



PUSAT JANTUNG  
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# Elevated uninhibited platelet reactivity and earlier platelet function recovery in aspirin resistant patients after aspirin withdrawal

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**Joint Meeting of Coronary Revascularization**

Sarawak General Hospital

**CRC**  
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*Research that matters to patients*

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# Preoperative Aspirin Management

- ♥ Traditionally stopped to **prevent bleeding**
- ♥ **Different practices** among surgeons and centres
- ♥ **Different recommendations** from guidelines  
(ACCF/AHA, ACCP, STS, EACTS)<sup>1-4</sup>
- ♥ **Balance** between **bleeding** and **thrombosis**

1. Hillis LD, et al. Circulation. 2011 Dec 6;124(23):2610-42.

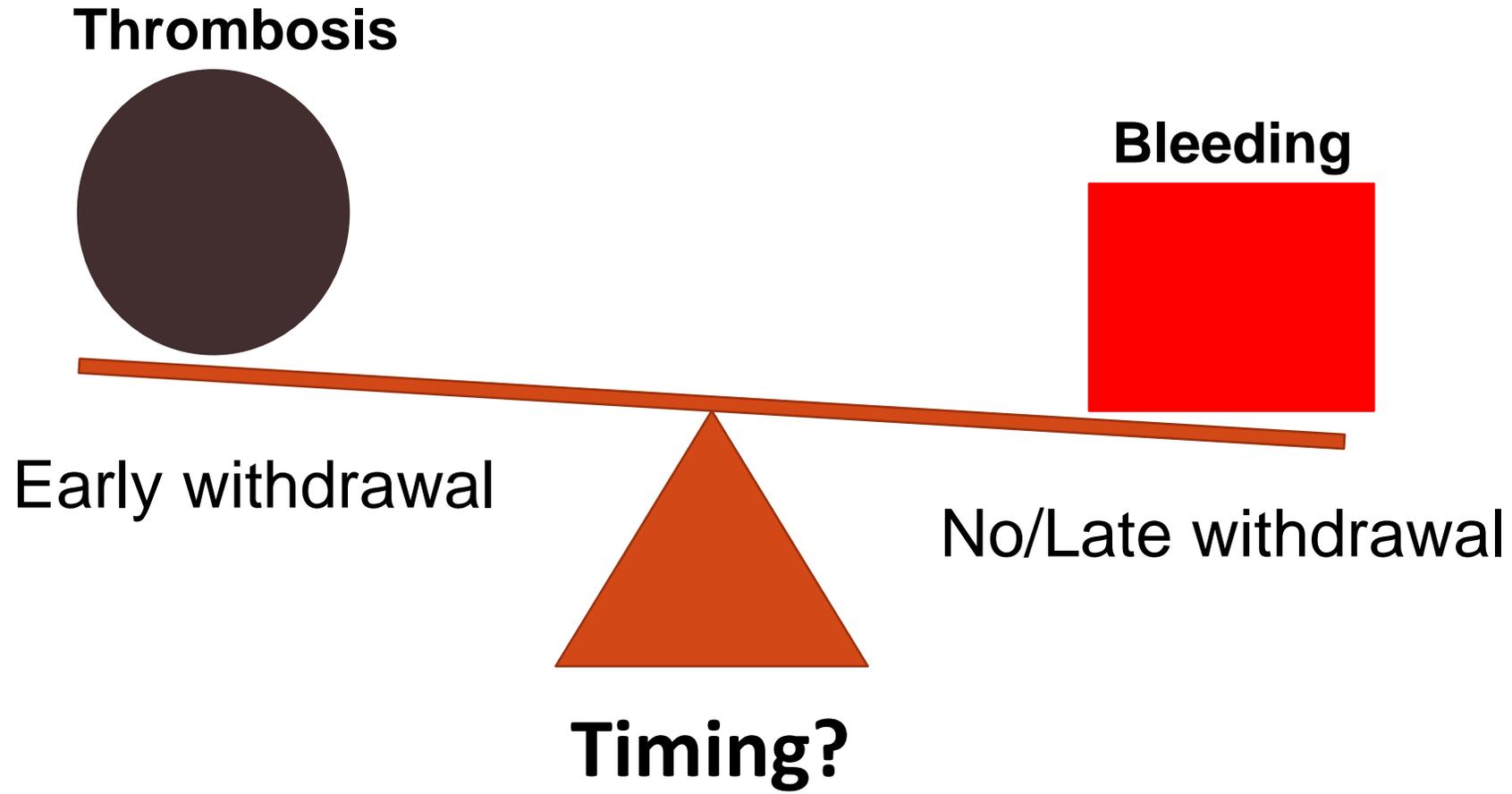
2. Douketis JD, et al. Chest. 2012 Feb;141(2 Suppl):e326S-e350S.

3. Ferraris VA, et al. Ann Thorac Surg. 2012 Nov;94(5):1761-81.

4. Sousa-Uva M, et al. Eur J Cardiothorac Surg. 2018 Jan 1;53(1):5-33



# Aspirin Discontinuation



# Platelet Function Recovery

- ♥ Duration of residual platelet function suppression after aspirin withdrawal
- ♥ **Normalized after 4-5 days<sup>1,2</sup>**
- ♥ **Effect of aspirin resistance?**

1. Cahill et al. J Am Coll Surg. 2005 Apr;200(4):564-73.

2. Kim et al. Curr Ther Res Clin Exp. 2014 Mar 25;76:26-31



# Objectives

1. To investigate **platelet function profile after aspirin withdrawal** in **aspirin resistant** and **non-resistant** patients.



# Methods

Recruited from Nov 2015 to Oct 2017

**Study subjects:** Elective CABG patients on aspirin

**Healthy Controls:** Antiplatelet-naïve healthy volunteers



# Study Subjects

## Inclusion

- ♥ Elective CABG
- ♥ 18 – 75 years old
- ♥ Taking 75 – 100mg ASA every day for >7 days

## Exclusion

- ♥ Urgent/emergency CABG
- ♥ Coronary event/stroke in the past 7 days
- ♥ Bleeding diathesis/platelet disorder
- ♥ Other antiplatelets
- ♥ Other NSAIDs or COX-2 inhibitors



# Healthy Controls

## Inclusion

- ♥ Healthy with no known chronic illness
- ♥ 18 – 55 years old
- ♥ Antiplatelet-naïve

## Exclusion

- ♥ Significant medical history
- ♥ Taking chronic medications
- ♥ Taking aspirin/other NSAID for the past 7 days as painkiller



# Platelet Function Test

Measure **platelet reactivity**

Assess **antiplatelet effect**<sup>1</sup>

Predict **outcomes after cardiac surgery**<sup>2-5</sup>

## Multiplate® Analyser

♥ Benchtop, point-of-care PFT

♥ Multiple electrode aggregometry

1. Bonello L, et al. *Cardiology*. 2010;56(12).

2. Rahe-Meyer N, et al. *Anesth Analg*. 2008 Dec;107(6).

3. Reece M, et al. *Anaesthesia*. 2011 Feb;66(2).

4. Ranucci M, et al. *Ann Thorac Surg*. 2011 Jan;91(1).

5. Weber CF, et al. *Anesthesiology*. 2012 Sept;117(3).



# Platelet Function Study

Practice in hospital

Stop aspirin for 7  
days

Every 24±1H post aspirin withdrawal



compared with

Normal platelet reactivity of antiplatelet-naïve healthy volunteers

Mann-Withney U Test;  $p < 0.05$



# Aspirin Resistance

**Aspirin Resistance (AspR)** defined as platelet reactivity  $\geq 300 \text{ AU}^* \text{min}$  on aspirin



ASPiRE-CABG Study

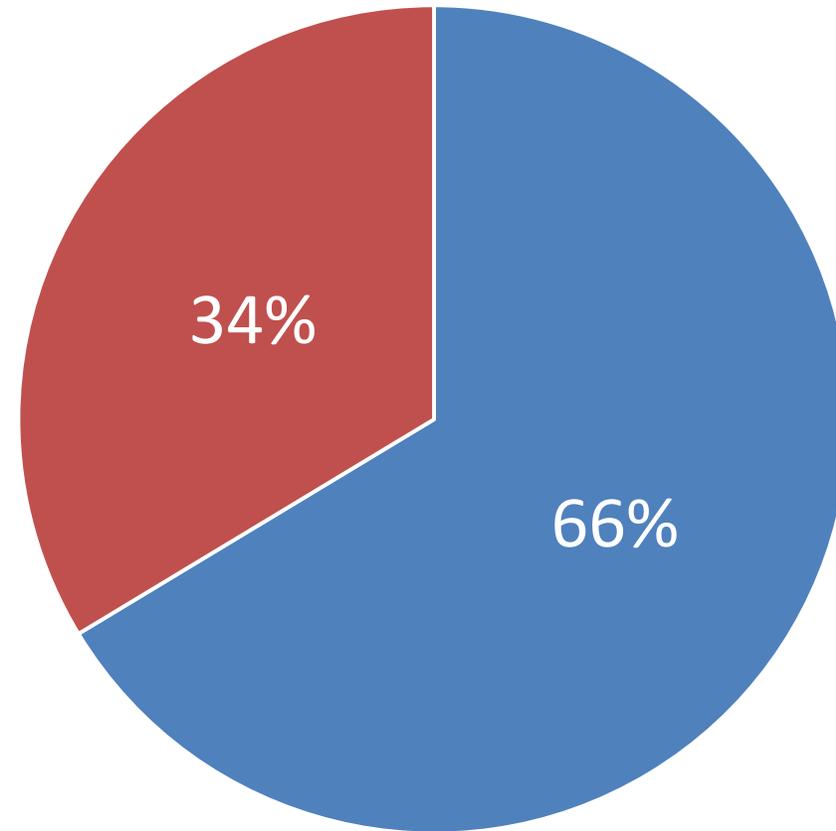
# RESULTS



# Subject Characteristics

Characteristics	Patients (n=101)	Healthy Volunteers (n=63)
Age	57.2±8.8	24.9±6.1
Male	90 (89.1)	53 (84.1)
BMI	27.5±3.9	23.8±4.1
Hypertension	94 (93.1)	N.A.
Hyperlipidaemia	82 (81.2)	N.A.
Diabetes mellitus	42 (41.6)	N.A.
Smoker	68 (67.3)	20 (31.7)

# AspR vs AspNR



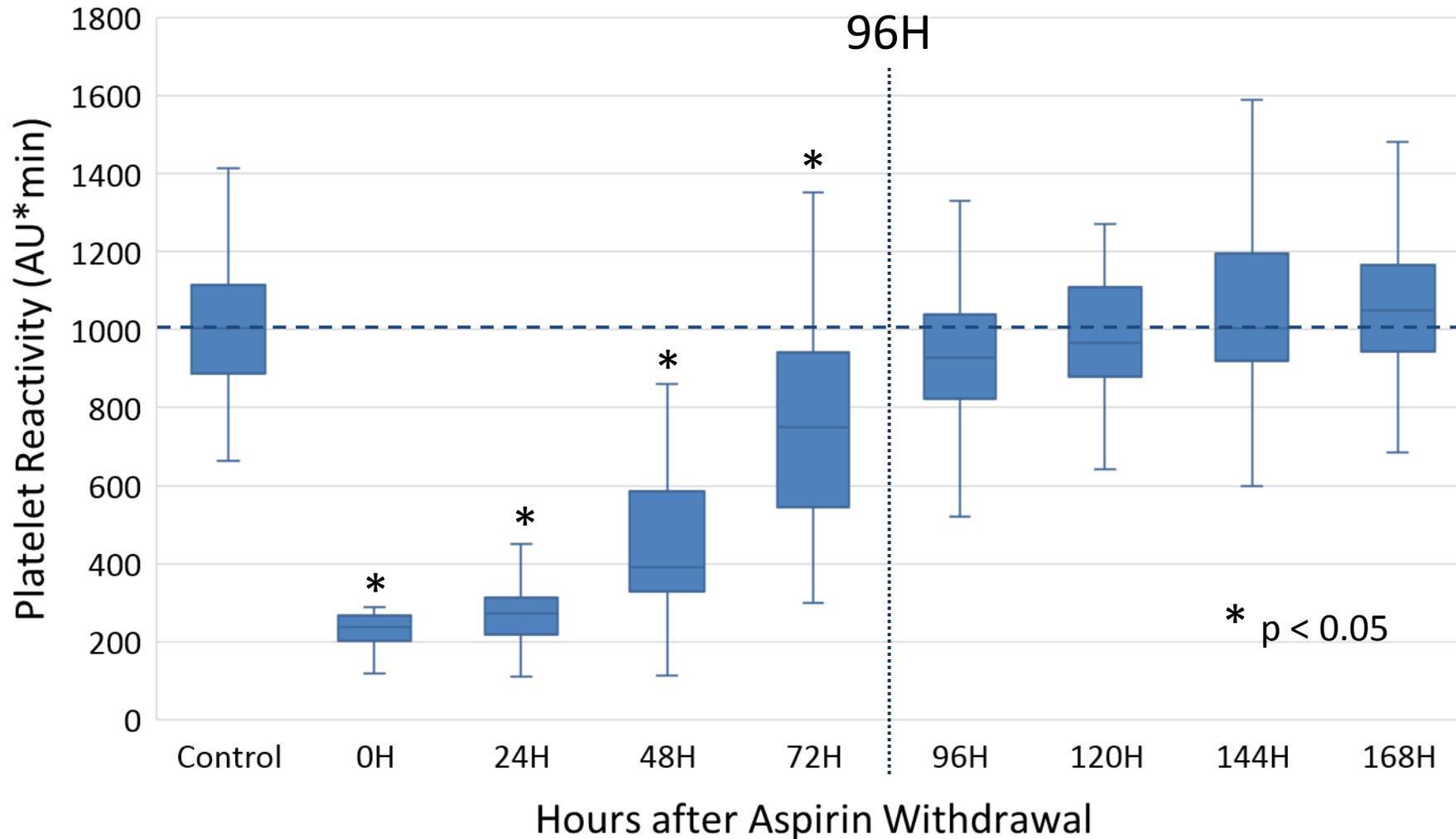
■ AspNR ■ AspR



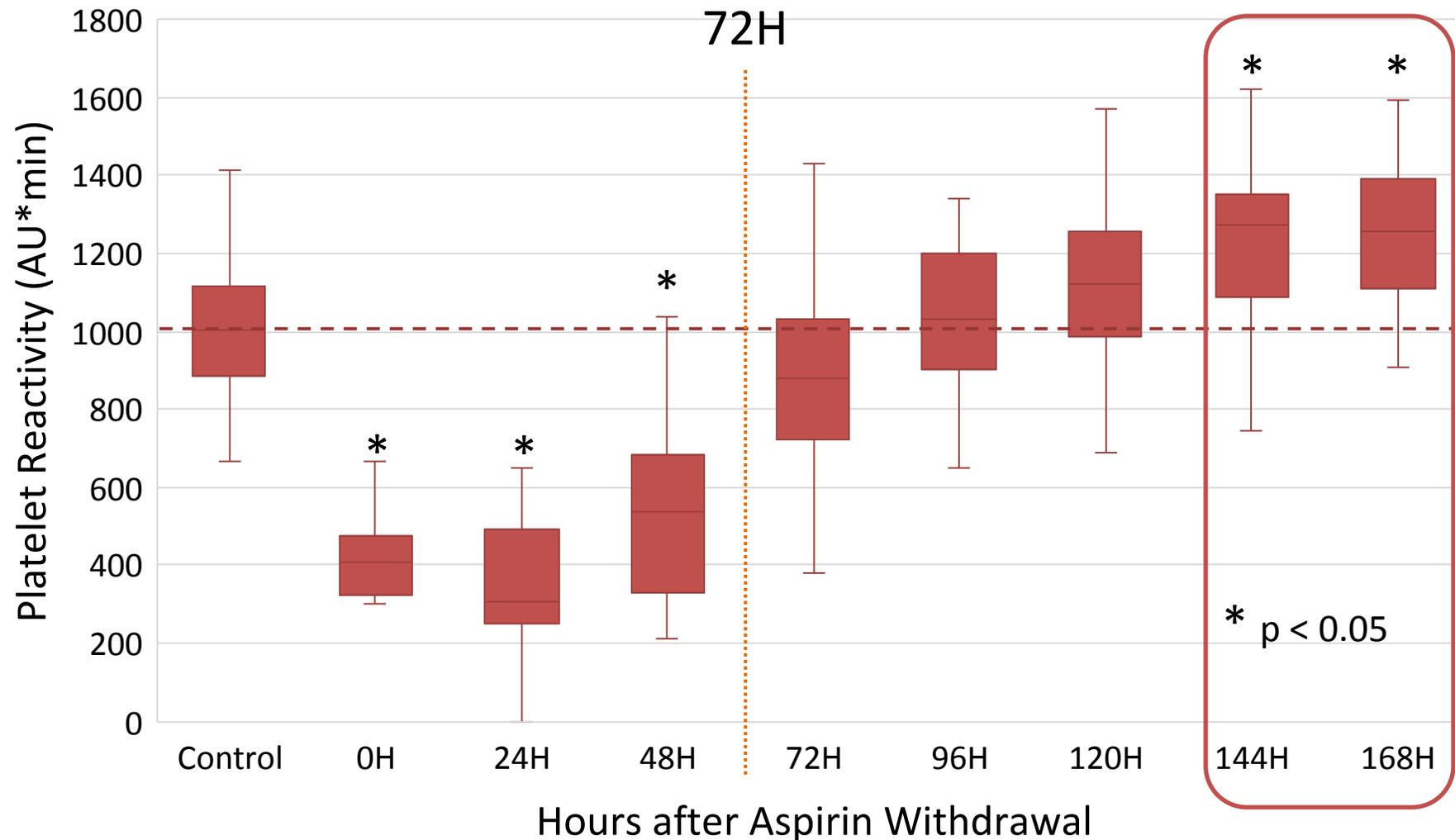
# AspR vs AspNR

Characteristics	AspR (n=34)	AspNR (n=67)	p-value
Age	55.9±10.4	57.8±7.8	0.29
Male	30 (88.2)	60 (89.6)	0.84
BMI	28.4±4.2	27.0±3.6	0.08
Hypertension	32 (94.1)	62 (92.5)	0.77
Hyperlipidaemia	26 (76.5)	56 (83.6)	0.39
Diabetes mellitus	17 (50.0)	25 (37.3)	0.22
Smoker	29 (85.3)	39 (58.2)	0.01
WBC, 10 <sup>9</sup> /L	9.0±2.2	7.9±1.9	0.01
Hb, g/dL	14.0±1.6	13.7±1.4	0.34
Platelet, 10 <sup>9</sup> /L	253.4±68.6	248.7±55.4	0.68

# Platelet Function Profile after Aspirin Withdrawal in AspNR Patients (n = 67)



# Platelet Function Profile after Aspirin Withdrawal in AspR Patients (n = 34)



# Discussion (1)

Overall, **platelet function recovered 3-4 days** after stopping aspirin in elective CABG patients.

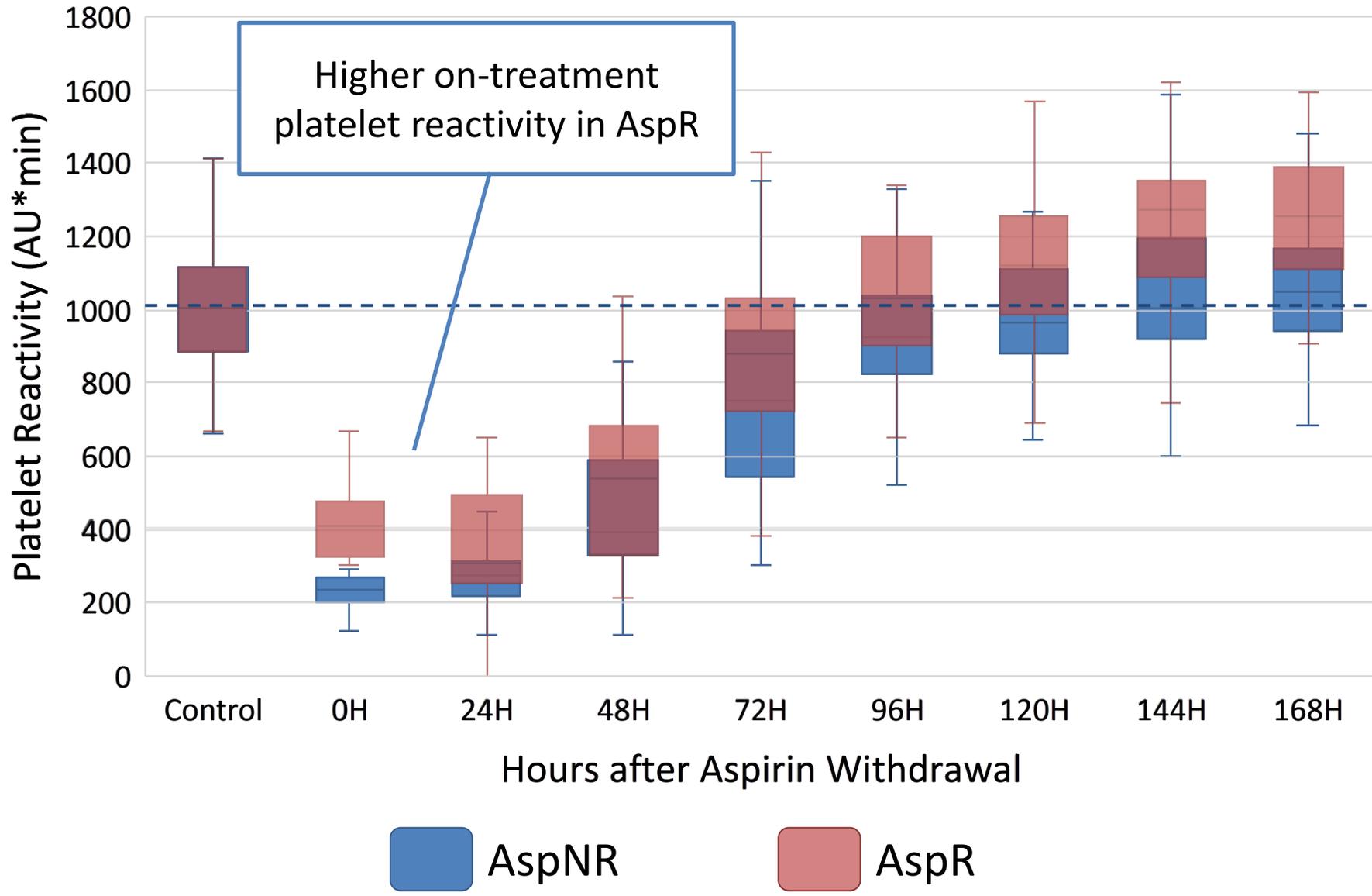
- ♥ Kim et al. PF recovered after **96 hours** after stopping aspirin for dental procedures in CVD patients<sup>1</sup>
- ♥ Cahil et al. Bleeding time normalized within **96 hours** while PF normalized within **144 hours** in healthy volunteers<sup>2</sup>

1. Kim et al. Curr Ther Res Clin Exp. 2014 Mar 25;76:26-31
2. Cahill et al. J Am Coll Surg. 2005 Apr;200(4):564-73.

# Discussion (2)

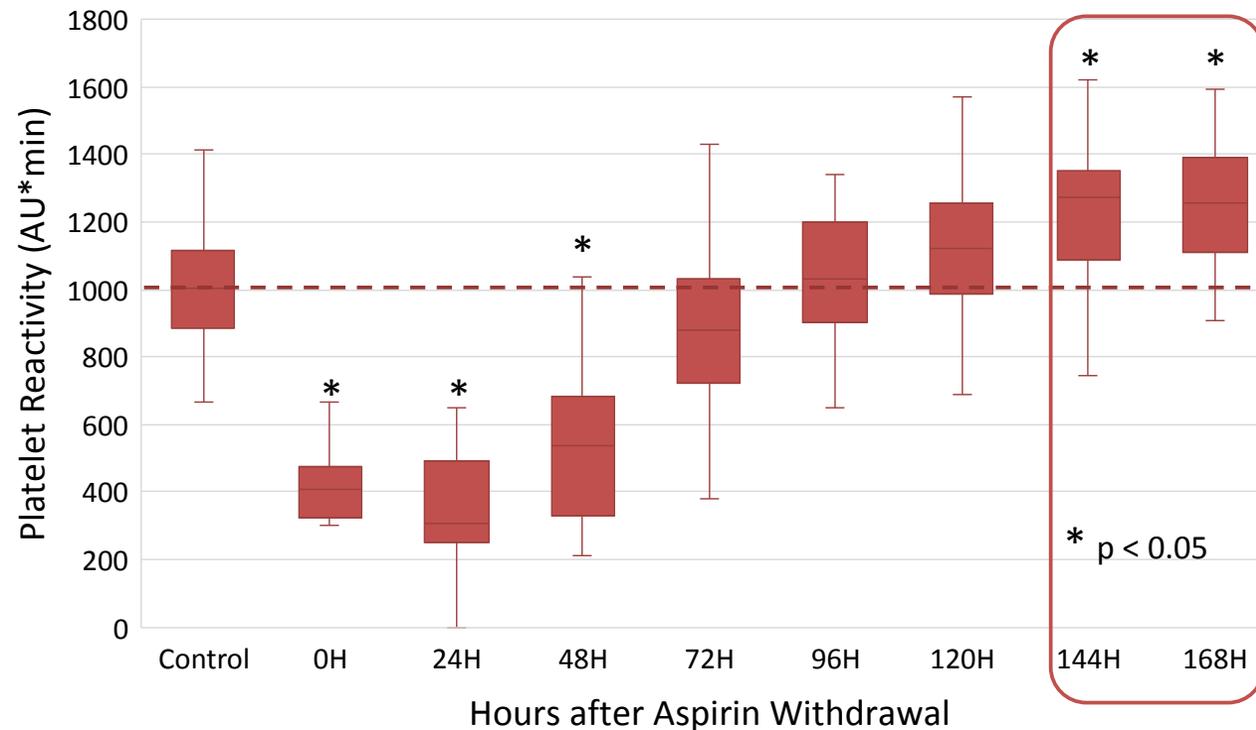
Platelet function of **AspR** patient **recovered faster** than **AspNR** patient after aspirin withdrawal.





# Discussion (3)

Higher platelet reactivity in AspR patients after aspirin was stopped for **>5 days**



# Discussion (3)

**Higher platelet reactivity in AspR patients after aspirin was stopped for >5 days**

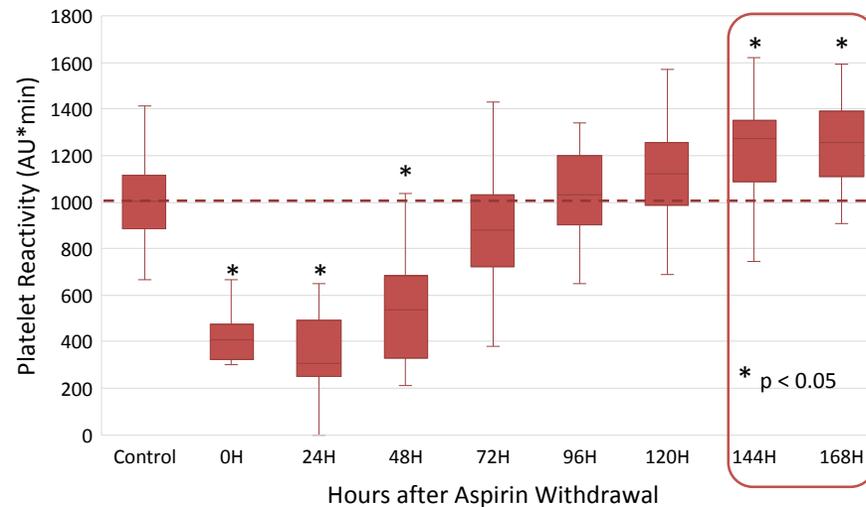
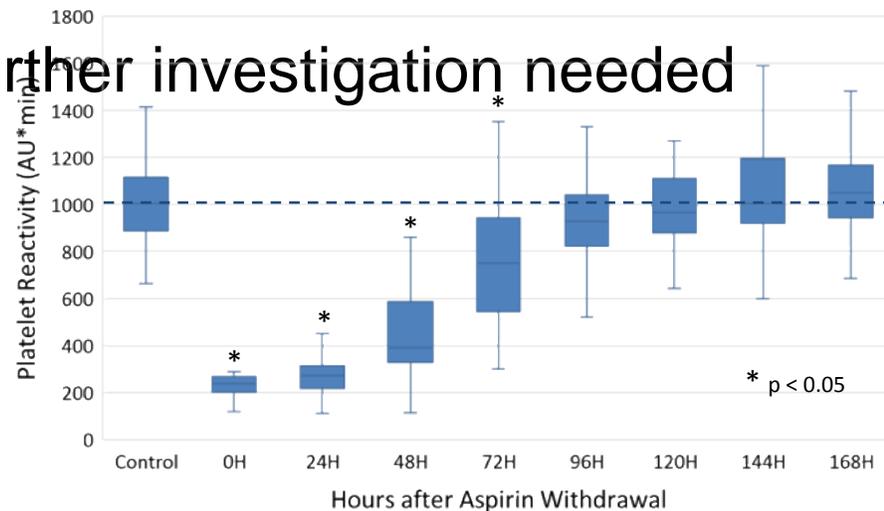
- ♥ Higher platelet aggregability → **higher clotting risk**
- ♥ **Explain higher thrombotic rate** in those stopped aspirin (>5d vs ≤5d) in observational studies<sup>1-3</sup>

1. Bybee et al. Circulation. 2005 Aug 30;112(9 Suppl):I286-92.
2. Cao et al. Ann Surg. 2012 Feb;255(2):399-404.
3. Yao et al. Ann Surg. 2015 Jan;261(1):207-12.

# Discussion (3) Cont.

Higher platelet reactivity in AspR patients after aspirin was stopped for **>5 days**

- ♥ Rebound effect?
- ♥ High baseline platelet reactivity?
- ♥ Further investigation needed



# RCTs on ASA before Surgery

Study	Surgery	Pre-Op Aspirin	Outcomes
Myles (2016) <sup>1</sup>	CABG	100mg enteric-coated	<b>No effect</b> on death or thrombotic complications and bleeding
Devereaux (2014) <sup>2</sup>	Non-cardiac	200mg	<b>No effect</b> on death and MI but <b>increased</b> risk of <b>bleeding</b>
Deja (2012) <sup>3</sup>	CABG	300mg	<b>May decreased</b> coronary event but <b>increased bleeding</b>
Morawski (2005) <sup>4</sup>	CABG	150mg 12h and 3h before	<b>Increased</b> blood transfusion

ASA stopped 4 – 10 days before surgery<sup>1-4</sup>.

**ASA dose & formulation on bleeding?**  
**Platelet reactivity?**  
**Timing?**

1. Myles PS, et al. N Engl J Med. 2016 Feb 25;374(8):728-37.  
 2. Devereaux PJ, et al. N Engl J Med. 2014 Apr 17;370(16):1494-503.

3. Deja MA, et al. J Thorac Cardiovasc Surg. 2012 Jul;144(1):204-9.  
 4. Morawski W, et al. J Thorac Cardiovasc Surg. 2005 Sep;130(3):791-6.



# Limitations

♥ **Observational study**

♥ **Small sample size**

♥ **No clinical evaluation of bleeding and thrombotic rate**



# Conclusion

1. Platelet function of **aspirin resistant** patients **recovered earlier** than **aspirin non-resistant** patients after aspirin withdrawal (**3 vs 4 days**).
2. **Stopping aspirin for too long**, i.e. **> 5 days** might **increase thrombotic risk** due to higher than normal uninhibited platelet reactivity in **aspirin resistant** patients.





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**THANK YOU**

