Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

Effectiveness and safety of ticagrelor compared with clopidogrel and prasugrel:

results from a cohort study

in the nationwide French claims and hospitalisation database (SNIIRAM)

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Conflicts of interest

- Study supported by an unconditional grant from AstraZeneca
- EMA EUPAS registry No.5987
- Supervised by an independent Scientific Committee
- Conducted and analysed independently by the Bordeaux PharmacoEpi platform

Rationale and background

- **Ticagrelor** *(antiplatelet agent – APA)*
  - European Market Authorization (2010) co-administered with acetylsalicylic acid (ASA), for the prevention of athero-thrombotic events (ATE) in adult patients
  - with acute coronary syndrome (ACS): unstable angina, non ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]
  - including patients managed medically, or with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG)
- Request from French Health Technology Assessment agency (HAS) for a risk-benefit evaluation in real-life settings

Objectives

- Estimate and compare the 1-year incidence of ACS, stroke, all-cause death and major bleeding in patients treated with APA for secondary prevention of ACS, between:
  - Ticagrelor versus clopidogrel
  - Ticagrelor versus prasugrel

Methods (1)

- **Cohort** of patients hospitalised in 2013
  - For unstable angina or MI (STEMI, NSTEMI)*
  - With intensive care unit (ICU) stay during the index hospitalisation
  - Followed ≥ 1 year in **the nationwide claims and hospitalisation database (SNIIRAM)**
- **Exposure**
  - First APA treatment prescribed within the month after discharge
- **Outcomes** *(hospitalization occurrence during period on initial APA treatment, among 1 year of follow-up)*
  - **Effectiveness**
    - Composite including ACS* (with ICU stay), stroke*, death
    - Each individual component of the composite
  - **Safety**
    - Major bleeding*

** main diagnosis of hospitalisation*

Methods (2)

- **Statistical analysis** *(ticagrelor vs clopidogrel, ticagrelor vs prasugrel)*
  - **Matching 1:1 on** gender, age (±1 year) and high dimensional propensity score (hdPS, ± 0.05) according to index hospitalisation (unstable angina, STEMI, NSTEMI)
  - Cox proportional hazards or Poisson model on matched patients, adjusted for:
    - ASA at index date
    - Incident ACS or naive antiplatelet agent (APA)
    - Time-dependent variables for exposure to beta-blockers, ASA, statins, ACEI or ARB (secondary cardiovascular prevention)

Results: populations

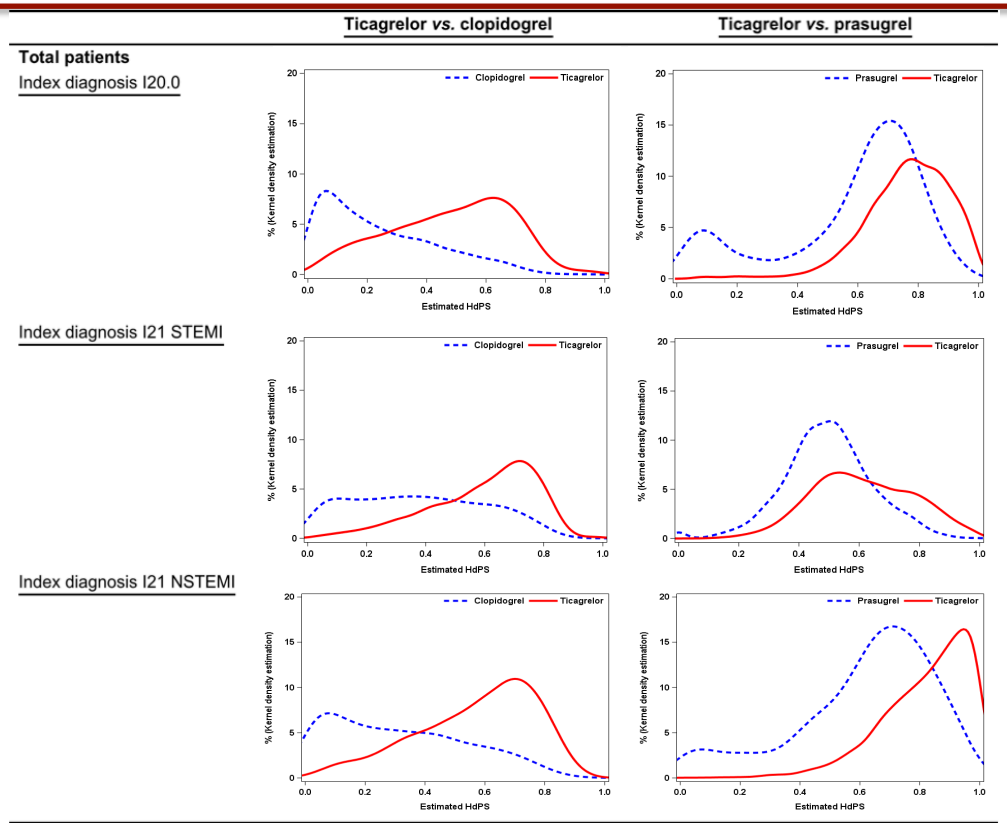
	Population n
Selection criteria - First hospitalisation with I20.0 or I21 primary diagnosis - Between 1 January 2013 and 31 December 2013 - Without history of ACS (I20.0, I21-24) in the 30 days before - In a teaching/regional hospital, other public or private hospital - With at least one day in an intensive care unit	**76 844**
Exclusion criteria	**22 747**
- Index hospitalisation duration = 0 day and alive at discharge	748
- Uncertain identification (several twins or beneficiaries)	68
- Less than 18 years at index date	6
- Less than 365 days of history in SNIIRAM before index date	2 095
- Death during index hospitalisation	3 911
- Alive at discharge and without any reimbursed healthcare in the 365 days after index date	1 888
- Rehabilitation centre in the 30 days after index date	14 031
Study population	**54 097**
- Clopidogrel (± ASA)	**19 796**
- Ticagrelor (± ASA)	**13 916**
- Prasugrel (± ASA)	**8 242**
- ASA alone	7 068
- No APA (no dispensation within 30 days after discharge)	5 026
- Others: other APA or association of several APA (± ASA)	49
1:1 matched populations *(on sex, age ± 1 year, hdPS ± 0.05, diagnosis of index ACS)*	
Ticagrelor versus clopidogrel (per group)	**9 224**
Ticagrelor versus prasugrel (per group)	**6 752**

Patients' characteristics at index date (study population)

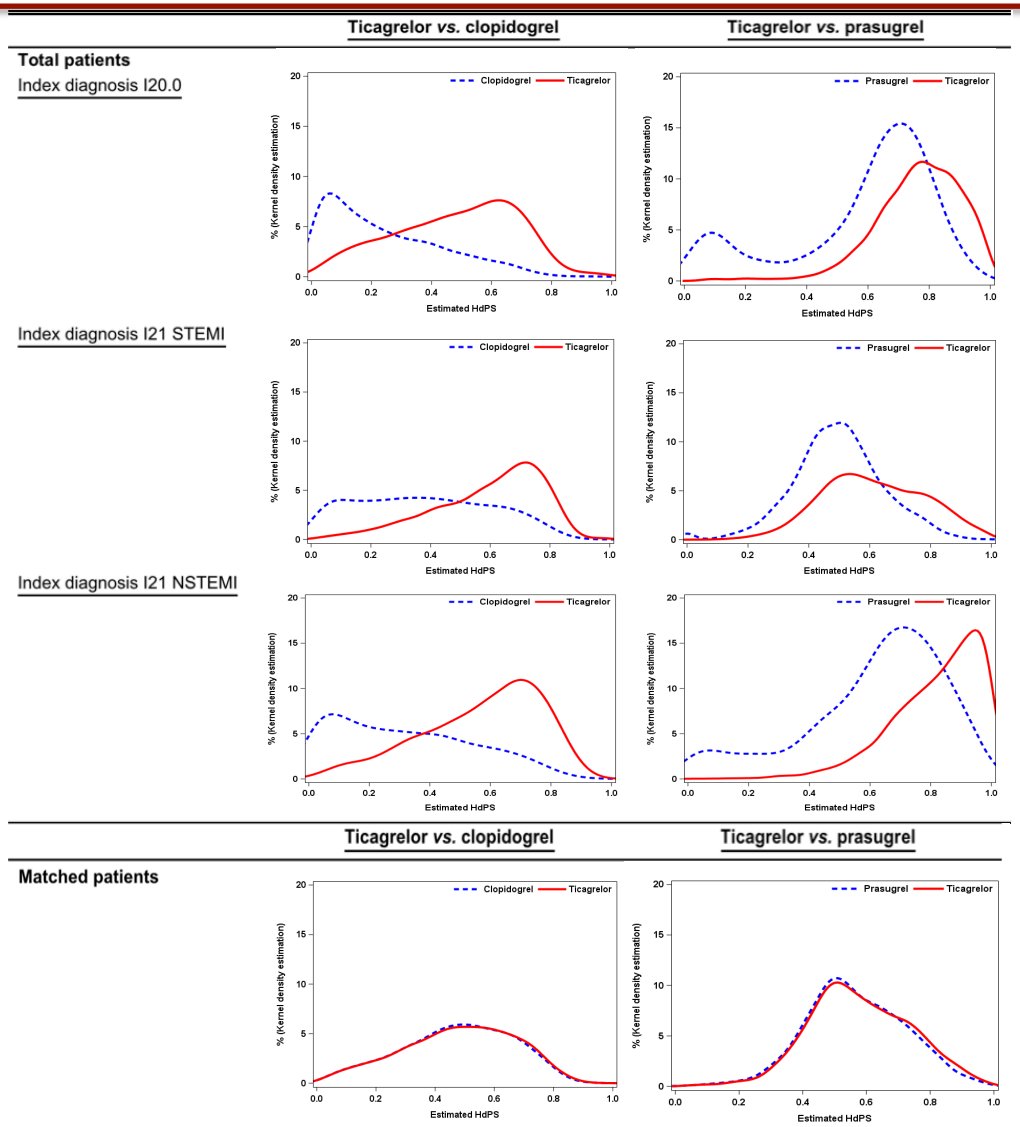
	Ticagrelor n = 13916	Clopidogrel n = 19796	SD* (Tica. vs Clo.)	Prasugrel n = 8242	SD* (Tica. vs Pra.)
Male	76.2%	67.6%	*19.2*	85.6%	*-24.1*
Age, Mean (± SD)	63.4 (12.7)	71.5 (13.1)	*-15.8*	58.1 (10.0)	*12.6*
Primary diagnosis at index ACS					
Unstable angina	27.1%	41.1%	*-29.9*	18.7%	*20.1*
STEMI	54.9%	41.6%	*26.9*	72.4%	*-37.0*
NSTEMI	18.0%	17.3%	*1.8*	8.9%	*26.9*
Procedures performed (index ACS)					
Percutaneous coronary intervention	88.8%	70.3%	*47.1*	93.9%	*-18.2*
Coronary artery by-pass grafting	0.1%	0.8%	*-10.5*	0.0%	*4.5*
Charlson comorbidity index					
[0-1]	3.7%	2.8%	*5.1*	3.0%	*3.9*
[2-3]	31.3%	15.9%	*36.9*	40.9%	*-20.1*
[4-5]	34.3%	27.4%	*15.0*	35.4%	*-2.3*
[6-7]	20.7%	28.7%	*-18.6*	15.4%	*13.8*
>7	10.1%	25.2%	*-40.4*	5.4%	*17.6*
Risk factors					
Diabetes mellitus	20.2%	27.1%	*-16.3*	20.7%	*-1.2*
Hypertension	14.1%	28.1%	*-34.8*	11.5%	*7.8*
Coronary artery disease	12.3%	22.1%	*-26.2*	10.9%	*4.4*
Congestive heart failure	2.6%	8.0%	*-24.3*	1.9%	*4.7*
Peripheral arterial disease	3.7%	8.4%	*-19.8*	2.9%	*4.5*
Acute coronary syndrome	6.7%	11.0%	*-15.2*	5.4%	*5.5*
Ischemic or undefined stroke	1.4%	3.5%	*-13.6*	0.7%	*6.9*
Major bleeding	1.2%	2.8%	*-11.4*	1.0%	*1.9*

* Crude standardized difference (%)

hdPS distributions



hdPS distributions



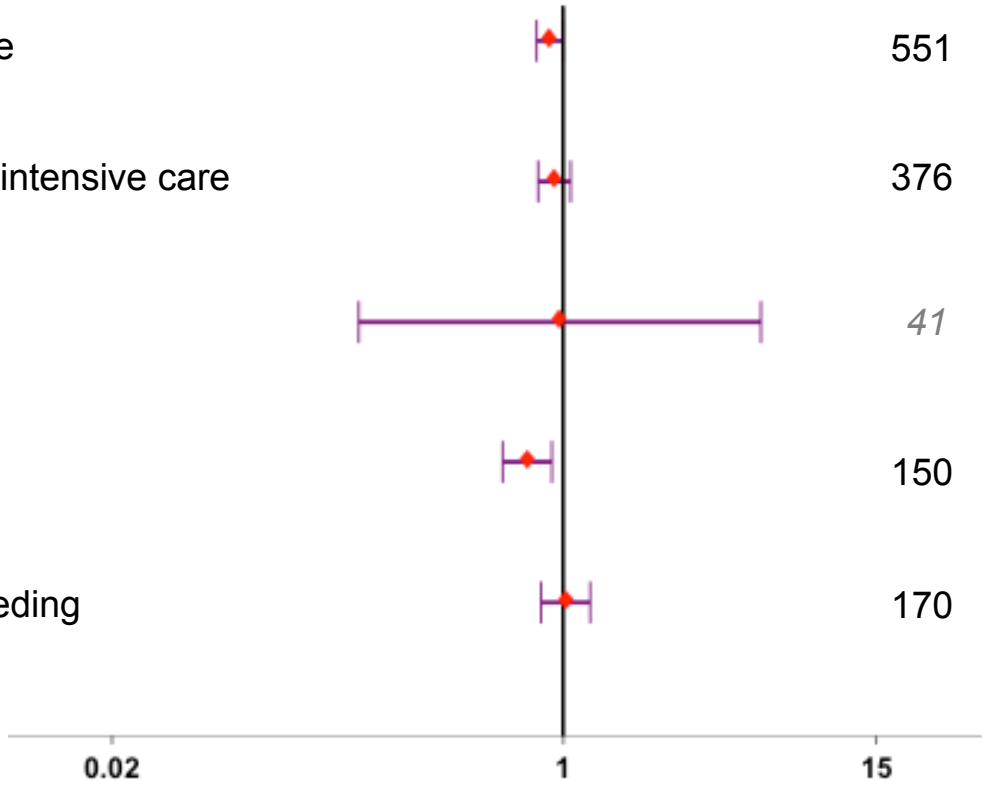
Patients' characteristics at index date (matched populations)

	Ticagrelor n = 9224	Clopidogrel n = 9224	*SD**	Ticagrelor n = 6752	Prasugrel n = 6752	*SD**
Male	73.5%	73.5%	*0.0*	84.9%	84.9%	*0.0*
Age, Mean (± SD)	66.5 (12.4)	66.5 (12.4)	*0.0*	58.4 (10.0)	58.5 (10.0)	*0.0*
Primary diagnosis at index ACS						
Unstable angina	31.4%	31.4%	*0.0*	18.5%	18.5%	*0.0*
STEMI	51.3%	51.3%	*0.0*	72.8%	72.8%	*0.0*
NSTEMI	17.3%	17.3%	*0.0*	8.7%	8.7%	*0.0*
Procedures performed (index ACS)						
Percutaneous coronary intervention	84.5%	84.7%	*-0.5*	94.5%	94.3%	*1.1*
Coronary artery by-pass grafting	0.2%	0.2%	*0.0*	0.0%	0.0%	-
Charlson comorbidity index						
[0-1]	3.5%	3.4%	*0.7*	2.9%	3.2%	*-1.7*
[2-3]	25.1%	23.9%	*2.8*	40.4%	41.5%	*-2.3*
[4-5]	32.7%	34.4%	*-3.6*	38.6%	34.6%	*8.2*
[6-7]	25.0%	24.7%	*0.7*	14.4%	15.3%	*-2.5*
>7	13.7%	13.7%	*0.2*	3.7%	5.4%	*-8.0*
Risk factors						
Diabetes mellitus	21.7%	22.5%	*-1.8*	17.5%	19.3%	*-4.6*
Hypertension	17.2%	17.9%	*-2.0*	8.9%	10.1%	*-4.1*
Coronary artery disease	13.9%	13.6%	*1.0*	8.9%	8.6%	*1.4*
Congestive heart failure	3.3%	3.4%	*-0.9*	1.5%	1.5%	*-0.4*
Peripheral arterial disease	4.7%	4.6%	*0.5*	2.7%	2.6%	*0.6*
Acute coronary syndrome	7.3%	7.1%	*0.7*	4.4%	3.9%	*2.8*
Ischemic or undefined stroke	1.7%	2.1%	*-2.7*	0.9%	0.7%	*3.3*
Major bleeding	1.4%	1.5%	*-1.1*	0.9%	0.9%	*-1.1*

* Standardized difference (%)

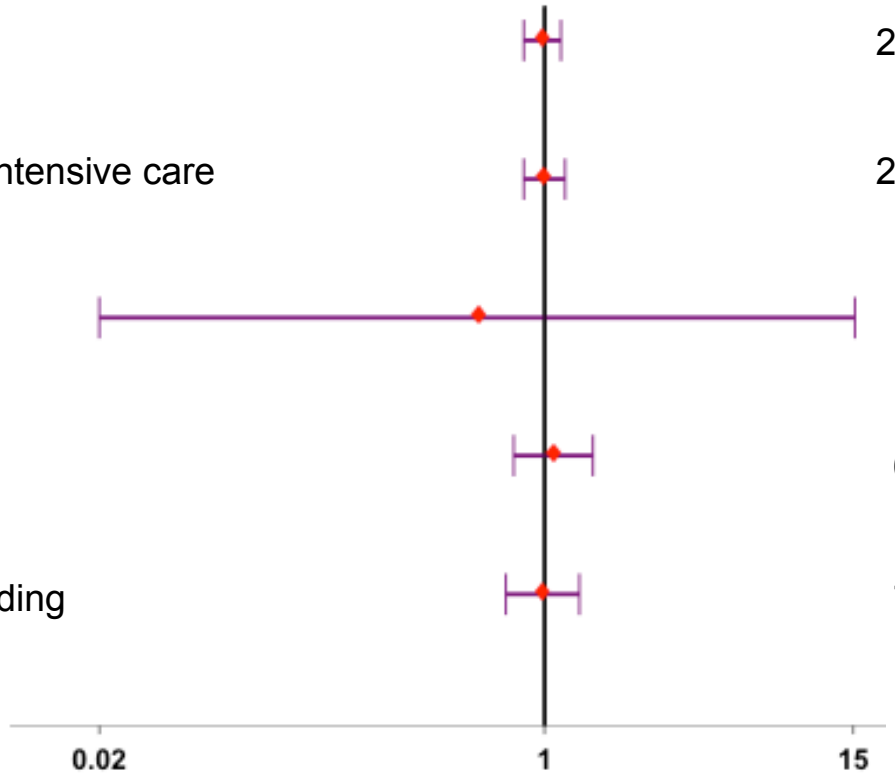
Ticagrelor versus clopidogrel

Outcomes	ticagrelor (n=9224) n events	clopidogrel (n=9224) n events	HR [95% CI]
Composite	551	658	**0.88 [0.79-0.99]**
ACS with intensive care	376	432	0.92 [0.80-1.06]
Stroke	*41*	*46*	*0.96 [0.17-5.53]*
Death	150	217	**0.73 [0.59-0.90]**
Major bleeding	170	163	1.02 [0.82-1.26]



Ticagrelor versus prasugrel

Outcomes	ticagrelor (n=6752) n events	prasugrel (n=6752) n events	HR [95% CI]
Composite	294	306	0.98 [0.83-1.15]
ACS with intensive care	221	226	0.99 [0.83-1.20]
Stroke	*14*	*26*	*0.56 [0.02-15.19]*
Death	64	61	1.08 [0.76-1.53]
Major bleeding	73	76	0.98 [0.71-1.36]



Discussion

- Nationwide database ➔ no selection nor attrition bias
- Limitations
  - Claims database
    - Lack of clinical information such as some cardiovascular risk factors (BMI, smoking) or disease severity (ECG and lab test)
    - Diagnosis miscoding (PPV 85%)
    - Drugs prescribed in hospital not available (short time use)
  - Indication bias between treatments, hdPS but some residual confounding could not be excluded
  - high degree of recanalization (PCI) and exposure to cardiopreventive treatments, that could impact extrapolability to other countries?

Conclusions

- **Ticagrelor versus clopidogrel**
  - Significant risk reduction for the composite criterion (12%) and all-cause death (27%)
  - But no statistical difference for ACS and stroke, and about same incidence for major bleeding
  - Consistent with those of PLATO trial *(Wallentin 2009)*: 16% reduction in composite endpoint (cardiovascular death, stroke, MI) and 22% reduction in all-cause death

- **Ticagrelor versus prasugrel**
  - No difference for all outcomes

Thank you for your attention

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