ISAR-REACT 5

Varvařovský Ivo

KCA Pardubice

17. konference ČAAK, 8.-10.12.2019, Karlovy Vary

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Methods

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Aim

- Head-to-head comparison of a Ticagrelor- versus a Prasugrel-based strategy in ACS patients with and without ST-segment elevation in terms of one-year clinical outcomes

Design

- Investigator-initiated, randomized, multicenter, open-label

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Vstupní kriteria

STEMI

NSTEMI (bolest ≥ 10’, do 48 hodin)

- pozitivní troponin
- denivelace ST
- 2 rizikové faktory

Vylučující kriteria

- CMP
- intrakraniální patologie
- aktivní krvácení
- anemie, trombocytopenie
- OAC
- těžká renální a jaterní insuficience
- CYP3A inhibitory nebo induktory

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Study Schedule

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STEMI

Randomization

- **Ticagrelor** 180 mg loading
- **Prasugrel** 60 mg loading

Angiography + PCI

- **Ticagrelor** 90 mg 1-0-1
- **Prasugrel** 10 mg 1-0-0*

Unstable Angina, NSTEMI

Randomization

- **Ticagrelor** 180 mg loading
- *Prasugrel# 60 mg loading*

Angiography

- **Prasugrel** 60 mg loading

PCI

- **Ticagrelor** 90 mg 1-0-1
- **Prasugrel** 10 mg 1-0-0*

Duration of ADP receptor therapy: 12 months
Concomitant ASA: 75-150 mg/d
In patients with known coronary anatomy
* Prasugrel 5 mg in patients ≥ 75 years of age or weight < 60 kg

Schulz (Schüpke) et al, J Cardiovasc Transl Research 2014

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End points

Primary end point

- Composite of death, myocardial infarction, or stroke at 12 months after randomization

Secondary end points

- Bleeding BARC type 3-5 (safety end point)
- Individual components of the primary end point
- Stent thrombosis (definite or probable)

Analysis population

- Intention-to-treat (primary end point and secondary efficacy end point): all patients as randomized
- Modified intention-to-treat (safety end point): all patients who received at least one dose of the randomly assigned study drug and were assessed for bleeding events up to 7 days after drug discontinuation

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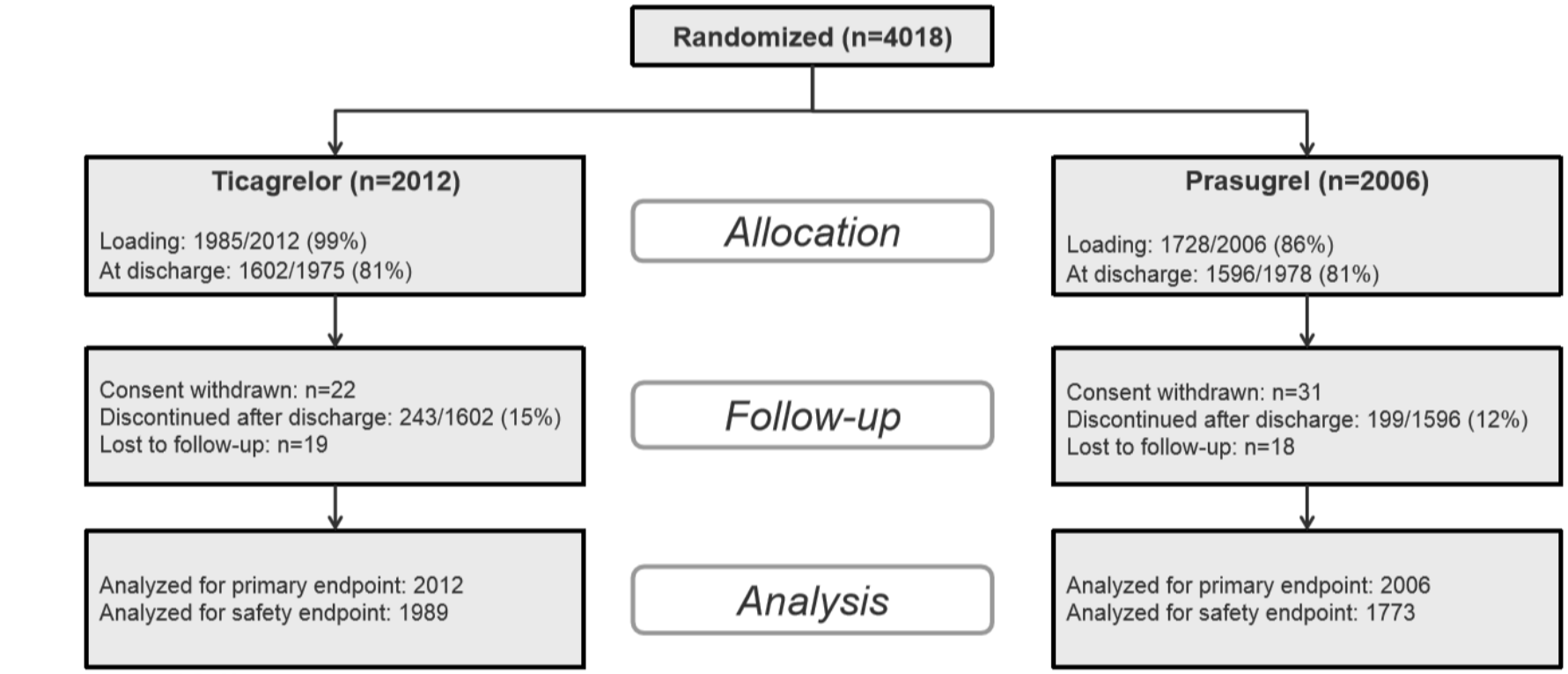
Study Flow



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Baseline Characteristics (1/2)

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	Ticagrelor	Prasugrel
Age – years	64.5 ± 12.0	64.6 ± 12.1
Women – %	23.8	23.8
Body mass index – kg/m²	27.8 ± 4.6	27.8 ± 4.4
Diabetes – %	23.0	21.4
– Insulin-treated – %	7.1	6.8
Current smoker – %	34.1	33.4
Arterial hypertension – %	71.3	69.1
Hypercholesterolemia – %	58.7	58.1
Prior MI – %	15.5	16.0
Prior PCI – %	22.5	23.1
Prior CABG – %	5.7	6.5
Cardiogenic shock – %	1.5	1.7

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Baseline Characteristics (2/2)

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	Ticagrelor	Prasugrel
Blood pressure		
– Systolic – mmHg	144 ± 25	143 ± 24
– Diastolic – mmHg	82 ± 15	82 ± 14
Heart rate – beats/min	77 ± 16	76 ± 16
Diagnosis at admission – %		
– Unstable angina	12.4	13.0
– NSTEMI	46.2	46.1
– STEMI	41.4	40.9
Coronary angiography – %	99.6	99.8
Treatment strategy – %		
– PCI	83.5	84.8
– CABG	2.3	1.8
– Conservative	14.2	13.4
– Other	<0.1	0

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Angiographic Characteristics
(Patients with Angiography)

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	Ticagrelor	Prasugrel
Access site – %		
– Femoral	62.2	63.0
– Radial	37.3	36.5
– Other	0.5	0.5
No. of diseased coronary vessels – %		
– No obstructive CAD	8.5	8.2
– One vessel	30.0	29.1
– Two vessels	26.0	27.7
– Three vessels	35.5	35.0
Left ventricular ejection fraction – %	51.6 ± 11.3	52.0 ± 11.2

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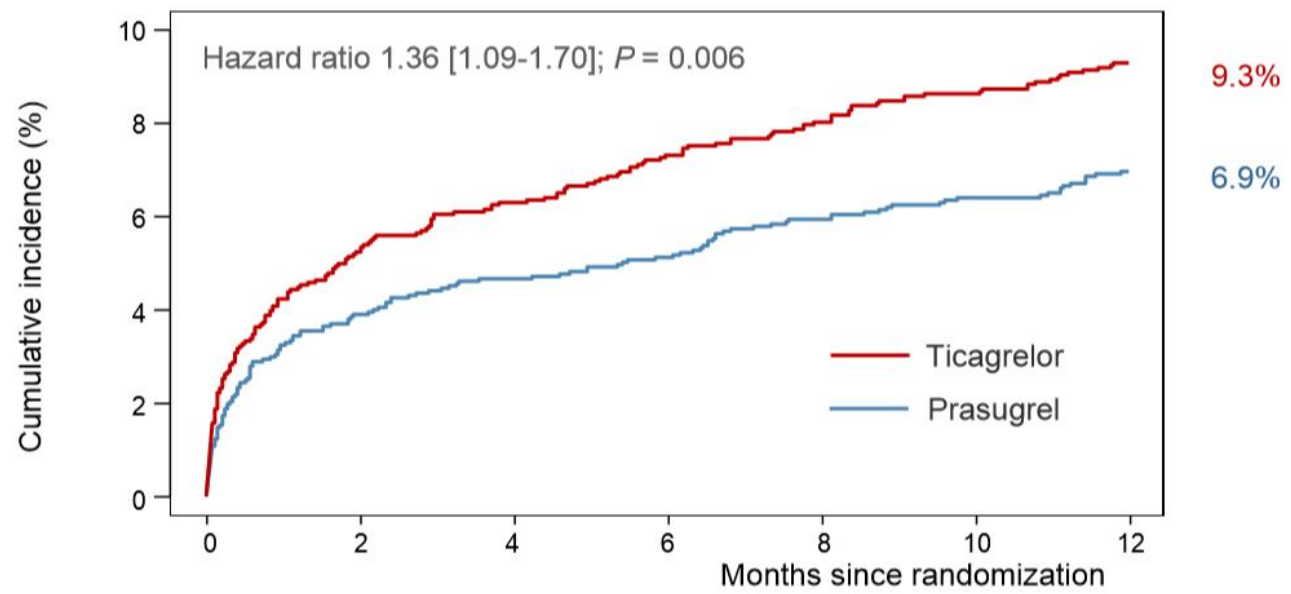
Primary End point
(Composite of Death, MI, or Stroke)



No. at Risk

Ticagrelor	2012	1877	1857	1835	1815	1801	1772
Prasugrel	2006	1892	1877	1862	1839	1829	1803

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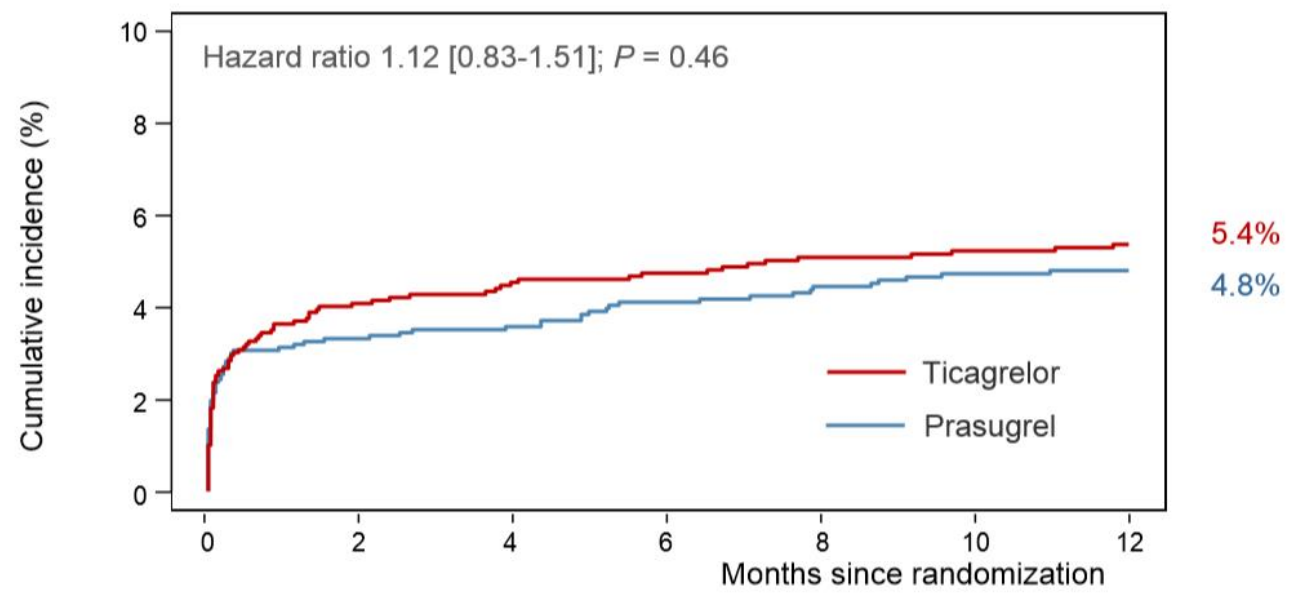
BARC Type 3-5 Bleeding
(Safety End point)



No. at Risk							
Ticagrelor	1989	1441	1399	1356	1319	1296	1266
Prasugrel	1773	1465	1427	1397	1357	1333	1307

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Clinical End Points

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	Ticagrelor (n=2012)	Prasugrel (n=2006)	HR [95% CI]
Death	90 (4.5)	73 (3.7)	**1.23 [0.91-1.68]**
– Cardiovascular	63 (3.2)	59 (3.0)	
– Non-cardiovascular	27 (1.4)	14 (0.7)	
Myocardial infarction	96 (4.8)	60 (3.0)	**1.63 [1.18-2.25]**
– STEMI	31	14	
Stroke	22 (1.1)	19 (1.0)	**1.17 [0.63-2.15]**
– Ischemic	16	17	
– Hemorrhagic	6	2	
Definite or probable stent thrombosis	26 (1.3)	20 (1.0)	**1.30 [0.72-2.33]**
Definite stent thrombosis	22 (1.1)	12 (0.6)	

ISAR-REACT 5 : periprocedurální infarkt myokardu !!!

Tab. 5. *Typ infarktu myokardu ve studii ISAR-REACT 5*

	Ticagrelor (n = 2012)	Prasugrel (n = 2006)	Rozdíl
1 (spontánní IM)	52	35	17
2 (nepoměr přísunu a spotřeby kyslíku)	4	3	1
4a (infarkt při PCI)	**19**	**11**	**8**
4b (infarkt při ST; definite or probable)	**20**	**11**	**9**
5 (infarkt při CABG)	1	0	1
Součet všech IM	***96***	***60***	***36***
Jistá (definite) ST	***22***	***12***	***10***
STEMI	***31***	***14***	***17***
Infarkt při revaskularizaci	***20***	***11***	***9***

IM – infarkt myokardu; PCI – koronární angioplastika; ST – trombóza stentu; CABG – chirurgická revaskularizace (koronární bypass); STEMI – infarkt myokardu s ST elevacemi

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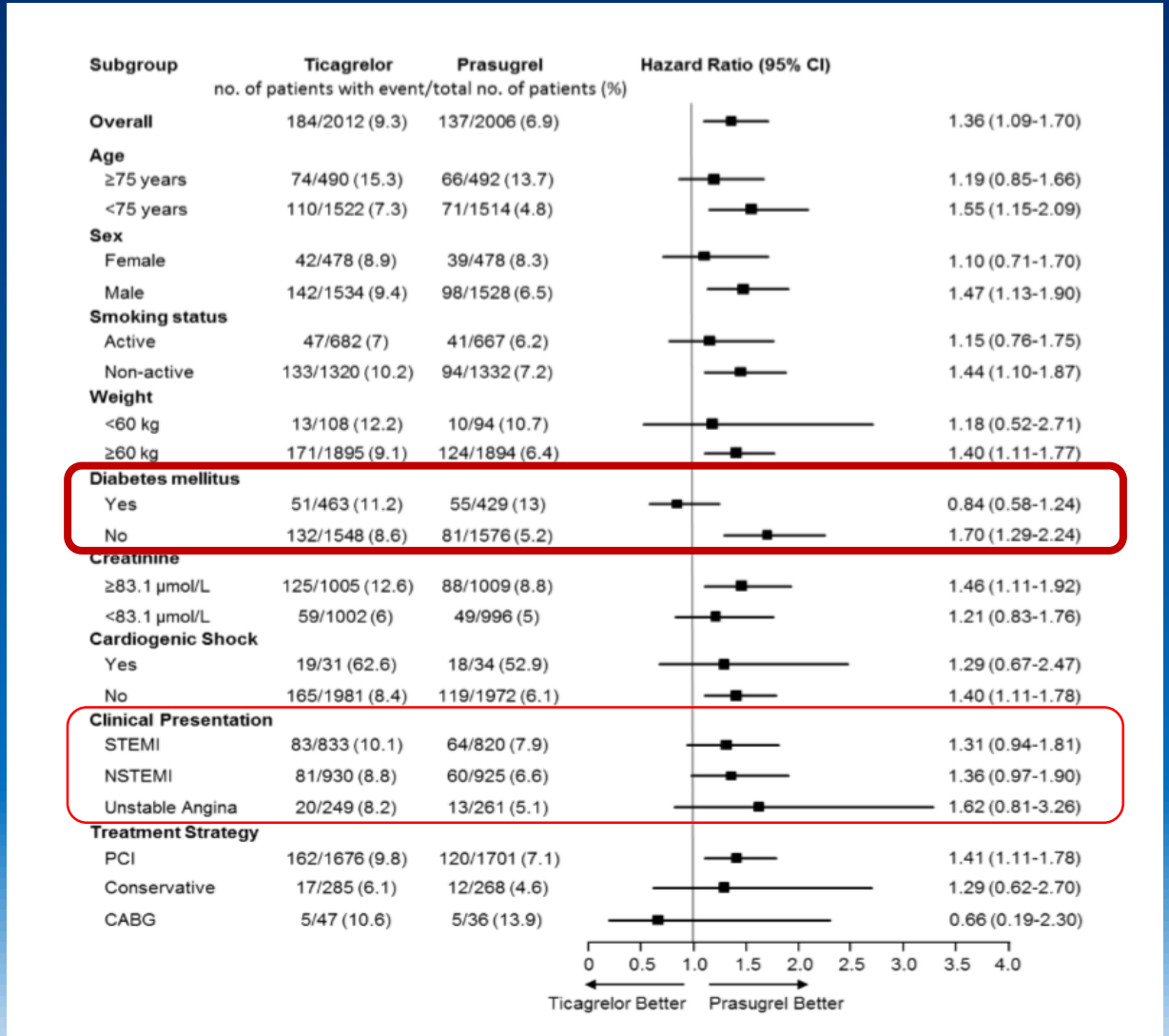

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Summary And Conclusion

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In ACS patients with or without ST-segment elevation, treatment with Prasugrel as compared with Ticagrelor significantly reduced the composite rate of death, myocardial infarction, or stroke without an increase in major bleeding.

ISAR-REACT 5 : otazníky

1. Nasycovací dávka : ticagrelor 98,7 % / prasugrel 86,1 % (257)
2. Vyřazeno z hodnocení : ticagrelor 23 vs prasugrel 233
3. Opačný efekt léků u pacientů s diabetes mellitus
4. Časový průběh KM-křivek opačný proti registračním studiím
5. **Nekardiální mortalita + periprocedurální infarkty myokardu**

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