Cost effectiveness of Ticagrelor: Markov model analysis in three hospitals in Indonesia

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Conflict of Interest

- Division of Pharmacoepidemiology & Pharmacoeconomy Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada (UGM).

- Clinical Epidemiology and Biostatistics Unit (CEBU) Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada (UGM) and Sardjito Hospital

- Study was funded by AstraZeneca Indonesia

Study background

- In ACS, current guidelines recommend 12 months aspirin and Clopidogrel. Ticagrelor in combination with aspirin for 12 months will only give if patients can not use Ticagrelor

- Efficacy of clopidogrel is hampered by
  - slow and variable transformation to the active metabolite
  - modest and variable platelet inhibition
  - increased risk of bleeding
  - risk of stent thrombosis and MI in poor responders

The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

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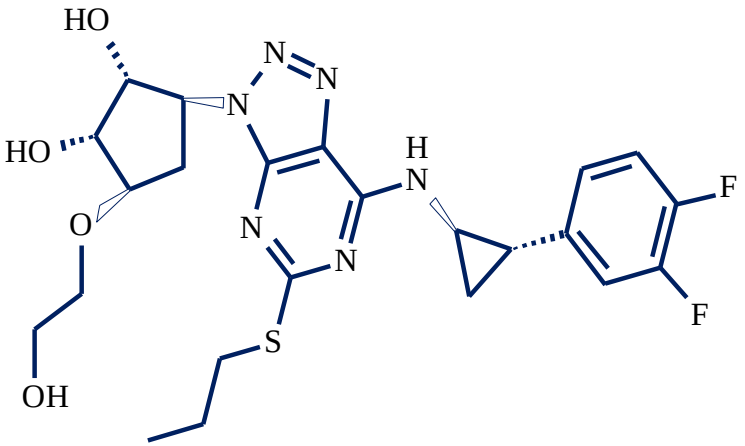
Ticagrelor (AZD 6140): an oral reversible $P2Y_{12}$ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- Direct acting
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- Reversibly bound
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets

PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

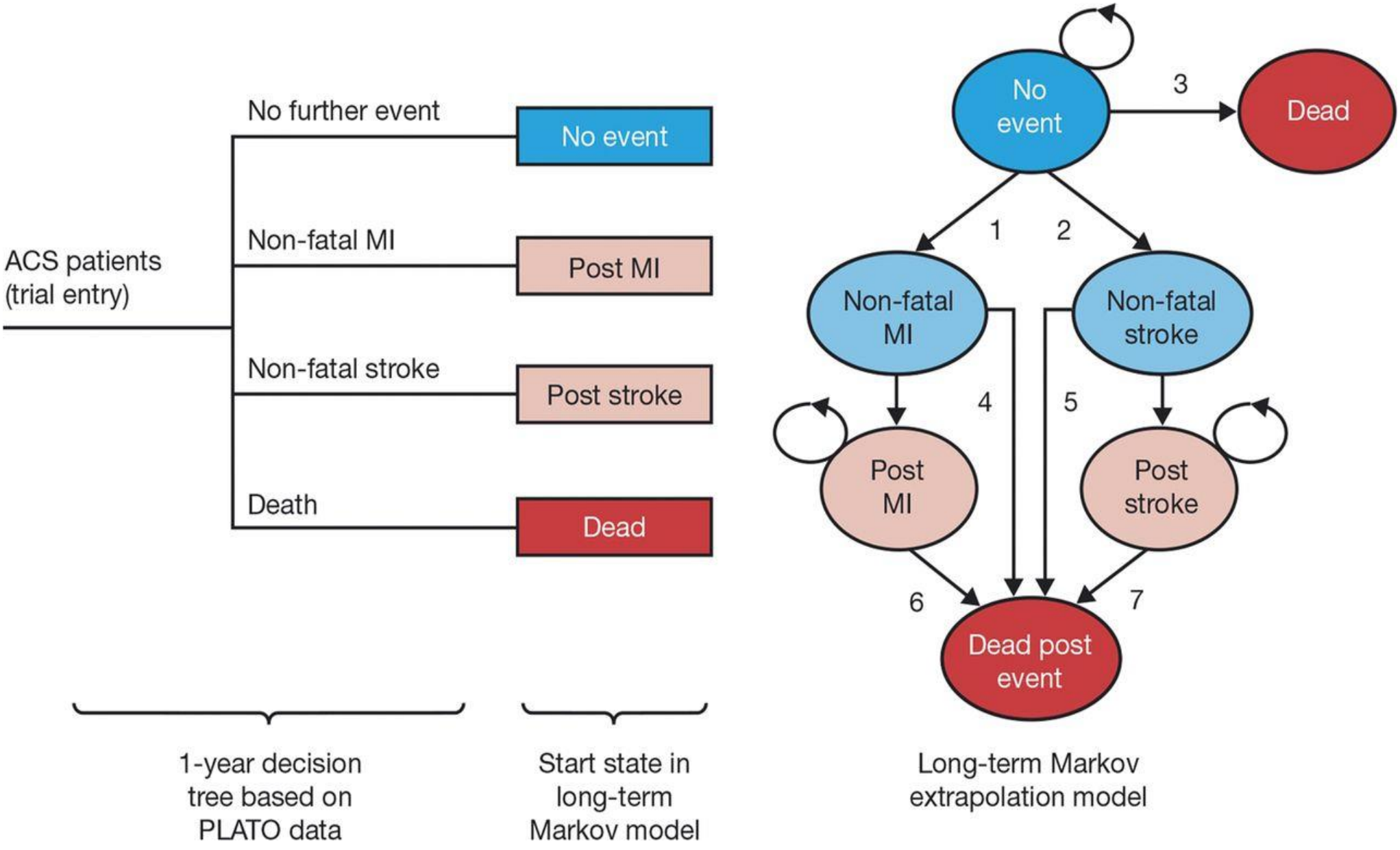
Major efficacy endpoints

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value†
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n (%)				
Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

Study Objective

- Evaluated cost effectiveness of ticagrelor to reduce cardiovascular death, myocardial infarction or stroke in acute coronary syndrome patients in Indonesia

Decision tree and Markov model. Markov model transitions shown in this figure: risk of non-fatal myocardial infarction (MI) for patients with no MI or stroke in the PLATO study.

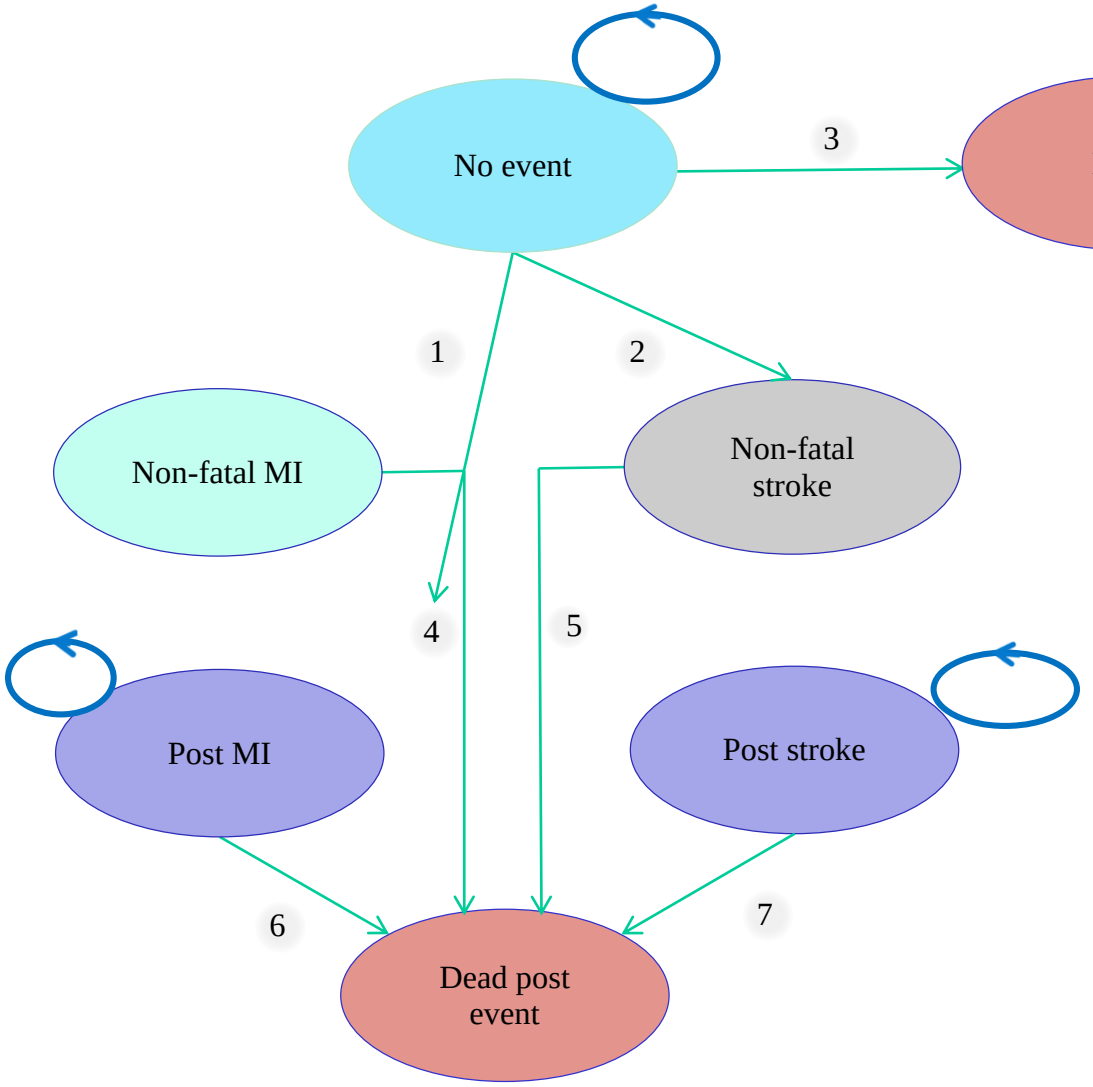


M Janzon et al. Heart 2015;101:119-125

Parameter one-year decision tree

One-year decision tree	Ticagrelor	Clopidogrel	Source
No event	0,8945	0,8750	PLATO trial
Non-fatal MI	0,0096	0,0575	PLATO trial
Non-fatal stroke	0,0497	0,0089	PLATO trial
Death caused any cause	0,0462	0,0586	PLATO trial

Long term Markov Model



1. Risk of non-fatal MI for patients with no further event in the PLATO study
2. Risk of non-fatal stroke for patients with no further event in the PLATO study
3. Mortality risk for patients with no further event in the PLATO study
4. Mortality risk first year after a non-fatal MI
5. Mortality risk first year after a non-fatal stroke
6. Mortality risk second and subsequent year after a non-fatal MI
7. Mortality risk second and subsequent year after a non-fatal stroke

Long-term Markov extrapolation model

Markov Model Probability PLATO and ASIAN PLATO

CE model base case values		PLATO	Asian	Sensititvity increase	Sensitivity probability
Probability dead within trial clopidogrel	0.0810858	0.054	0.093	1.71	0.1385
Probability MI within trial clopidogrel	0.0619390	0.064	0.063	0.99	0.0611
Probability stroke within trial clopidogrel	0.0109512	0.011	0.02	1.75	0.0192
Probability dead within trial ticagrelor	0.0641855	0.043	0.073	1.71	0.1096
Probability MI within trial ticagrelor	0.0534936	0.054	0.064	1.19	0.0634
Probability stroke within trial ticagrelor	0.0119245	0.013	0.02	1.49	0.0178

Costs associated outcomes

- Health care (provider) perspective
- Costs (2015-2016 in Indonesia rupiah/IDR, converted into USD) was generated from retrospective data in a private
  - Private hospital: Bina Waluya hospital
  - Public hospital (National): Harapan Kita Hospital
  - Public hospital (Regional): Sardjito Hospital

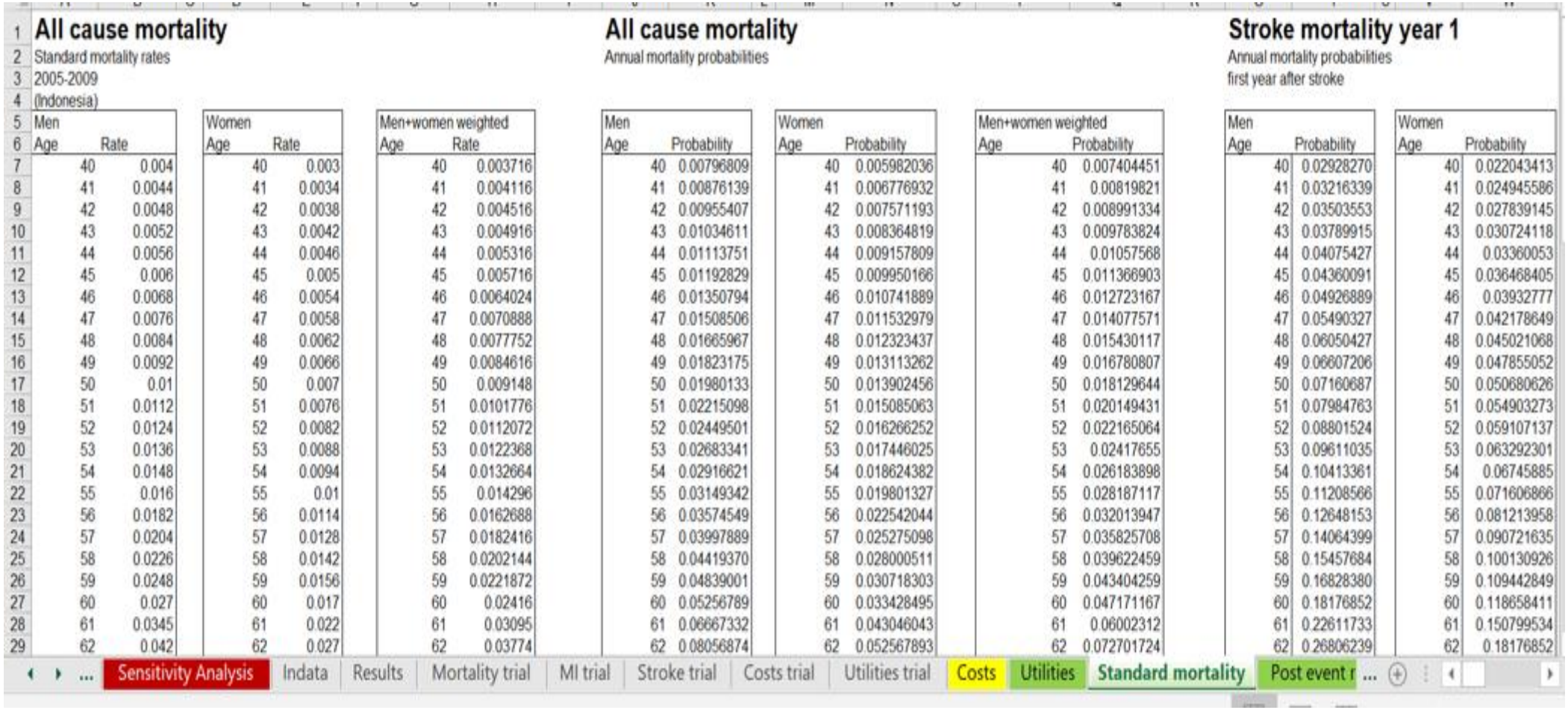
Costs associated outcomes

- The costs were included in the analysis are
  - costs of ticagrelor and clopidogrel,
  - costs related to bleeding,
  - costs of diagnosis, treatment, hospitalization and monitoring visit for
    - acute coronary syndrome
    - non fatal stroke (hemorrhagic and non hemorrhagic)
    - non fatal myocardial infarction,
    - and death due to cardiovascular causes.

Study Outcome

- The primary outcome:
  - QALYs (quality adjusted life years)
- The secondary outcome:
  - life years gained (LYG).
- Indonesia standard mortality is used to generate population mortality, and provided the utility associated with PLATO study outcomes.
- Costs and outcomes beyond the first year were discounted at 3% per annum in Indonesia.

Generating Mortality of ACS and Stroke
Based on PLATO probability and Indonesia Standard Mortality



All cause mortality

Standard mortality rates
2005-2009
(Indonesia)

Men Age	Men Rate	Women Age	Women Rate	Men+women weighted Age	Men+women weighted Rate
40	0.004	40	0.003	40	0.003716
41	0.0044	41	0.0034	41	0.004116
42	0.0048	42	0.0038	42	0.004516
43	0.0052	43	0.0042	43	0.004916
44	0.0056	44	0.0046	44	0.005316
45	0.006	45	0.005	45	0.005716
46	0.0068	46	0.0054	46	0.0064024
47	0.0076	47	0.0058	47	0.0070888
48	0.0084	48	0.0062	48	0.0077752
49	0.0092	49	0.0066	49	0.0084616
50	0.01	50	0.007	50	0.009148
51	0.0112	51	0.0076	51	0.0101776
52	0.0124	52	0.0082	52	0.0112072
53	0.0136	53	0.0088	53	0.0122368
54	0.0148	54	0.0094	54	0.0132664
55	0.016	55	0.01	55	0.014296
56	0.0182	56	0.0114	56	0.0162688
57	0.0204	57	0.0128	57	0.0182416
58	0.0226	58	0.0142	58	0.0202144
59	0.0248	59	0.0156	59	0.0221872
60	0.027	60	0.017	60	0.02416
61	0.0345	61	0.022	61	0.03095
62	0.042	62	0.027	62	0.03774

All cause mortality

Annual mortality probabilities

Men Age	Men Probability	Women Age	Women Probability	Men+women weighted Age	Men+women weighted Probability
40	0.00796809	40	0.005982036	40	0.007404451
41	0.00876139	41	0.006776932	41	0.00819821
42	0.00955407	42	0.007571193	42	0.008991334
43	0.01034611	43	0.008364819	43	0.009783824
44	0.01113751	44	0.009157809	44	0.01057568
45	0.01192829	45	0.009950166	45	0.011366903
46	0.01350794	46	0.010741889	46	0.012723167
47	0.01508506	47	0.011532979	47	0.014077571
48	0.01665967	48	0.012323437	48	0.015430117
49	0.01823175	49	0.013113262	49	0.016780807
50	0.01980133	50	0.013902456	50	0.018129644
51	0.02215098	51	0.015085063	51	0.020149431
52	0.02449501	52	0.016266252	52	0.022165064
53	0.02683341	53	0.017446025	53	0.02417655
54	0.02916621	54	0.018624382	54	0.026183898
55	0.03149342	55	0.019801327	55	0.028187117
56	0.03574549	56	0.022542044	56	0.032013947
57	0.03997889	57	0.025275098	57	0.035825708
58	0.04419370	58	0.028000511	58	0.039622459
59	0.04839001	59	0.030718303	59	0.043404259
60	0.05256789	60	0.033428495	60	0.047171167
61	0.06667332	61	0.043046043	61	0.06002312
62	0.08056874	62	0.052567893	62	0.072701724

Stroke mortality year 1

Annual mortality probabilities
first year after stroke

Men Age	Men Probability	Women Age	Women Probability
40	0.02928270	40	0.022043413
41	0.03216339	41	0.024945586
42	0.03503553	42	0.027839145
43	0.03789915	43	0.030724118
44	0.04075427	44	0.03360053
45	0.04360091	45	0.036468405
46	0.04926889	46	0.03932777
47	0.05490327	47	0.042178649
48	0.06050427	48	0.045021068
49	0.06607206	49	0.047855052
50	0.07160687	50	0.050680626
51	0.07984763	51	0.054903273
52	0.08801524	52	0.059107137
53	0.09611035	53	0.063292301
54	0.10413361	54	0.06745885
55	0.11208566	55	0.071606866
56	0.12648153	56	0.081213958
57	0.14064399	57	0.090721635
58	0.15457684	58	0.100130926
59	0.16828380	59	0.109442849
60	0.18176852	60	0.118658411
61	0.22611733	61	0.150799534
62	0.26806239	62	0.18176852

Sensitivity Analysis | Indata | Results | Mortality trial | MI trial | Stroke trial | Costs trial | Utilities trial | Costs | Utilities | Standard mortality | Post event r ...

Markov Model inputs

Parameter	Value	Sources
Annual QALY for no event state	0,875	PLATO trial
Annual QALY decrement		
Non-fatal MI state	0,063	PLATO trial
Post MI-state	0,063	PLATO trial
Non-fatal stroke	0,138	PLATO trial
Post stroke state	0,138	PLATO trial

Costs of Illness (USD)

Cost of Illness	Harapan Kita	Bina Waluya	Dr. Sardjito
MI	1525,40	7189,22	3546,80
Post MI	165,30	1848,26	1848,26
Stroke	127,30	3733,52	3733,52
Post Stroke	147,90	1576,08	1576,08
No Event	165,30	1848.26	1848,26

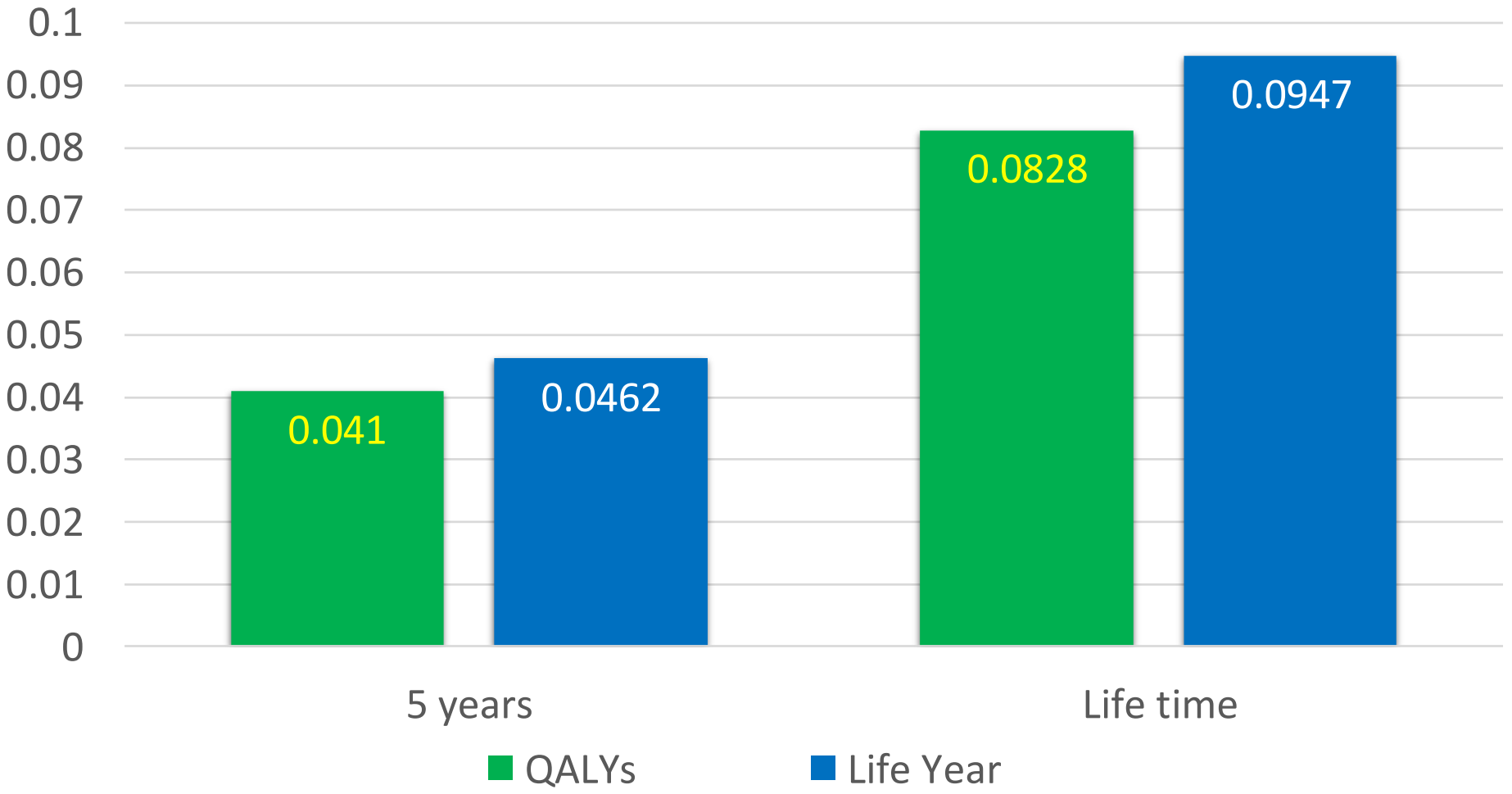
There are significantly high cost if the patient on MI compare with no event and after get MI.

Costs of Illness (USD)

Diagnosis	Number	Drugs Cost	Procedure	Total Cost
STEMI	713	412,68	2193,22	3513,94
NSTEMI	560	297,60	2051,89	3437,86
SH	243	1228,54	2334,01	4352,04
SNH	745	597,73	2159,84	3708,09

Total cost consisted of drugs and procedure cost and some criteria that we didn't show like: administration, accommodation, ambulance, gas, lab, facilities, physiotherapy, radiology

QALYs & Life Years Gained in 3 Hospital



Harapan Kita Cardiac Hospital

Deterministic analysis costs and effects discounted

Lifetime

	Ticagrelor	Clopidogrel	Incremental	ICER
Costs	15,621.48	15,305.89	315.58	
Life-years	7.0751	6.9804	0.0947	3,332.402
QALYs	6.0543	5.9716	0.0828	3,813.638

5 years

	Ticagrelor	Clopidogrel	Incremental	ICER
Costs	9,694.73	9,470.97	223.76	
Life-years	3.9354	3.8892	0.0462	4,844.411
QALYs	3.4070	3.3660	0.0410	5,453.987

Dr. Sardjito General Hospital

Deterministic analysis costs and effects discounted

Lifetime

	Ticagrelor	Clopidogrel	Incremental	ICER
Costs	8407,28	8301,49	105,79	
Life-years	7.0751	6.9804	0.0947	1,117.047
QALYs	6.0543	5.9716	0.0828	1,278.361

5 years

	Ticagrelor	Clopidogrel	Incremental	ICER
Costs	7,810.11	7,713.98	96.14	
Life-years	3.9354	3.8892	0.0462	2,081.369
QALYs	3.4070	3.3660	0.0410	2,343.269

Bina Waluya Hospital

Deterministic analysis costs and effects discounted

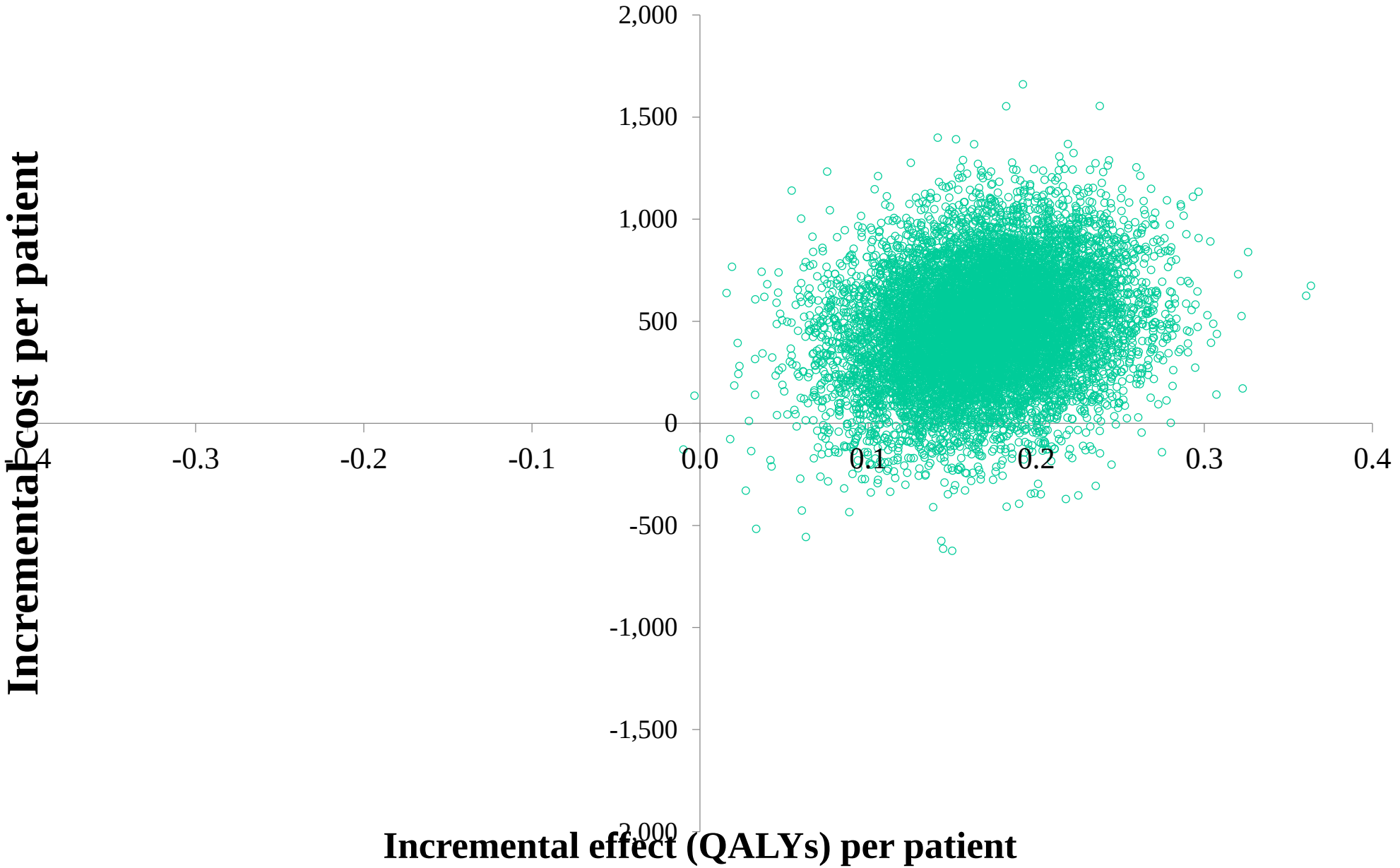
Lifetime

	Ticagrelor	Clopidogrel	Incremental	ICER
Costs	21,317.03	21,119.24	197.80	
Life-years	7.0751	6.9804	0.0947	2,088.652
QALYs	6.0543	5.9716	0.0828	2,390.276

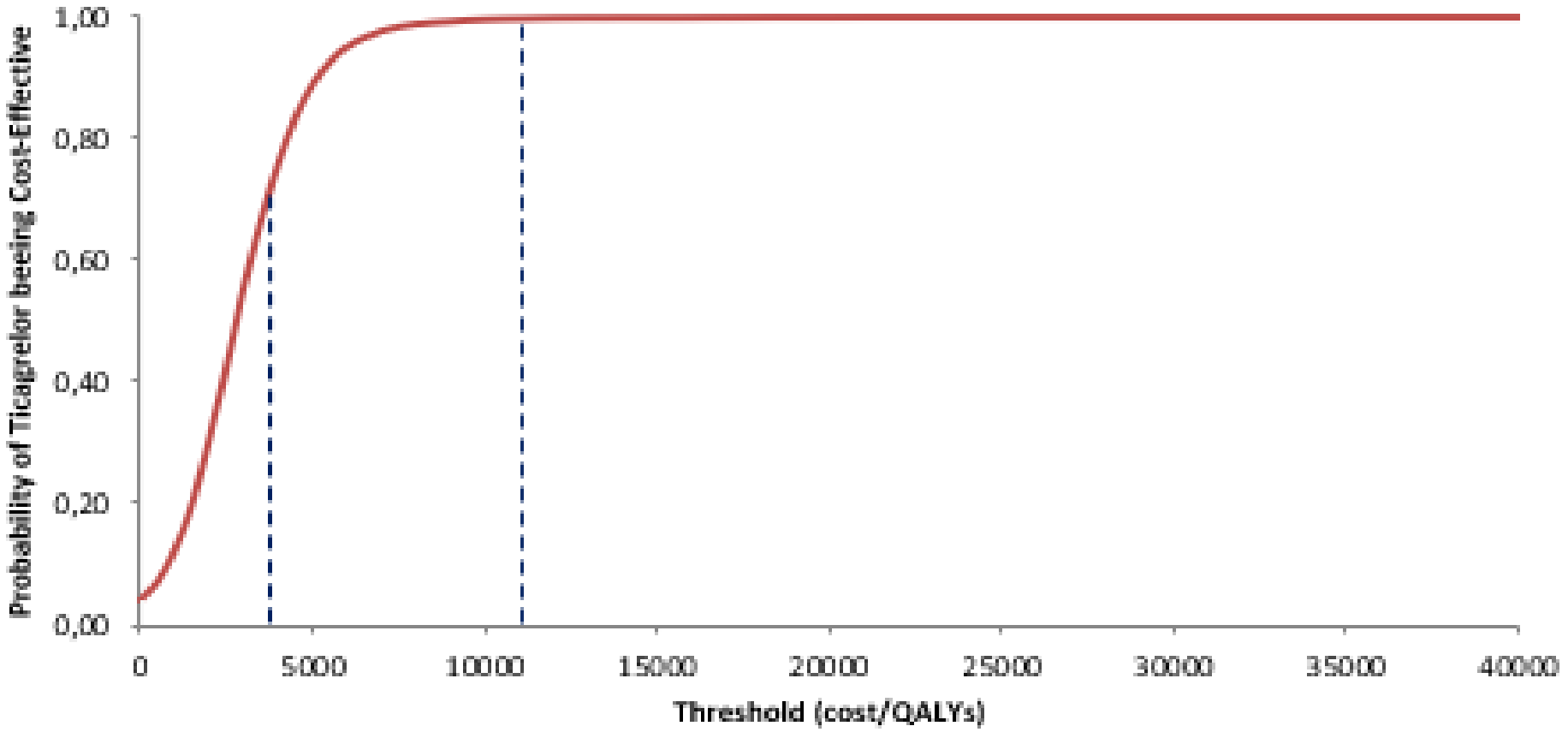
5 years

	Ticagrelor	Clopidogrel	Incremental	ICER
Costs	15,178.96	15,077.57	101.39	
Life-years	3.9354	3.8892	0.0462	2,195.172
QALYs	3.4070	3.3660	0.0410	2,471.392

Cost-effectiveness plane: Ticagrelor versus clopidogrel

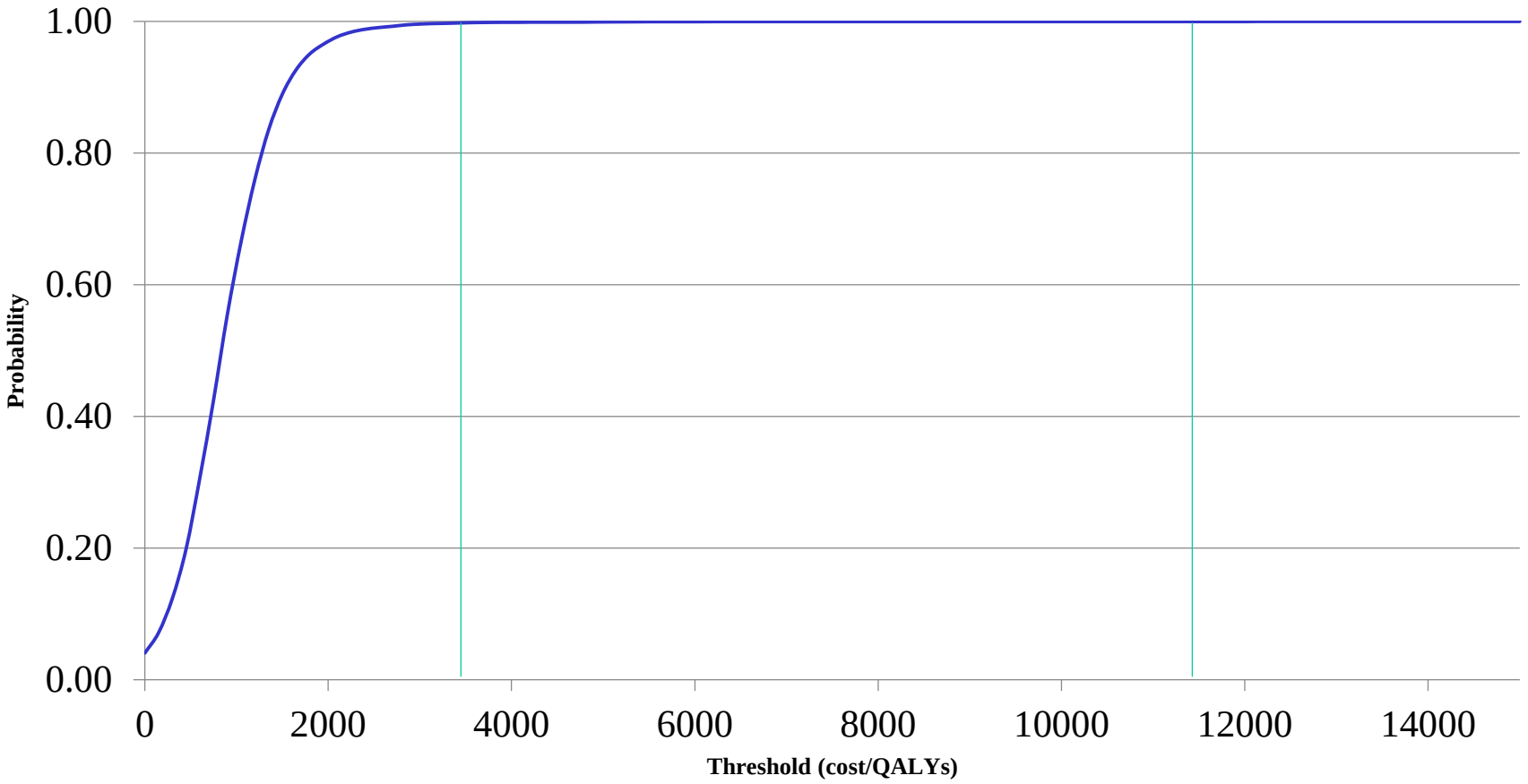


Cost-effectiveness Acceptability Curve (5 years)



This study using Indonesian GDP as baseline for acceptability. GDP1 was USD 3900 were in the five-year trial showed the ICER of Sardjito hospital USD 2343,269 and Bina Waluya hospital USD 2471,392 under the GDP1 value. Only the ICER of Harapan Kita hospital got above the GDP1. For the lifetime trial all the ICER of three hospitals showed under GDP1. The probability of Ticagrelor being cost-effective as compared to clopidogrel was **66,6% on five-year trial and 99,7% for lifetime with WTP (willingness to pay) USD 3,900**. It means that ticagrelor highly cost effectiveness than clopidogrel

Cost-effectiveness Acceptability Curve (life time)



For the lifetime trial all the ICER of three hospitals showed under GDP1. The probability of Ticagrelor being cost-effective as compared to clopidogrel was **99,9% for one GDP** and **100% for3 times GDP lifetime** with WTP (willingness to pay) USD 3,900. It means that ticagrelor highly cost effectiveness than clopidogrel

Conclusions

- Clopidogrel was a standard therapy that recommended to treat ACS patient. Compare to the ticagrelor as same antiplatelet drugs, the result showed that QALYs and life year gained higher when using ticagrelor than clopidogrel.
- Regarding the high cost of ticagrelor, the ICER of the lifetime decision tree showed under GDP1 so it mean using ticagrelor was highly cost effective and acceptable to apply in clinical setting in Indonesia.

Thank you for study collaborators

- **Sardjito Hospital**

  Lucia Krisdinarti, MD, SpJP(K), PhD

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- **Harapan Kita Hospital**

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  Dr. Rr. Arum Ramadhyan Suryandari
- **Binawaluya Hospital**

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