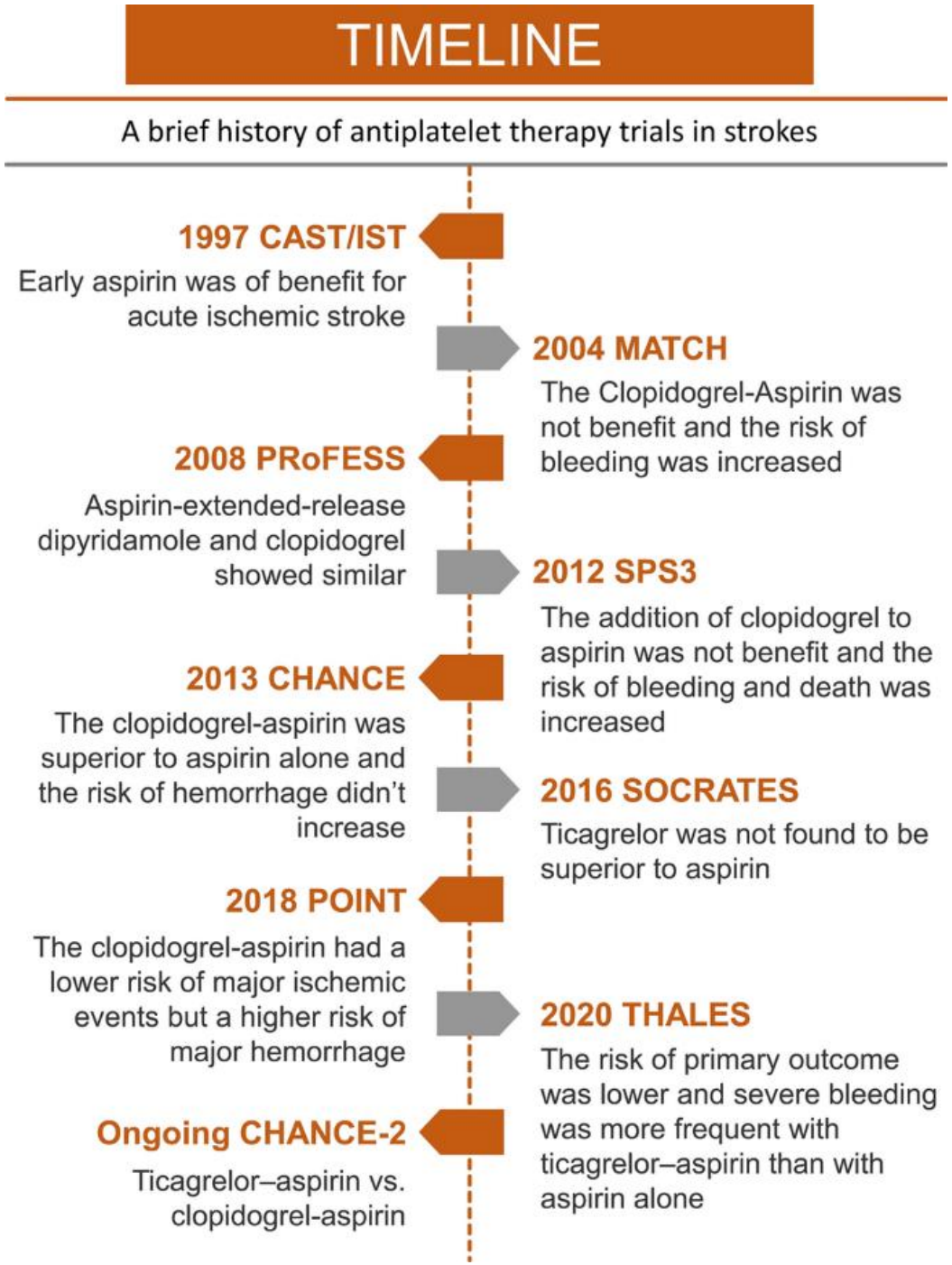
Ticagrelor nella prevenzione di ictus e declino cognitivo dei pazienti ad elevato rischio cardiovascolare: risultati di una metanalisi

Background

- Stroke is the second most common cause of death in the world, and it has become the main cause of affecting the quality of human life.
- Related anti-stroke drugs play an important role in the current treatment, especially antiplatelet drugs.
- Aspirin, clopidogrel and ticagrelor can inhibit platelet aggregation and have proved to be effective in the secondary prevention of stroke.

X. Li et al., IJC 353 (2022) 96–102

Antiplatelet therapy in stroke



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CHANCE 2 trial

Among Han Chinese pts with a minor ischemic stroke or high-risk TIA who carried CYP2C19 loss-of-function alleles, ticagrelor plus aspirin was superior to clopidogrel plus aspirin for preventing new stroke, without an increase in the risk of severe or moderate bleeding. Overall bleeding events, however, occurred more often with ticagrelor

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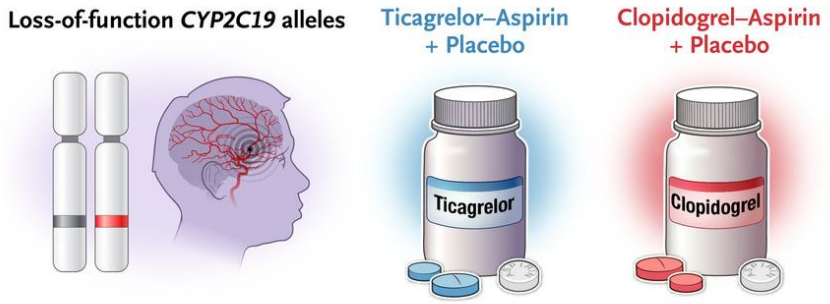

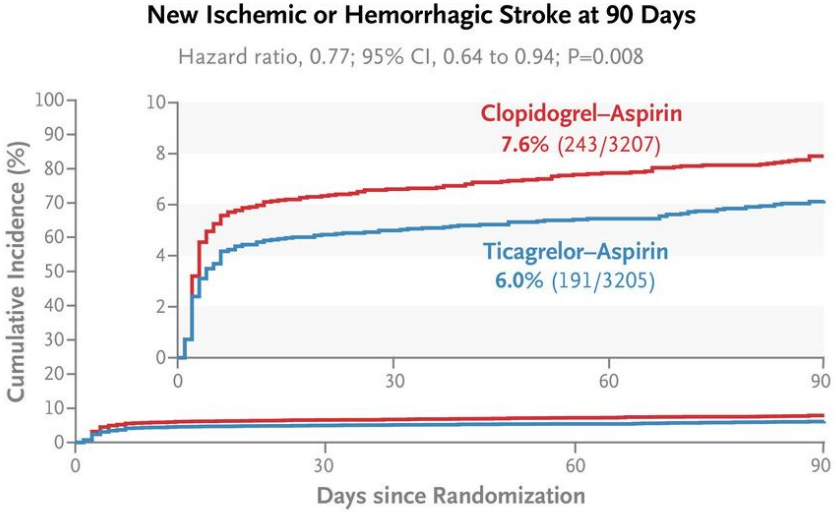

Severe or Moderate Bleeding at 90 Days

	Ticagrelor–Aspirin (N=3205)	Clopidogrel–Aspirin (N=3207)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Severe or moderate bleeding	9 (0.3)	11 (0.3)	0.82 (0.34 to 1.98)	0.66
Any bleeding	170 (5.3)	80 (2.5)	2.18 (1.66 to 2.85)	

Review

Ticagrelor for prevention of stroke and cognitive impairment in patients with vascular high-risk factors: A meta-analysis of randomized controlled trials

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X. Li et al., IJC 353 (2022) 96–102

Methods

- Meta-analysis to compare ticagrelor with other antiplatelet treatment in patients with vascular high-risk factors disease, defined as
  - acute coronary syndrome or coronary artery disease
  - stroke or transient ischemic attack,
  - peripheral artery disease.
- Authors searched the PubMed, Embase, and Cochrane libraries for published randomized controlled trials and additional available data from ClinicalTrials.gov.
- The primary outcome was related adverse stroke events and the secondary outcome was cognitive function related adverse events.
- The outcomes were statistically analyzed using Peto odds ratio.

X. Li et al., IJC 353 (2022) 96–102

Characteristics of included studies

12 RCTs with 105,654 patients were included in meta-analysis

Study name	Trialr	Age of TIC group (SD or IQR)	Male (%, TIC group)	Patient type	Experiment (dose)	N	Control	N
Cannon 2007	DISPERSE-2	64 ± 12.1/63 ± 11.4	204 (61.0)/211 (64.1)	ACS	TIC (90/180 mg)	334/329	CLO	327
Wallentin 2009	PLATO	62.1 ± 11.2[a]	6678 (71.6)	ACS	TIC (90 mg)	9333	CLO	9291
Goto 2015	PHILO	67 ± 12	306 (76.3)	ACS	TIC (90 mg)	401	CLO	400
Bonaca 2015	PEGASUS-TIMI 54	65.4 ± 8.4/65.2 ± 8.4	5368 (76.1)/5384 (76.4)	ACS	TIC (90/60 mg)	7050/7045	ASP+PLA	7067
Tang 2016	–	64.4 ± 11.4	142(71.0)	ACS	TIC (90 mg)	200	CLO	200
Johnston 2016	SOCRATES	65.8 ± 11.2	3830(58.1)	Stroke/TIA	TIC (90 mg)	6589	ASP	6610
Hiatt 2017	EUCLID	66(60–72)	8838(72.5)	PAD	TIC (90 mg)	6930	CLO	6955
Berwanger 2018	TREAT	59(51.6–65.2)	1480(77.4)	ACS	TIC (90 mg)	1913	CLO	1886
Steg 2019	THEMIS	66.0(61.0–72.0)	6576(68.4)	CAD	TIC (90 mg)	9619	ASP+PLA	9601
Wang 2019	PRINCE	61.1 ± 8.5	245(72.9)	Stroke/TIA	TIC (90 mg)	336	CLO	339
Johnston 2020	THALES	65.2 ± 11.0	3415(61.8)	Stroke/TIA	TIC (90 mg)	5523	ASP	5493
Silvain 2020	ALPHEUS	66.0 ± 9.2	764(81.1)	CAD	TIC (90 mg)	941	CLO	942

X. Li et al., IJC 353 (2022) 96–102

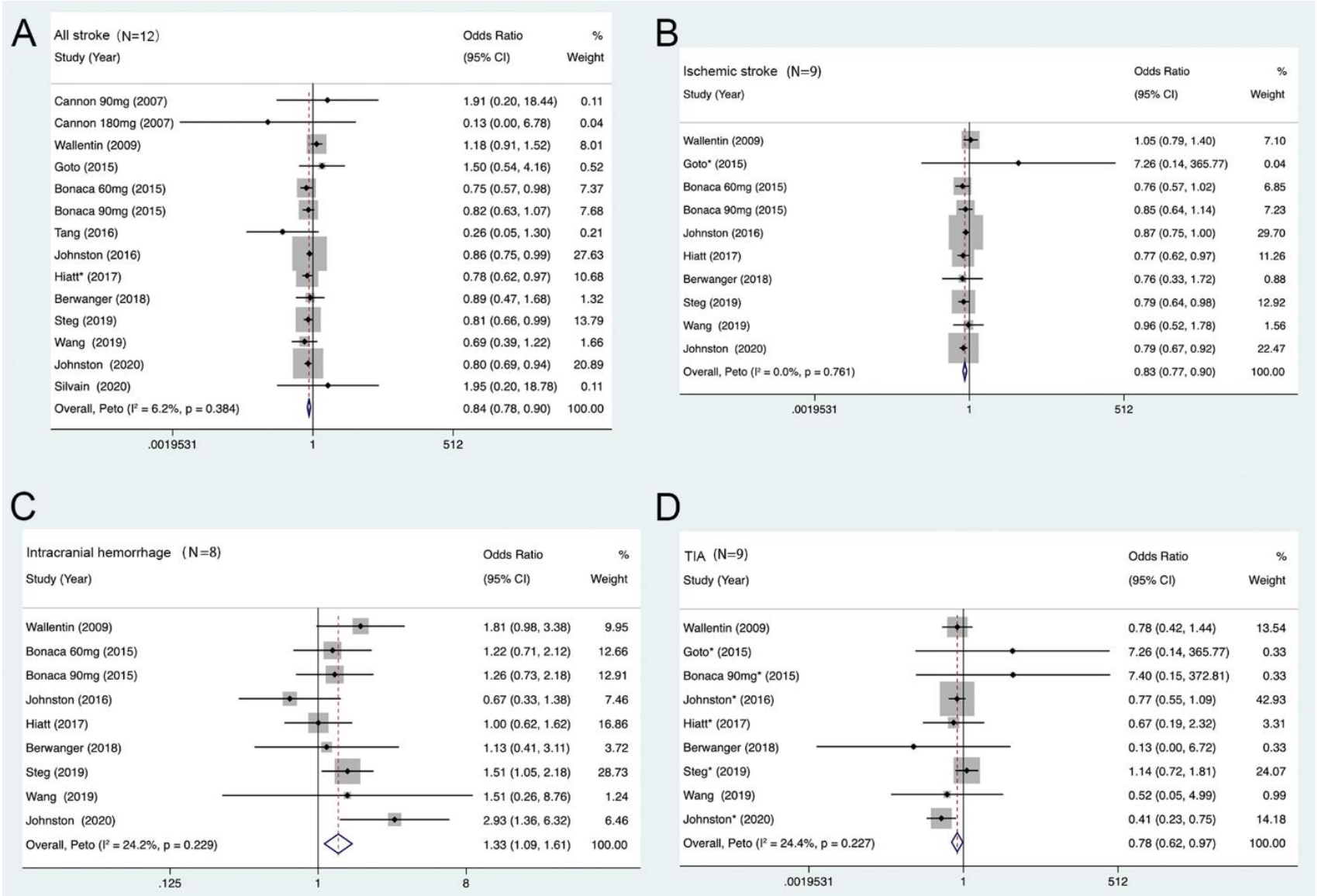
Relevant adverse events

Outcome	Trial N[a]	Ticagrelor n/N	Control n/N	OR (95%CI)	P Value	I^2 (%)	Heterogeneity P value
All stroke	12	1359/56543	1607/56505	0.84 (0.78, 0.90)	0.000	6.2	0.384
Ischemic stroke	9	1235/54725	1484/54689	0.83 (0.77, 0.90)	0.000	0.0	0.761
Hemorrhagic stroke	8	73/54072	64/54045	1.14 (0.81, 1.59)	0.448	29.6	0.182
Intracranial hemorrhage	8	230/54014	173/53962	1.33 (1.09, 1.61)	0.005	24.2	0.229
TIA	9	133/47501	171/47429	0.78 (0.62, 0.97)	0.029	24.4	0.227
Death (all-cause)	12	3691/56543	3842/56505	0.95 (0.91, 1.00)	0.058	27.9	0.157
Headache	8	716/52867	696/52854	1.02 (0.92, 1.14)	0.655	54.1	0.021
Dizziness	8	102/52878	73/52854	1.39 (1.03, 1.87)	0.032	0.0	0.529
Epilepsy	6	23/51823	18/51820	1.28 (0.69, 2.35)	0.435	33.9	0.169
Parkinson's Disease	6	4/45661	16/45619	0.30 (0.12, 0.72)	0.007	0.0	0.668
Cognitive Disorder	4	4/39751	4/39746	1.00 (0.25, 4.00)	0.998	0.4	0.404
Dementia	6	4/51823	15/51820	0.31 (0.13, 0.77)	0.012	17.6	0.296
Anxiety	7	20/52210	16/52200	1.25 (0.65, 2.40)	0.507	24.8	0.232
Depression	5	49/46300	46/46327	1.07 (0.71, 1.59)	0.754	0.0	0.688
Insomnia	5	95/33885	67/33848	1.45 (1.05, 2.00)	0.026	0.0	0.639

X. Li et al., IJC 353 (2022) 96–102

Forest plot of ticagrelor and control groups

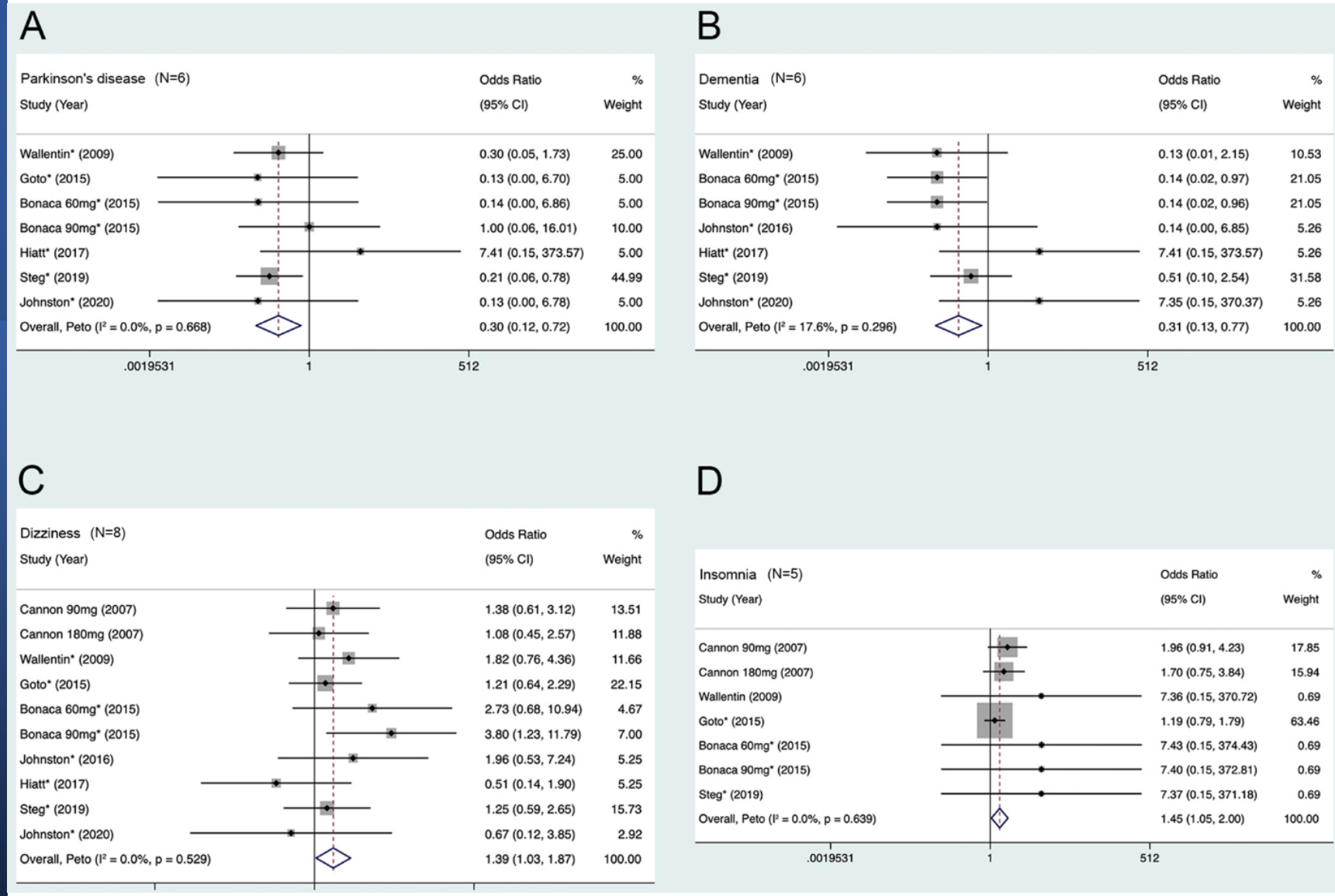
A: all stroke (OR 0.84, 0.78–0.90, P < 0.001);
B: ischemic stroke (OR 0.83, 0.77–0.90, P < 0.001);
C: intracranial hemorrhage (OR 1.33, 1.09–1.61, P = 0.005)
D: TIA: Transient ischemic attack (OR 0.78, 0.62–0.97, P = 0.029)



X. Li et al., IJC 353 (2022) 96–102

Forest plot of ticagrelor and control groups

A: Parkinson's disease (OR 0.30, 0.12–0.72, P = 0.007);
B: dementia (OR 0.31, 0.13–0.77, P = 0.012);
C: dizziness (OR: 1.39, 1.03–1.87, P = 0.032);
D: insomnia (OR 1.45, 1.05–2.00, P = 0.026



X. Li et al., IJC 353 (2022) 96–102

Limitations

- Patients with different types of diseases are included, and it is suggested that researchers classify the patients with different diseases in the future.
- There are different definitions for the diagnosis of cognitive diseases.
- The original texts and ClinicalTrials.gov of some studies cannot collect available data, so we have to exclude these studies in the analysis.
- The number of adverse event reports is very small.
- The follow-up time of less than one year in some included studies may be a limitation.

Conclusions

- The results of the meta-analysis suggests a protective effect of ticagrelor against all-cause stroke.
- Secondary outcomes suggest that ticagrelor has a protective effect on ischemic stroke and TIA, but the incidence of intracranial hemorrhage, dizziness, and insomnia should not be ignored.
- Ticagrelor may reduce the risk of dementia and Parkinson's disease, although data are limited.