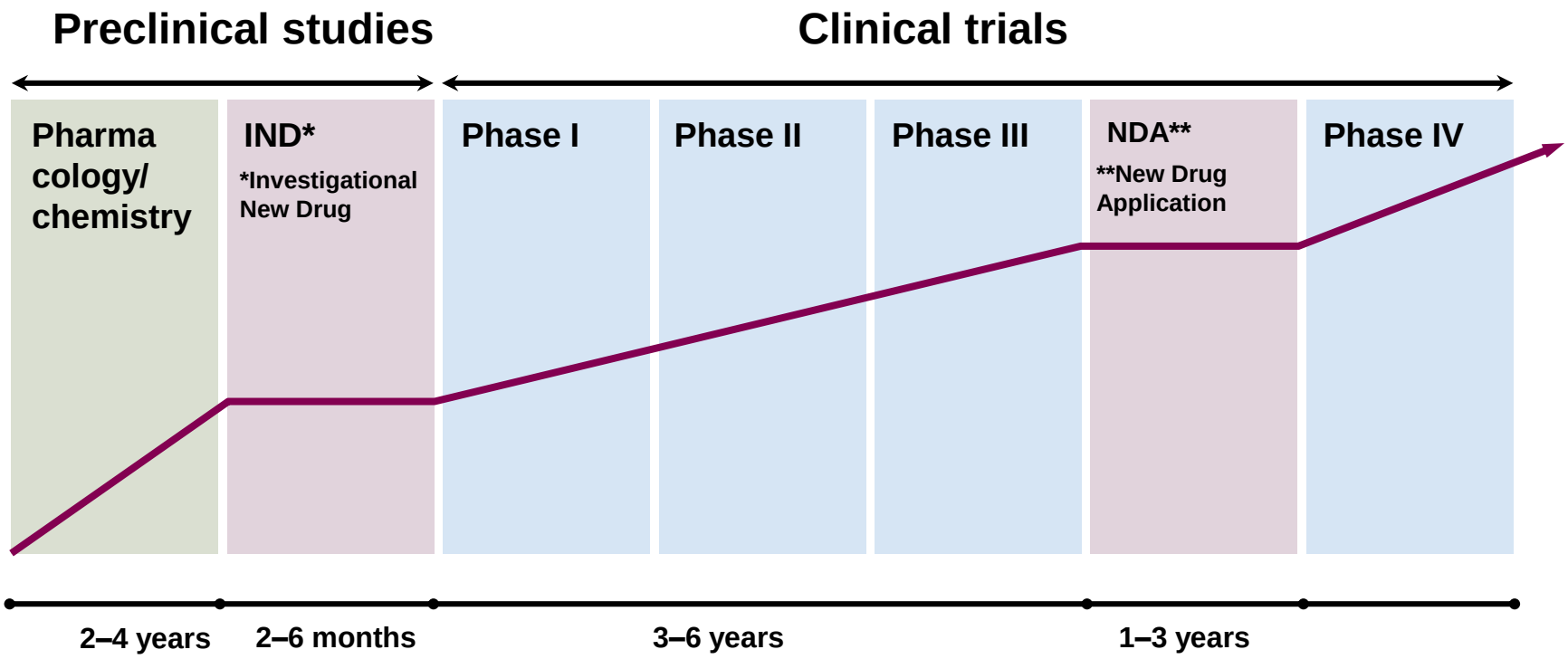
Real world evidence studies: A fully integrated part of drug development

Pål Hasvold
Medical Evidence Scientific Lead CV
AstraZeneca Nordic-Baltic

AstraZeneca

Need for real world data in a life cycle of a drug?



RWE study program

RWE a fully integrated part of drug development

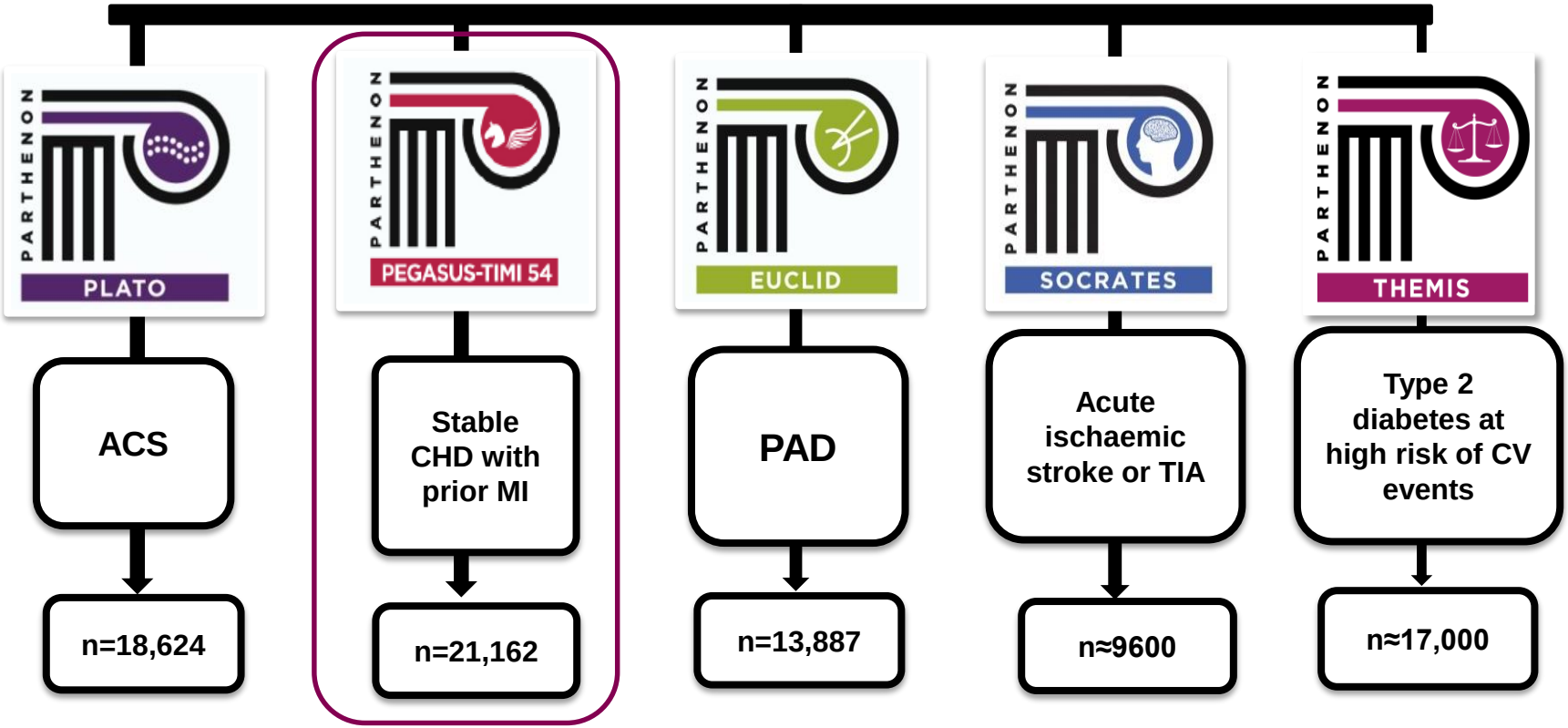
Unmet medical need	RCT results into clinical perspective	How are the drugs used?
•How large is this patient population? •How are they treated? •Outcome/risk? •Which are the high risk groups? •What are the cost of treating/not treating them?	•An RCT population vs. real life •Who would benefit most of treatment?	•Who are treated? •For how long? •Switch pattern? •Disturbing signals? •Do we deliver the story?

Administrert sammen med acetylsalisylsyre (ASA), er indisert for profylakse mot aterotrombotiske hendelser hos voksne pasienter med akutt koronarsyndrom

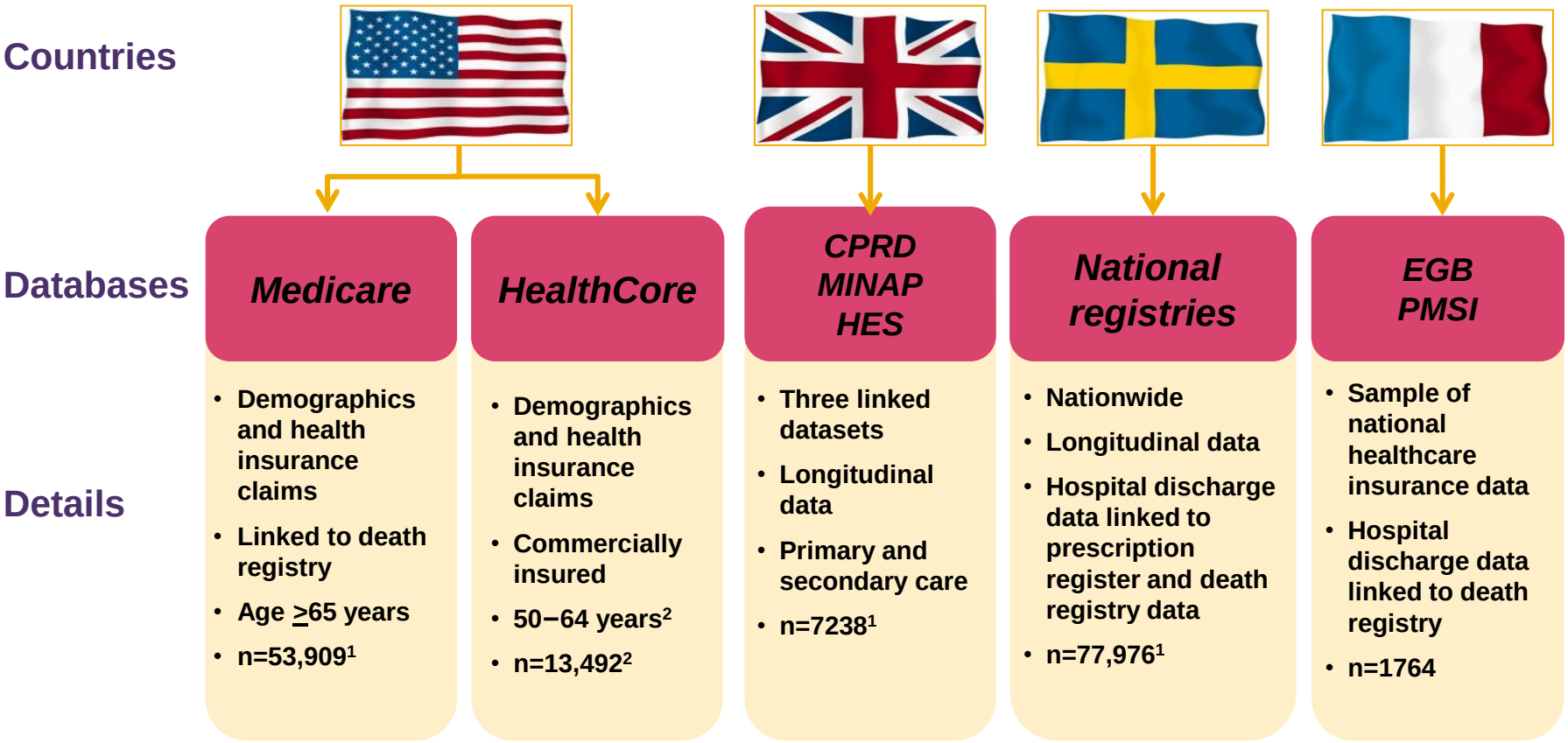
Forlenget behandling?

Brilique (ticagrelor)

Clinical trial program



APOLLO: 5 individual studies in 4 countries encompassing >150,000 patients



[1]Rapsomaniki E, et al. ESC Late Breaking Registry abstract 2014: In press; [2] DeVore S, et al. ISPOR poster 2014;

European Heart Journal Advance Access published January 13, 2015

European Heart Journal
doi:10.1093/eurheartj/ehu505

CLINICAL RESEARCH
Acute Coronary Syndrome

Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective

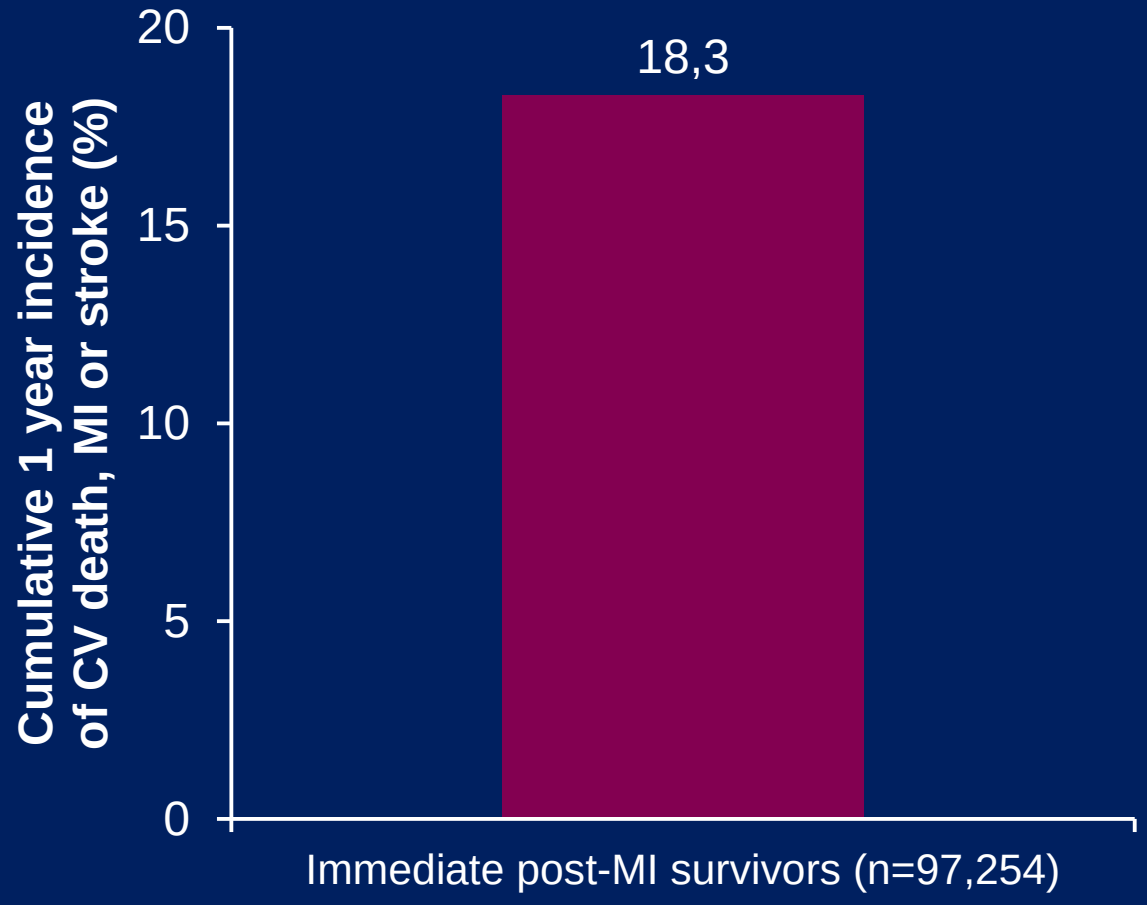
Tomas Jernberg[1]*, Pål Hasvold[2], Martin Henriksson[2], Hans Hjelm[3], Marcus Thuresson[4], and Magnus Janzon[5,6]

[1]Department of Medicine, Huddinge, Karolinska Institutet, Department of Cardiology, Karolinska University Hospital, 141 86 Stockholm, Sweden; [2]AstraZeneca NordicBaltic, Södertälje, Sweden; [3]Nyköping Hospital, Nyköping, Sweden; [4]Statisticon AB, Uppsala, Uppsala 753 22, Sweden; [5]Department of Cardiology, Linköping University, Linköping, Sweden; and [6]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

Received 18 July 2014; revised 4 December 2014; accepted 16 December 2014

CV Death, MI or stroke within 365 days of index MI

~1 in 5 patients will suffer a MI, stroke or CV death within the first year after a MI

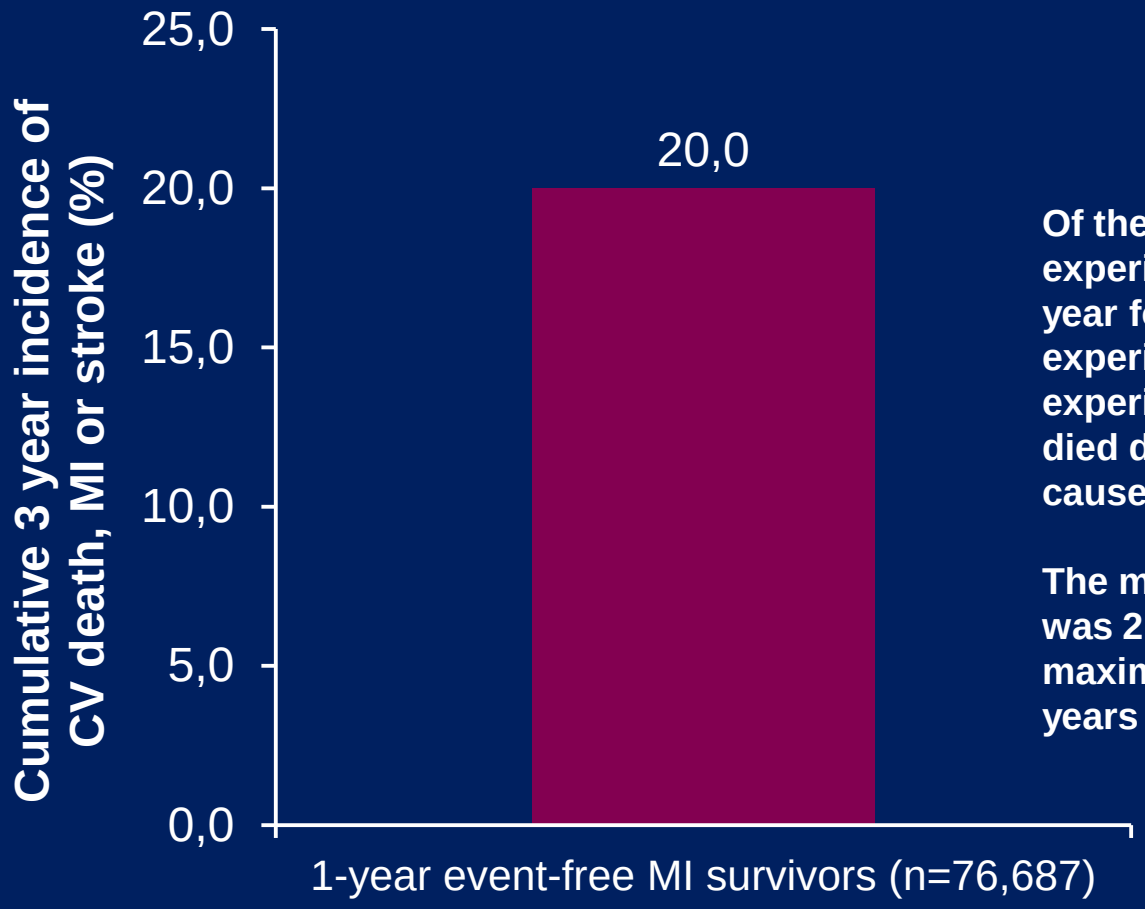


CV, cardiovascular; MI, myocardial infarction.

Jernberg T. et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehu505

CV Death, MI or stroke in the 1 year post-MI event free population

~1 in 5 patients, event-free for 1 year post-MI, will suffer a MI, stroke or CV death within 3 years



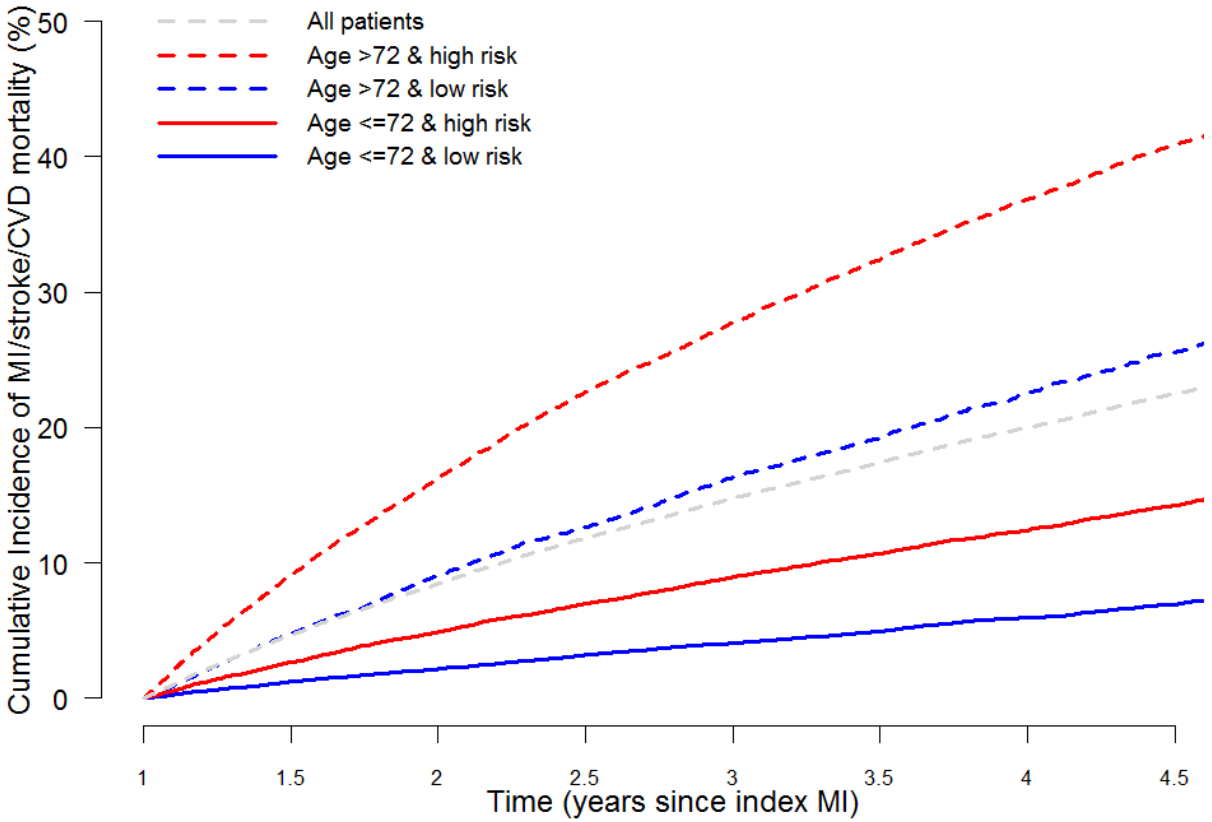
Of the 20% of patients who experienced an event in the 3 year follow up , 40.8% experienced an MI, 18.6% experienced stroke, and 40.6% died due to cardiovascular causes as their first event

The mean duration of follow-up was 2.54 years and the maximum follow-up was 5.5 years

CV, cardiovascular; MI, myocardial infarction.

Jernberg, T et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehu505

Kaplan-Meier estimated of the risk of the combined endpoint after 365 days after the index myocardial infraction until end of study for stable post-myocardial patients, stratified by age and high- vs. low-risk patients



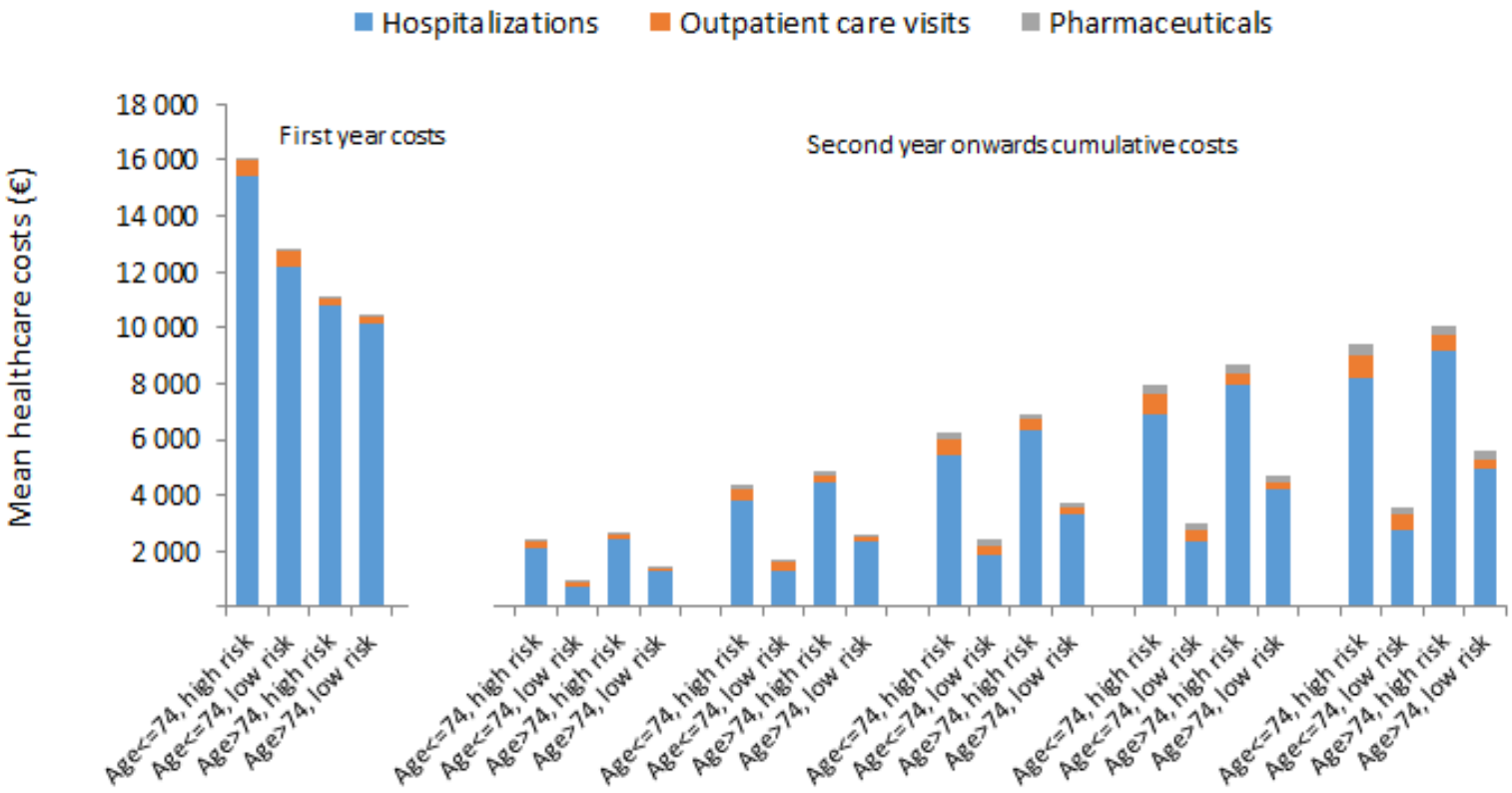
Number at risk

<=72 LR	18935	18631	16735	14874	12899	10964	9021	7161
<=72 HR	20111	19438	16874	14558	12393	10540	8711	6847
>72 LR	13584	12705	10831	9208	7651	6301	4981	3787
>72 HR	24057	21207	17337	13948	11249	9000	6866	5111

Jernberg T. et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehu505

Burden of disease

High risk post-MI patients….



Year of follow-up	1	2	3	4	5	6
No of patients:						
age<=74, high risk	17 850	16 560	14 167	10 707	7 620	4 553
age<=74, low risk	32 497	31 909	28 399	21 832	15 511	9 224
age>74, high risk	26 742	19 205	14 050	9 303	5 691	2 904
age>74, low risk	20 165	17 597	14 375	10 215	6 702	3 556

Data on file. Janzon M, et al. ESC abstract 2015: Accepted

Table II. Baseline characteristics

Baseline characteristic	N = 21,162
Age, y, median (IQR)	65 (59-71)
Female	24%
White	87%
Weight, kg, median (IQR)	81 (70-92)
BMI, median (IQR)	28 (25-31)
Region enrolled	
Asia/Australia	11%
Europe/South Africa	59%
North America	18%
South America	12%
Qualifying Event and Cardiovascular History	
Time from MI to rando (y), median (IQR)	1.7 (1,2)
Qualifying-NSTEMI	41%
Qualifying-STEMI	54%
Qualifying-MI, type not specified	5%
History of PCI	83%
History of CABG	5%
History of PAD	5%
Qualifying risk factors	
Age ≥65 years	55%
Diabetes mellitus requiring medication	28%
A second prior MI	17%
Multivessel CAD	59%
Chronic renal dysfunction*	6%

Data based on interim snapshot taken July 2013 after completion of enrollment but during ongoing trial and data cleaning. Not based on 100% clean data.
*Non-end stage renal dysfunction with stable estimated creatinine clearance <60 mL/min.

	Stable post-MI (*n* = 76 687)
Age, years	
Mean (SD)	71.5 (12.5)
Median (range)	72 (20-105)
Gender, *n* (%)	
Male	48 543 (63.3)
Female	28 144 (36.7)
Qualifing Event and Cardiovascular History	
PCI, *n* (%)	37 497 (48.9)
CABG, *n* (%)	5438 (7.1)
Peripheral arterial disease, *n* (%)	4885 (6.4)
Qualifying risk factors	
Age≥65 years, *n (%)*	53 686 (69.9)
Diabetes mellitus, *n* (%)	17 712 (23.1)
Previous MI, *n* (%)	6436 (8.4)
Chronic renal dysfunction, *n* (%)	983 (1.3)

Bonaca MP el al. Heart J 2014, 167:437-444

Jernberg,T. et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehu505

Myocardial Infarction Survivors with Diabetes Have a Substantially Increased Event Rate: Impact of PEGASUS-TIMI 54 Trial Risk Factors in a Nationwide Real-life Setting in Sweden

Magnus Janzon[1], Pål Hasvold[2], Hans Hjelm[3], Marcus Thuresson[4], and Tomas Jernberg[5]

[1]Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [2]AstraZeneca NordicBaltic, Södertälje, Sweden; [3]Nyköping Hospital, Nyköping, Sweden; [4]Statisticon AB, Uppsala, Sweden; [5]Department of Medicine, Huddinge, Karolinska Institutet; Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden

INTRODUCTION

- Acute coronary syndromes (ACS) represent a common, symptomatic manifestation of coronary artery disease, the leading cause of death worldwide.[1]
- Whereas dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor antagonist has been shown to reduce subsequent cardiovascular (CV) events in patients presenting with ACS,[2,3] the optimal duration of therapy following myocardial infarction (MI) remains unclear.
- Few studies have reported CV outcomes in post-MI sur
  the available data are mostly limited to 12 months and t
  of patients from clinical trials.[4,5]
- However, in a contemporary, nationwide, real-life cohor
  that the risk of CV events remains high after the first 12
  MI, particularly in those patients with additional risk fact
- The PEGASUS-TIMI 54 trial (NCT01225562) investigat
  intensive (i.e. long-term treatment >12 months) DAPT c
  CV events in high-risk, post-MI survivor patients.[7]
- Based on the patient characteristics of the population s
  PEGASUS-TIMI 54 trial, we assessed the influence of s
  on the incidence of CV events in post-MI survivor patie

STUDY DESIGN

- This contemporary, nationwide, real-life cohort study (N
  analyzed morbidity, mortality, and medication data from
  Swedish national registries: The National Inpatient Reg
  Prescribed Drug Register, and the Cause of Death Reg
- We identified patients who were admitted to Swedish h
  diagnosis of primary MI between July 1, 2006, and Jun
  were alive 1 week following discharge.
- Patients who survived for 12 months without experienci
  stroke, who were aged ≥50 years, and who had at leas
  factor (aged ≥65 years, diabetes mellitus, ≥1 MI prior to
  diagnosis of chronic renal dysfunction) were eligible for
  current analysis.
- Patients who met any of the following criteria were excl
  analysis: diagnosis of stroke, bleeding disorder, severe
  or kidneys (requiring dialysis), chronic use of oral anticc
  therapy/low-molecular-weight heparin during the 12 mo
  index MI or the 12 months prior to the stable post-MI pe
  onward).
- Follow-up data were collected from the time of the inde
  December 31, 2012, or patient death.
- The primary end point of risk for non-fatal MI, non-fatal
  was estimated for Day 366 through to study completion
  by Kaplan-Meier analysis. The event rate analyses wer
  steps for age and sex, and then for multiple risk factors

RESULTS

- Between July 1, 2006, and June 30, 2011, 108,315 patients were admitted to hospital with a diagnosis of primary MI (**Figure 1**).
  - 97,254 (90%) survived the index MI and were alive 1 week after discharge.
- A total of 46,061 patients survived for 12 months following the index MI and met the criteria for inclusion in the current analysis (**Figure 1**).

- For each risk factor assessed, the event rate for the cumulative primary end point was increased in patients with a specific risk factor versus those without (**Figure 2**).
  - Also, in patients with a risk factor present, the event rate substantially increased over time.

SUMMARY

- It has previously been shown that the risk of CV events remains high for the period after the first 12 months after index MI, particularly in those patients with additional risk factors.[6]
- In this contemporary, nationwide, real-life study, the post-MI survivor patients were generally older than the population recruited for the PEGASUS study,[7] and our findings showed that age is an important risk factor for recurrent CV events.

mellitus and a history of more than one MI was associated with an event rate in post-MI survivor patients.

s event rates (31–45%) were highest in patients with chronic ysfunction, this subgroup of patients represented only a small ion of the overall study population.

y, our findings indicate that elderly (≥65 years) post-MI survivor nd patients with diabetes mellitus and a history of more than one nefit from additional monitoring and management with prevention

	Observed % (95% CI)	Age and sex adjusted[1] % (95% CI)	Multiple adjusted[2] % (95% CI)
Age ≥65 years			
No	10.0 (9.1–10.9)	10.5 (9.7–11.4)	8.7 (7.9–9.4)
Yes	23.8 (23.3–24.3)	23.6 (23.1–24.0)	23.7 (23.2–24.2)
Diabetes			
No	21.2 (20.7–21.7)	16.8 (16.4–17.3)	16.9 (16.4–17.4)
Yes	24.4 (23.5–25.2)	26.5 (25.6–27.3)	26.0 (25.1–26.9)
More than one prior MI			
No	21.3 (20.8–21.8)	18.0 (17.5–18.4)	17.8 (17.3–18.3)
Yes	25.0 (24.0–26.1)	25.4 (24.4–26.4)	24.9 (23.9–25.8)
Chronic renal disease			
No	21.3 (20.9–21.8)	18.9 (18.5–19.4)	18.8 (18.3–19.2)
Yes	44.7 (41.5–47.7)	33.9 (31.5–36.1)	30.7 (28.5–32.8)

CI, confidence interval

[1]Adjusted for age except for age subgroup analyses. Reported CV-related risk at the third year of follow-up for reference patient characteristics: age 76 years old (median age of the study population) and gender-weighted relative to the proportion of women.

[2]Adjusted for age (except for age subgroup analyses), sex, diabetes, more than one MI, and renal disease. Reported CV-related risk at the third year of follow-up for reference patient characteristics: age 76 years old (median age of the study population), other factors weighted relative to the proportion of women, diabetes, more than one prior MI, and chronic renal disease.

Table 2. Observed event rate of the primary end point in stable post-MI patients with additional CV-related risk factors.

NCES

Loncar D. PLoS Med 2006;3:e442.
al. N Engl J Med 2001;345:494–502.
et al. N Engl J Med 2009;361:1045–57.
et al. N Engl J Med 2012;366:1404–13.
al. JAMA 2006;295:180–9.
et al. Eur Heart J 2015; *epub ahead of print.*
et al. Am Heart J 2014;167:437–44.

edgments

funded by AstraZeneca. Medical writing support (in the form of writing assistance, les and figures, collating author comments, grammatical editing and referencing) was sa Michel, PhD, at Zoetic Science (Macclesfield, UK), and was funded by AstraZeneca.

res

d by AstraZeneca. **MT** is employed by an independent statistical consultant company, which AstraZeneca is a client. **MJ, HH,** and **TJ** have no conflicts to disclose.

the American College of Cardiology, 64th Annual Scientific Session & Expo 2015, , USA, March 14–16, 2015.

Janzon M, et al. ACC abstract 2015: In press

Supportive data for long term use of dual antiplatelet therapy in post myocardial infarction patients

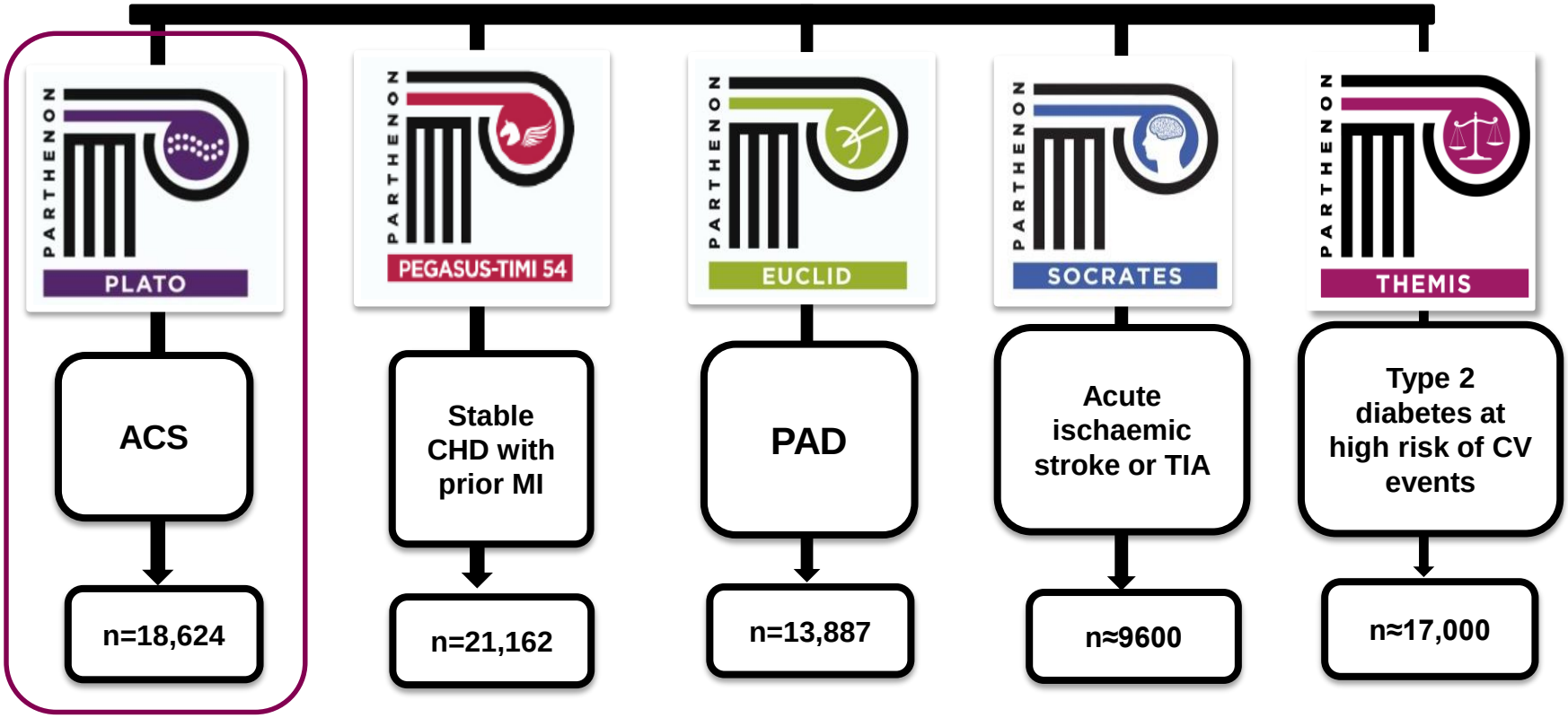
Clinical paper/Abstracts:
"Cardiovascular risk in post myocardial infarction patients; nationwide real world data demonstrate the importance of a long term perspective"

Health economic paper:
"Cardiovascular risk in post myocardial infarction patients; nationwide real world data demonstrate the continued high long term health care costs for these patients"

When RCT results available:
Results into clinical perspective
Selection of patient groups

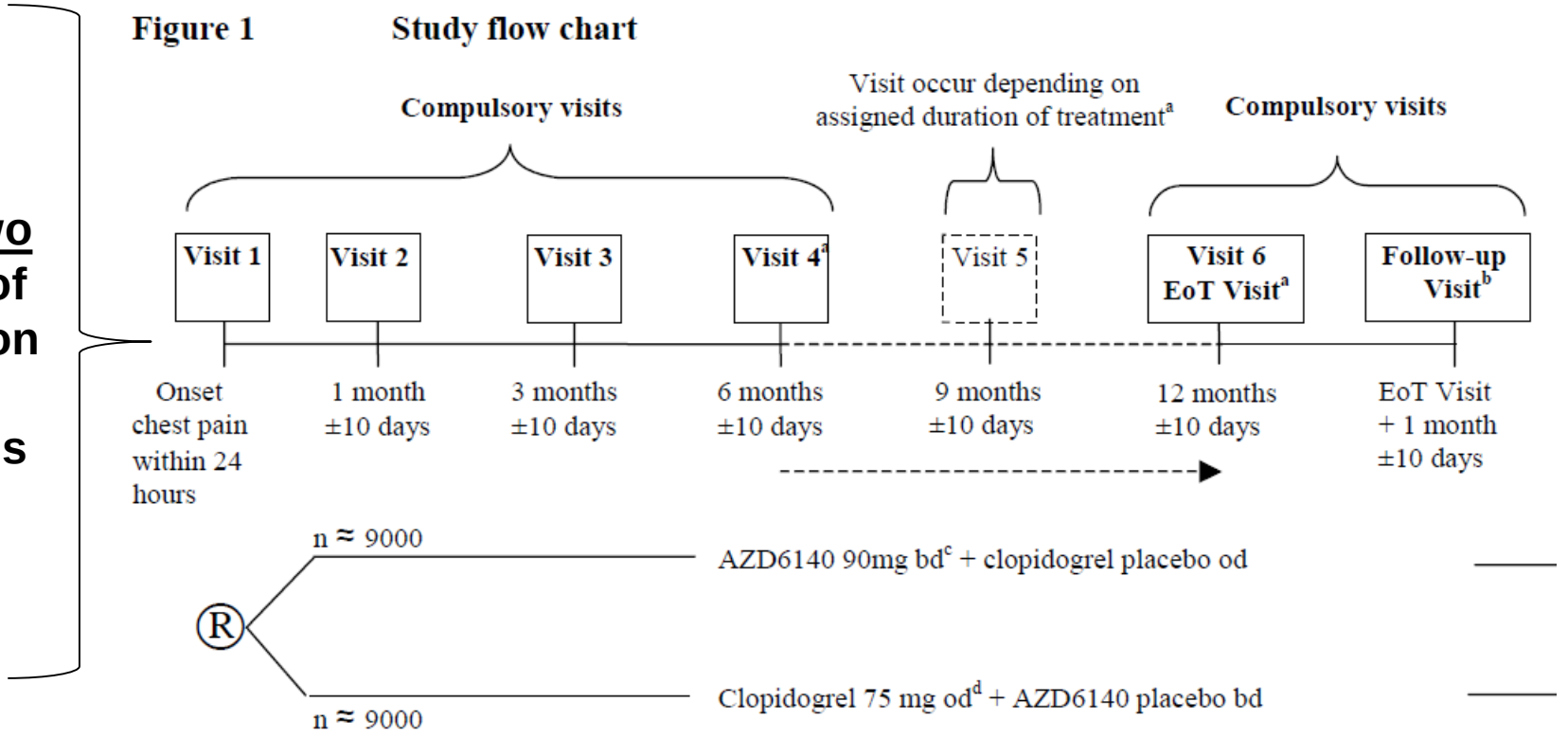
Brilique (ticagrelor)

Clinical trial program



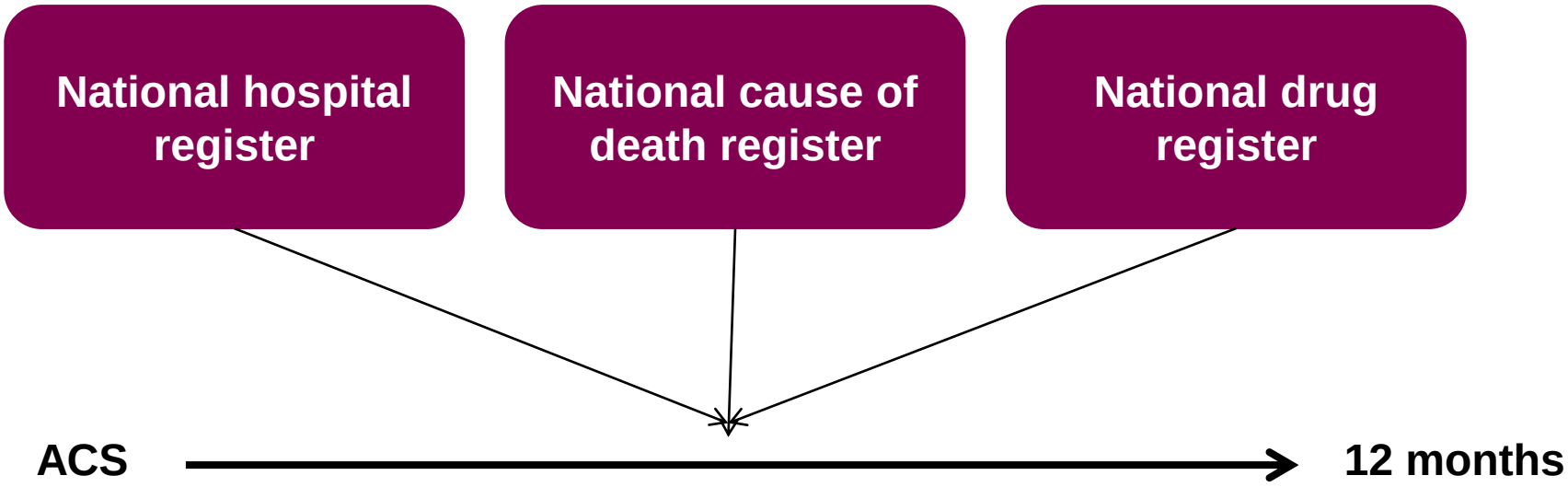
Do we need more or other types of documentation?

Only <u>two pages</u> of inclusion and ex criteria's



ACS treatment in real life?

Initiation and persistence of dual antiplatelet therapy after acute coronary syndrome

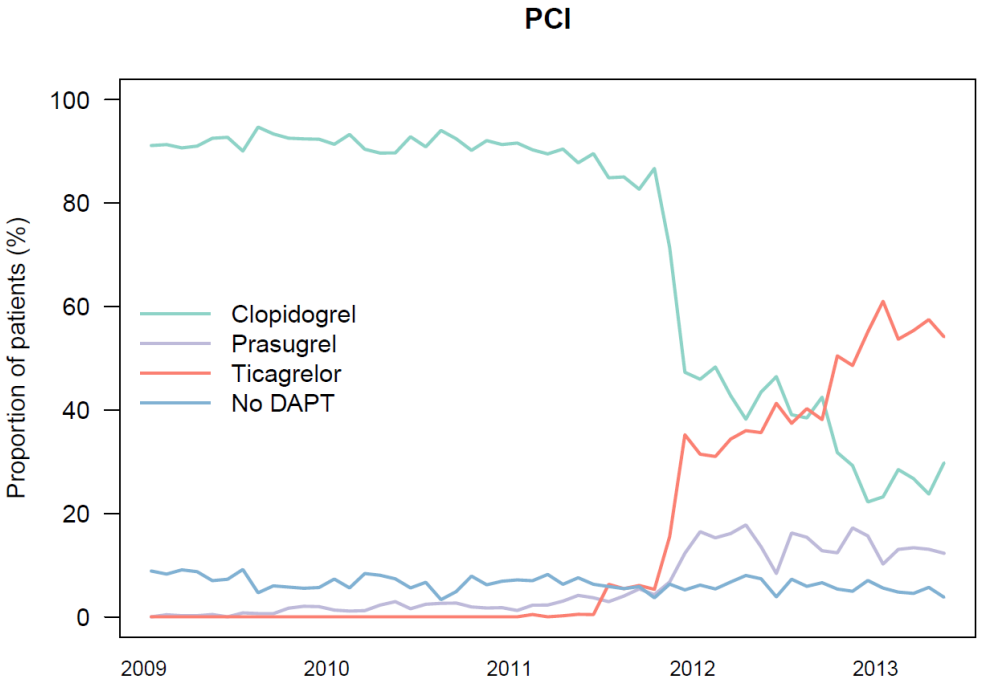


How are patients treated:

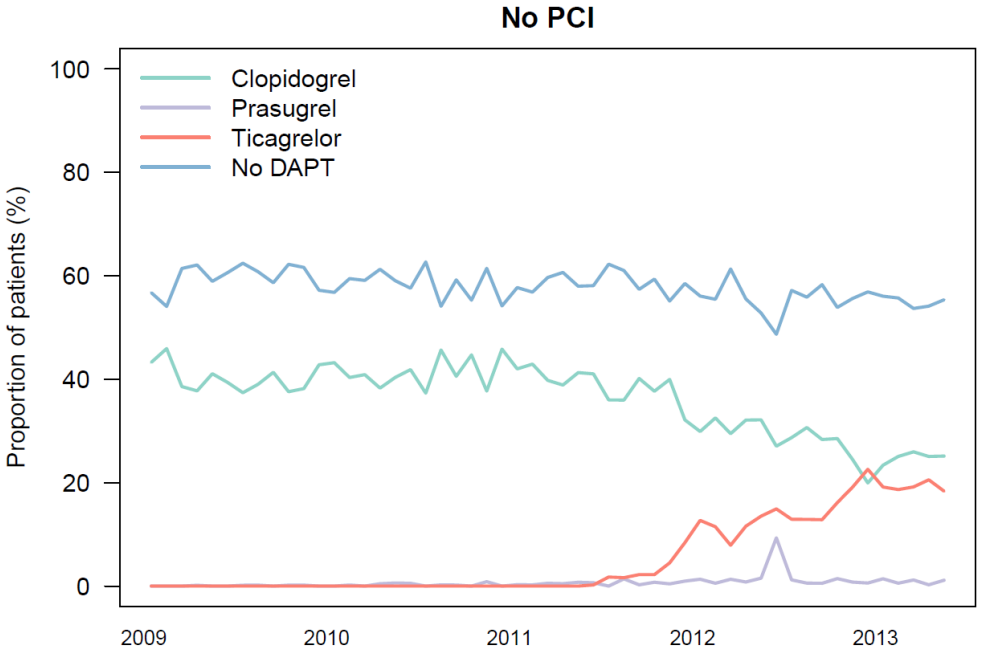
- **Type of antiplatelet treatment?**
- **For whom?**
- **For how long?**
- **Are they switched?**

NORWAY

PCI, n=5500



Non- PCI, n=5777



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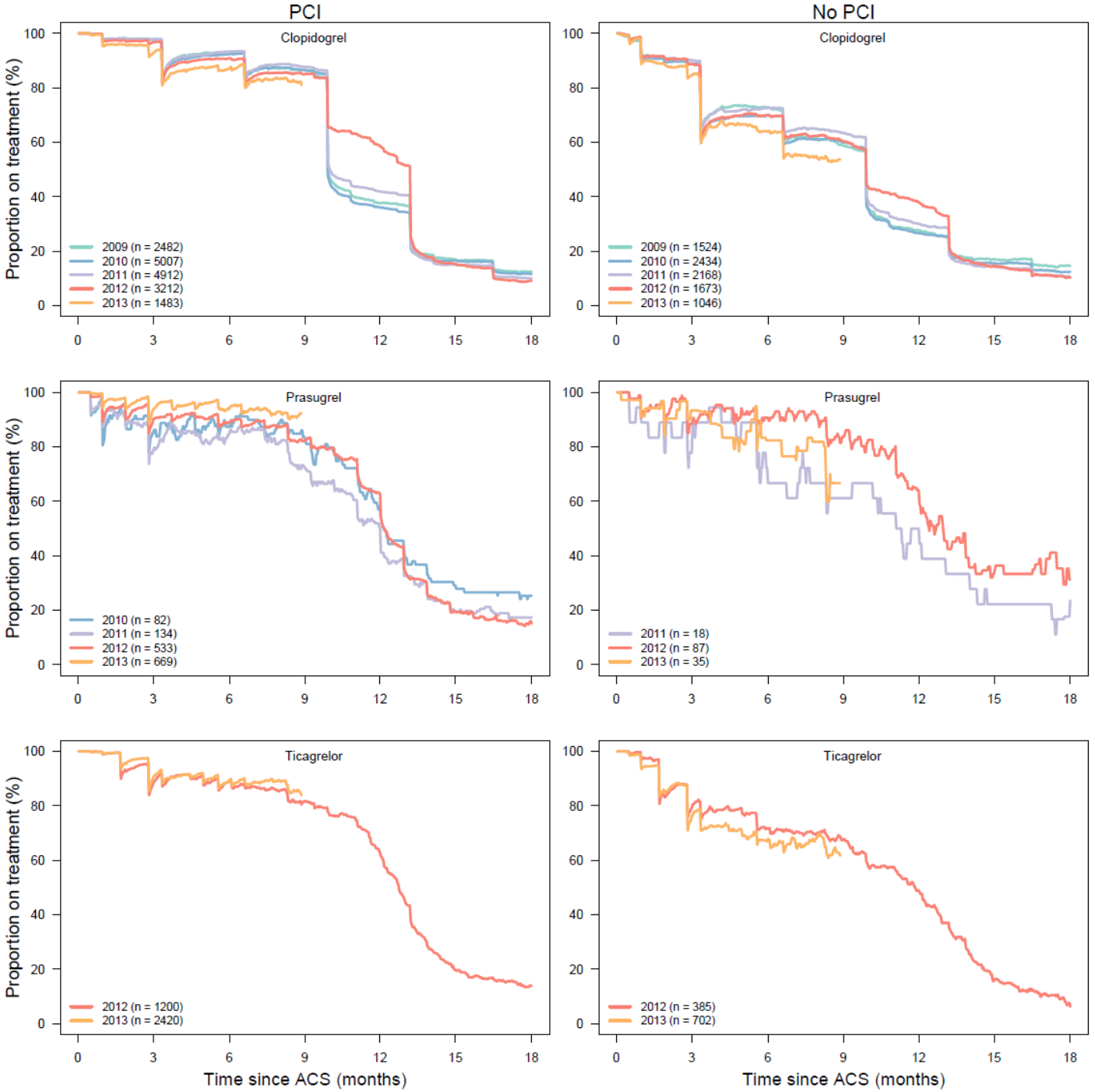
NORWAY



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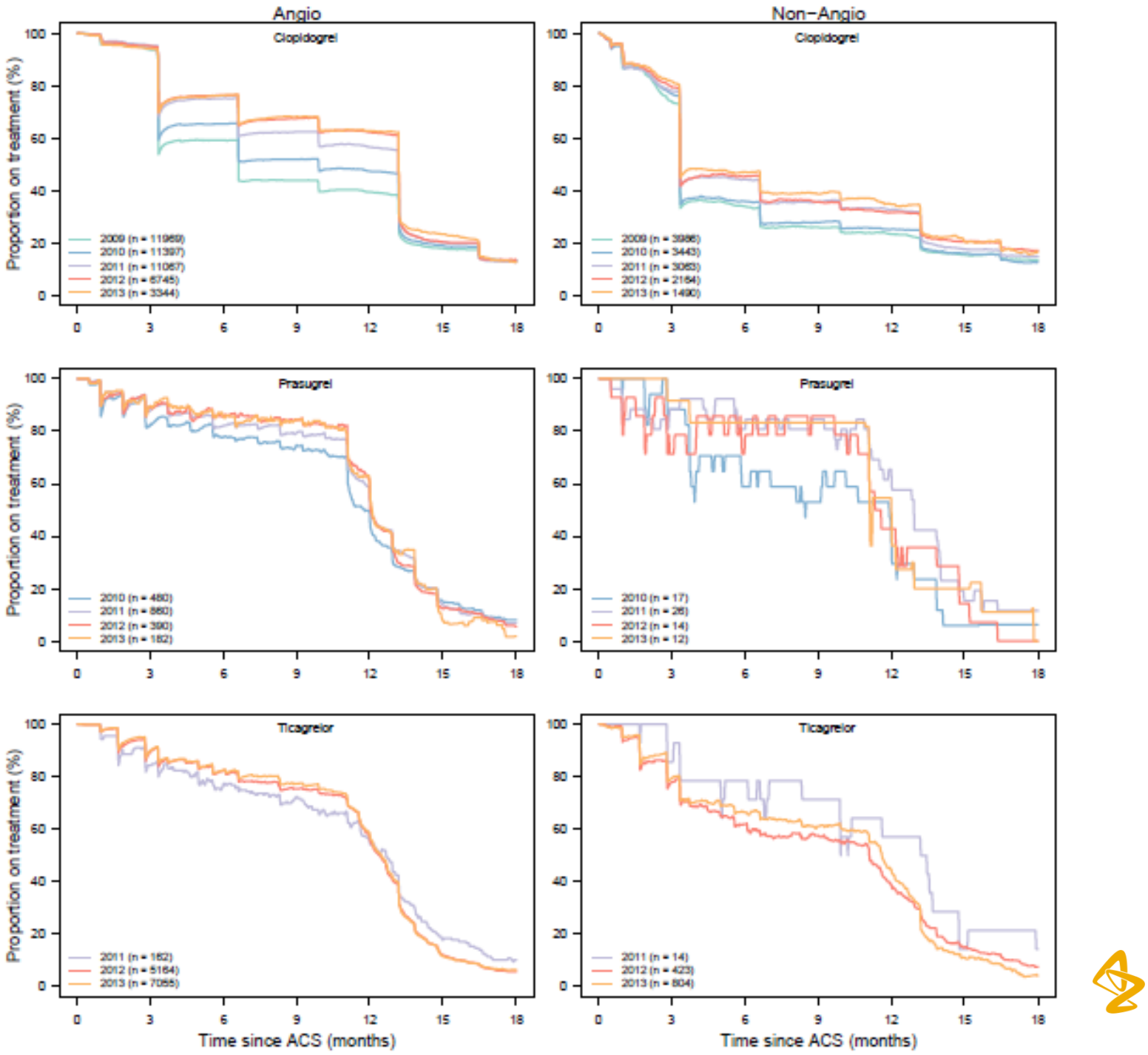
SWEDEN



Data on file

Conclusions

- RWE data/studies are a fully integrated part of drug development programs in AstraZeneca
- We are in the middle of the smørgåsbord