5)	19 760 (15.5)	513 (15.3)	0.013
Chronic kidney disease[c]	891 (0.7)	867 (0.7)	24 (0.7)	0.002
Heart failure	1934 (1.5)	1882 (1.5)	51 (1.5)	0.002
Atrial fibrillation	2315 (1.8)	2250 (1.8)	65 (1.9)	0.011
Venous thromboembolism	4381 (3.3)	4287 (3.4)	94 (2.8)	0.036
Major bleeding[d]	7040 (5.4)	6896 (5.4)	144 (4.3)	0.056
Obesity[e]	4863 (3.7)	4741 (3.7)	122 (3.6)	0.007
Medical treatment				
Aspirin (in baseline month)	3166 (94.1)	NA	3166 (94.1)	NA
Clopidogrel (in baseline month)	197 (5.9)	NA	197 (5.9)	NA
Statin[f]	44 901 (34.2)	43 720 (34.2)	1181 (35.1)	0.007
Antihypertensive[f]	65 176 (49.7)	63 428 (49.7)	1748 (52.0)	0.030
Antidiabetic[f]	8422 (6.4)	8209 (6.4)	213 (6.3)	0.008

Abbreviations: AAA, abdominal aortic aneurysm; IPTW, inverse probability of treatment weights; NA, not applicable.

[a] Values less than 0.1 indicate no significant difference between groups.

[b] Registered smokers, previous and current.

[c] Disease registered more than 5 years prior to inclusion.

[d] Gastrointestinal, intracranial, and other major bleeding registered more than 6 months prior to inclusion.

[e] Registered body mass index greater than 25 (calculated as weight in kilograms divided by height in meters squared).

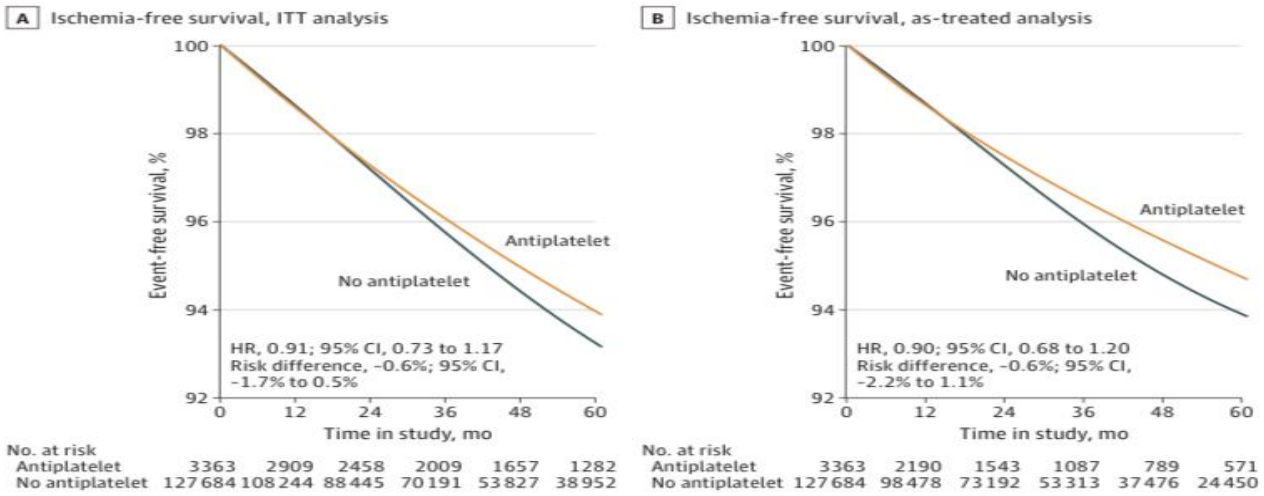
[f] Prescription fill within 1 year prior to inclusion.

Table 2. Estimated Intention-to-Treat and As-Treated HRs of Ischemic Events and Major Bleeding Outcomes With vs Without Antiplatelet Therapy

Outcome	Target trial emulation[a]									
	Estimated intention-to-treat effect					Estimated as-treated effect				
	Initiator (n = 3363)		Noninitiator (n = 127 684)			Initiator (n = 3363)		Noninitiator (n = 127 684)		
	No. of events	Event-free survival	No. of events	Event-free survival	Effect estimate, HR (95% CI)	No. of events	Event-free survival	No. of events	Event-free survival	Effect estimate, HR (95% CI)
Ischemic events	182	0.937	5602	0.931	0.91 (0.73-1.17)	114	0.943	4331	0.937	0.90 (0.68-1.20)
Myocardial infarction	66	0.977	2264	0.972	0.81 (0.57-1.23)	40	0.979	1904	0.972	0.76 (0.50-1.24)
Ischemic stroke	118	0.959	3442	0.957	0.95 (0.73-1.17)	74	0.965	2465	0.964	0.96 (0.73-1.20)
Major bleeding	129	0.947	3212	0.958	1.26 (0.97-1.58)	86	0.951	2349	0.961	1.21 (0.82-1.72)

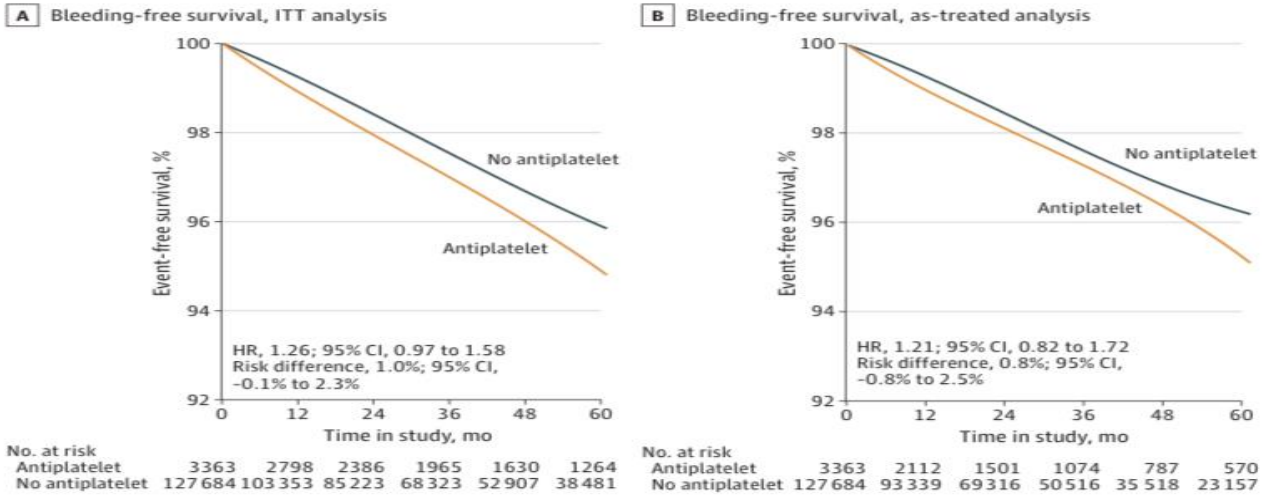
Abbreviation: HR, hazard ratio.

[a] Confidence intervals determined using nonparametric bootstrapping with 500 samples.



HR indicates hazard ratio; 95% CIs were determined using nonparametric bootstrapping with 500 samples.

Figure 3. Bleeding-Free Survival Estimates for Intention-to-Treat (ITT) and Treatment Analyses



HR indicates hazard ratio. Point estimates were determined using regression; 95% CIs were determined using nonparametric bootstrapping with 500 samples.

Safety Estimates for Bleeding Events

- , 129 events occurred among initiators and 3212 events among non initiators during follow-up
- The ITT HR for major bleeding events was 1.26 (95% CI, 0.97-1.58) (Table 2). The event free survival difference between initiators and noninitiators was 1.0% (95% CI, −0.1% to 2.3%) at 5 years' follow-up.

- For patients receiving concomitant statin therapy ; no significant difference for ischemic events and for bleeding events
- s for those not using statin therapy, the difference was more pronounced,
- or patients aged 80 years or older, data on only 568 initiators and 31 655 non initiators were available for analyses and showed a higher risk of ischemic events and bleeding

Discussion

- In this target trial emulation including patients with AAA without symptomatic atherosclerosis
- , we observed a trend toward lower risk of ischemic events among those receiving antiplatelet therapy but a higher risk of major bleeding.

, this is the largest-scale study to formally investigate the estimated effectiveness of antiplatelet therapy vs no treatment on the risk of ischemic events and bleeding in an AAA population without symptomatic atherosclerosis.

- Based on results from the ARRIVE and ASCEND trials, suggesting no or moderate ischemic risk reduction at the expense of an increased risk of bleeding,
- 5 Antiplatelet therapy is no longer recommended routinely but is considered beneficial only in specific patients at very high cardiovascular risk and with minimal risk of bleeding.

our findings, based on nationwide high-quality data, add to the evidence against recommending antiplatelet therapy for patients with AAA without symptomatic atherosclerosis

- trials investigating secondary prevention in atherosclerotic cardiovascular disease and from retrospective studies. They suggest lower all-cause mortality among patients with AAA receiving antiplatelet therapy.
- a more recent meta-analysis found no survival difference associated with antiplatelet therapy in patients with small AAAs (defined by an aneurysm diameter between 3 and 5.5 cm.
- while antiplatelet therapy was associated with lower all-cause mortality in a patients undergoing AAA repair

- A dedicated trial investigating the effect of antiplatelet therapy in patients with AAA with and without symptomatic atherosclerosis is still warranted
- Yet, based on the number of outcome events registered in our study, sample size calculations indicate the need of including more than 5000 individuals in such a trial (2500 in each treatment arm) to identify a difference in the risk of ischemic events.

Strengths

- large sample size,
- the broad variety of available variables,
- the long follow-up period,
- and the high validity of inclusion and outcome diagnosis
- r analyses of rare, and potentially late, outcomes, such as major bleeding

limitatoyions

- A key challenge in analyses using data from routine clinical practice is that treatment is not randomly assigned.
- n clinical practice, physicians may tend to initiate treatment in patients with expected high ischemic risk, but at the same time with a low risk of bleeding.
- study without selection bias might find higher risk of bleeding.
- Differences in unmeasured characteristics, potentially confounding our results, cannot be excluded
- n addition, since few patients initiated clopidogrel in this study, conclusions on the effectiveness of this drug specifically are limited

Conclusions

- antiplatelet therapy in patients with AAA without concomitant symptomatic atherosclerotic vascular disease, the absolute differences in risk between initiators and noninitiators of antiplatelet therapy were negligible, indicating no clinically meaningful difference.
- this study highlights the necessity for an RCT.
- , careful consideration in prescribing prophylactic antiplatelet therapy should be given for all patients with AAA.