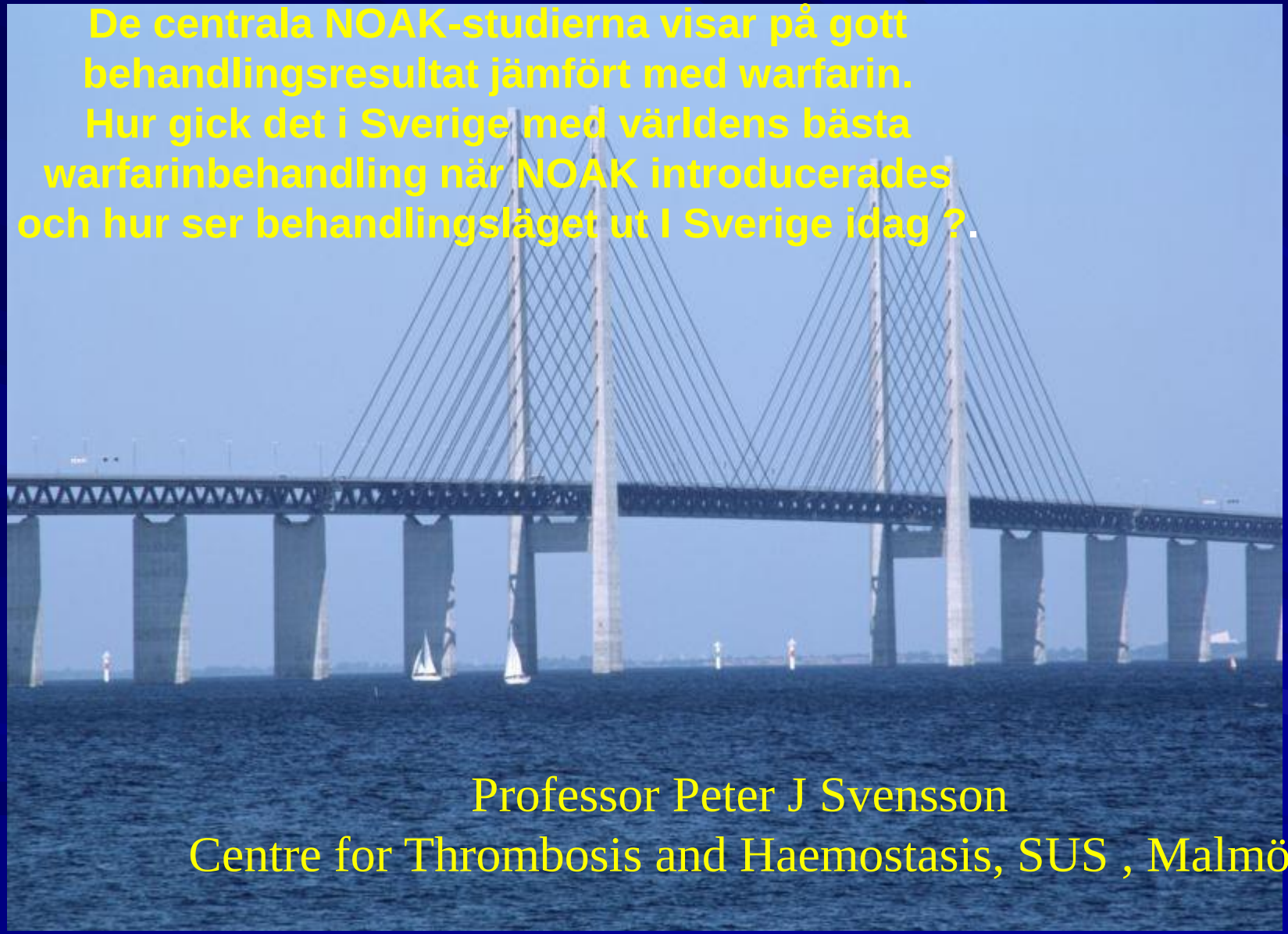
De centrala NOAK-studierna visar på gott behandlingsresultat jämfört med warfarin. Hur gick det i Sverige med världens bästa warfarinbehandling när NOAK introducerades och hur ser behandlingsläget ut I Sverige idag ?.



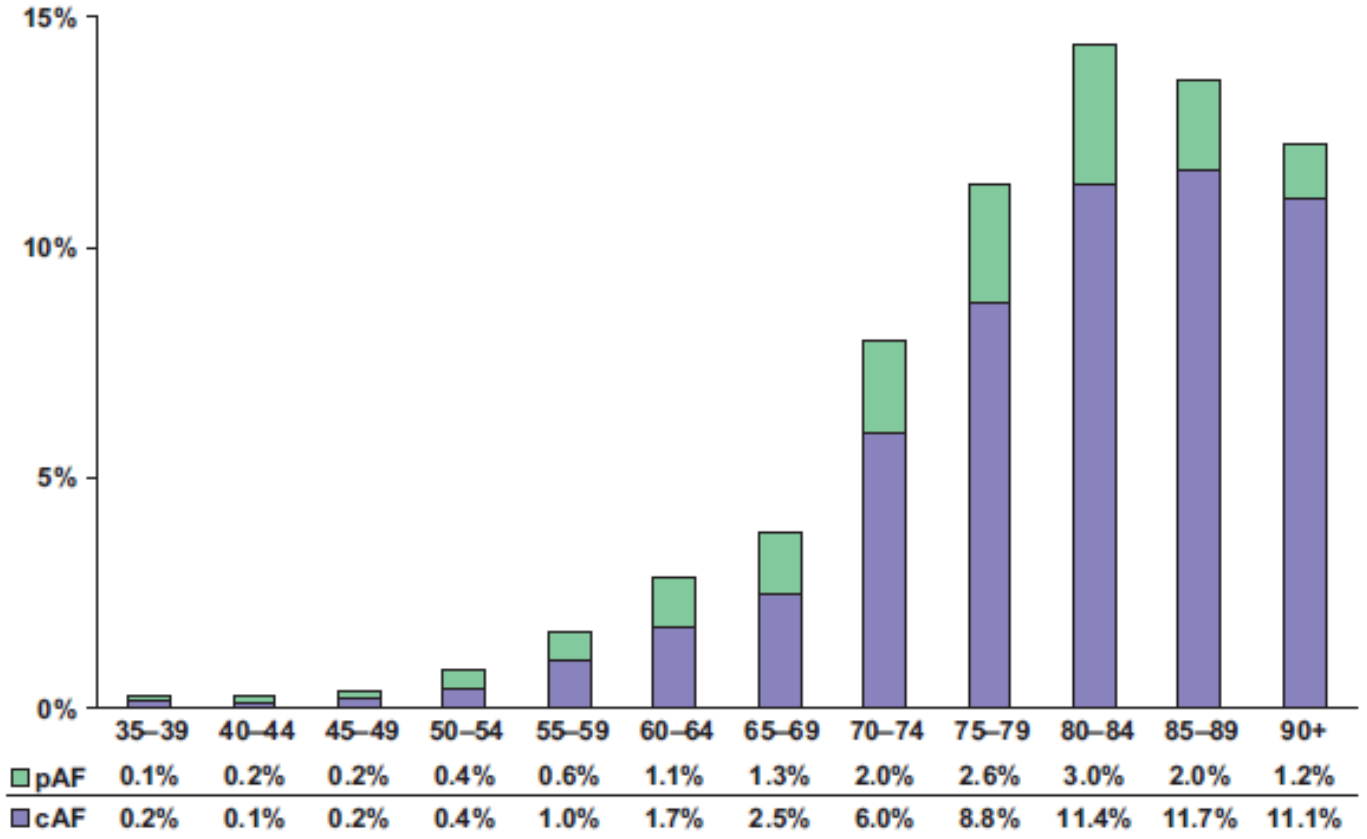
Professor Peter J Svensson
Centre for Thrombosis and Haemostasis, SUS , Malmö

Conflict of interest

- ACCP Guidelines 2012
- Auricula (Nationellt kvalitetsregister)
- Läkemedelsverket 2017

- Bayer
- BMS/Pfizer
- Boeringer
- CSL Behring
- MSD
- Octapharma

Prevalence of atrial fibrillation
> 2.5 % in the general population

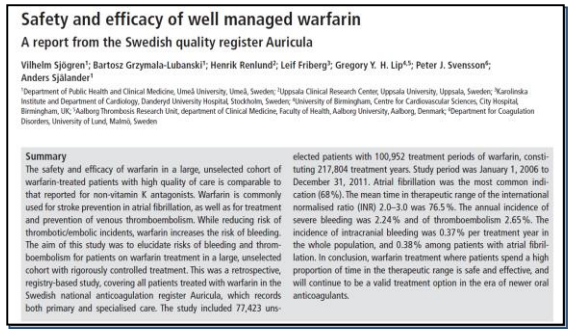


Andersson et al JIM 2012, SBU 2013 april
Friberg et al JIM 2013

Indications for OAC

- Atrial fibrillation > 80%
- VTE 10%
- Mechanical heart valves 5%
- Other 5%

- Increase of OAC with 5-10% per year
- ***30 % is over the age of 80 years among patients with OAC***
- *Around 300.000 patients on OAC in Sweden*



Safety and efficacy of well managed warfarin

A report from the Swedish quality register Auricula

Vilhelm Sjögren[1]; Bartosz Grzymala-Lubanski[1]; Henrik Renlund[2]; Leif Friberg[3]; Gregory Y. H. Lip[4,5]; Peter J. Svensson[6]; Anders Själander[1]

[1]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [2]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; [3]Karolinska Institute and Department of Cardiology, Danderyd University Hospital, Stockholm, Sweden; [4]University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [5]Aalborg Thrombosis Research Unit, department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark; [6]Department for Coagulation Disorders, University of Lund, Malmö, Sweden

Summary

The safety and efficacy of warfarin in a large, unselected cohort of warfarin-treated patients with high quality of care is comparable to that reported for non-vitamin K antagonists. Warfarin is commonly used for stroke prevention in atrial fibrillation, as well as for treatment and prevention of venous thromboembolism. While reducing risk of thrombotic/embolic incidents, warfarin increases the risk of bleeding. The aim of this study was to elucidate risks of bleeding and thromboembolism for patients on warfarin treatment in a large, unselected cohort with rigorously controlled treatment. This was a retrospective, registry-based study, covering all patients treated with warfarin in the Swedish national anticoagulation register Auricula, which records both primary and specialised care. The study included 77,423 unselected patients with 100,952 treatment periods of warfarin, constituting 217,804 treatment years. Study period was January 1, 2006 to December 31, 2011. Atrial fibrillation was the most common indication (68%). The mean time in therapeutic range of the international normalised ratio (INR) 2.0–3.0 was 76.5%. The annual incidence of severe bleeding was 2.24% and of thromboembolism 2.65%. The incidence of intracranial bleeding was 0.37% per treatment year in the whole population, and 0.38% among patients with atrial fibrillation. In conclusion, warfarin treatment where patients spend a high proportion of time in the therapeutic range is safe and effective, and will continue to be a valid treatment option in the era of newer oral anticoagulants.

Warfarin in Sweden

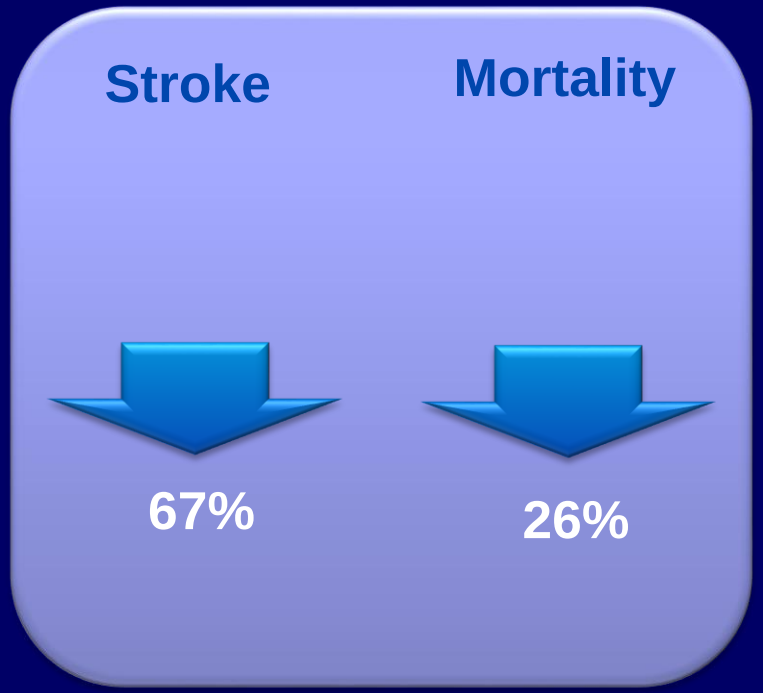
Outcomes and age

	Age group					
	<50	50–60	60–70	70–80	80–90	>90
Bleeding						
Intracranial	0.12 (0.04–0.21)	0.24 (0.18–0.30)	0.28 (0.25–0.30)	0.39 (0.37–0.42)	0.45 (0.42–0.48)	0.83 (0.67–1.00)
Gastrointestinal	0.12 (0.04–0.21)	0.34 (0.27–0.41)	0.43 (0.39–0.47)	0.70 (0.66–0.73)	0.93 (0.88–0.97)	1.20 (1.00–1.40)
Other	0.49 (0.32–0.66)	0.73 (0.63–0.83)	0.76 (0.71–0.81)	0.99 (0.95–1.03)	1.55 (1.49–1.61)	2.13 (1.86–2.39)
Thrombosis						
Stroke/TE/TIA	0.44 (0.22–0.66)	0.13 (0.11–0.15)	1.31 (1.22–1.39)	1.71 (1.64–1.77)	2.28 (2.19–2.36)	2.56 (2.23–2.90)
Venous thromboembolism	0.12 (0.04–0.21)	0.07 (0.04–0.1)	0.08 (0.07–0.10)	0.10 (0.09–0.11)	.12 (0.10–0.14)	-
Myocardial infarction	0.55 (0.30–0.79)	0.58 (0.46–0.70)	0.92 (0.85–0.99)	1.26 (1.21–1.32)	1.67 (1.60–1.74)	2.10 (1.80–2.39)

Sjögren et al, Efficacy and safety of well-managed warfarin, Thrombosis and Haemostasis 113.6/2015

Warfarin as prophylax for stroke in patients with atrial fibrillation

- *Globaly 3.000.000 stroke is associated to atrial fibrillation*
- *Oral anticoagulants reduces the risk for stroke and mortality*



Hart RG et al. *Ann Intern Med*. 2007;146:857-867

New Oral Anti-Coagulants NOAC
Non vitamin K Oral Anti-Coagulants NOAC
Direct Oral Anticoagulants DOAC

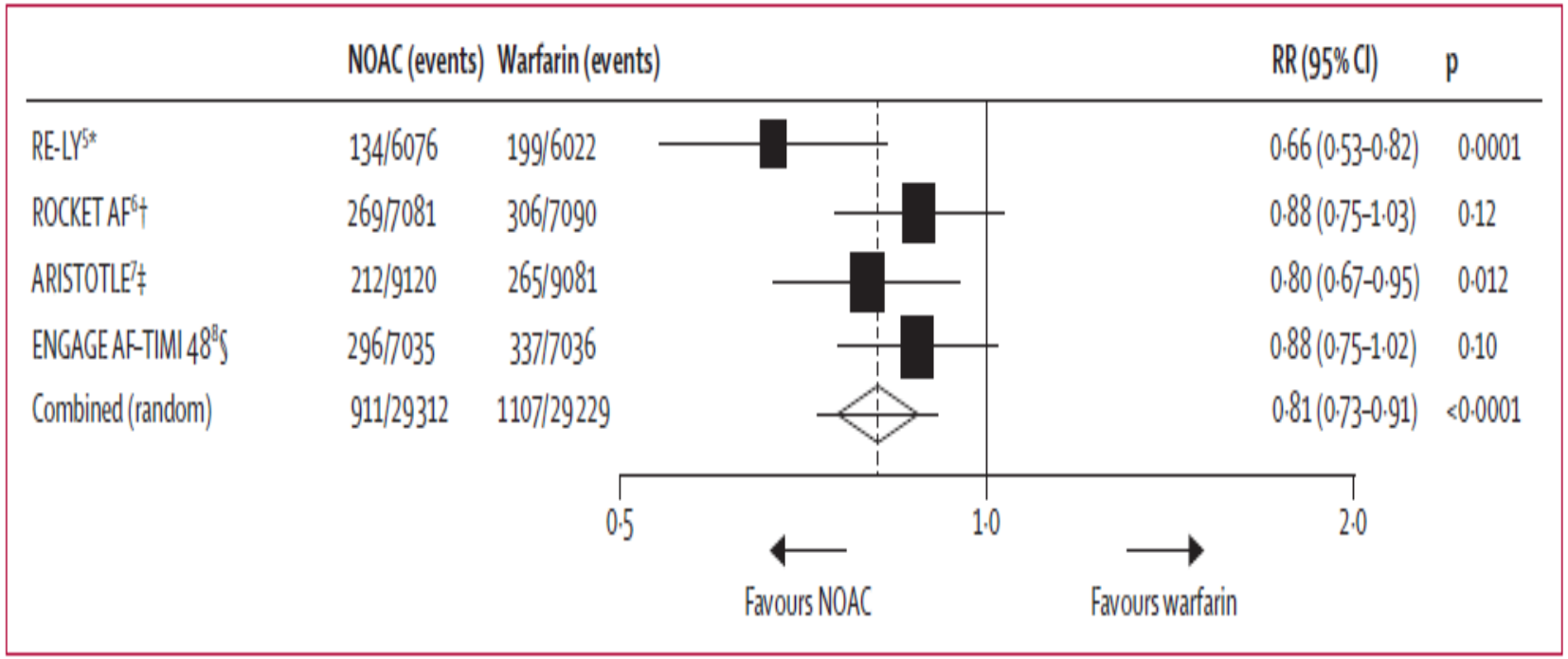
	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)	Warfarin (Waran)
Prodrug	yes	no	no	no	no
Factor Xa-inhibitor	no	yes	yes	yes	yes
Trombin inhibitor	yes	no	no	no	no
Bioavailability (%)	6	>80	>50	45	100
Time to peak (h)	2	3	3	1,5	120
T½ (h)	12-17	9	9-14	9-11	50
Interactions	Proton pump inhibitors P-glyco-protein	CYP3A4 P-glyco-protein	CYP3A4 P-glyco-protein	CYP3A4 P-glyco-protein	Long list
Renal excretion (%)	80	33	25	35	1
Antidot (specific)	yes	no	no	no	yes

Själander A och Svensson P , http://www.internetmedicin.se/dyn_main.asp?page=4356

Atrial Fibrillation

Stroke or systemic embolic events

NOACs 42.411 participants vs 29.272 participants received warfarin

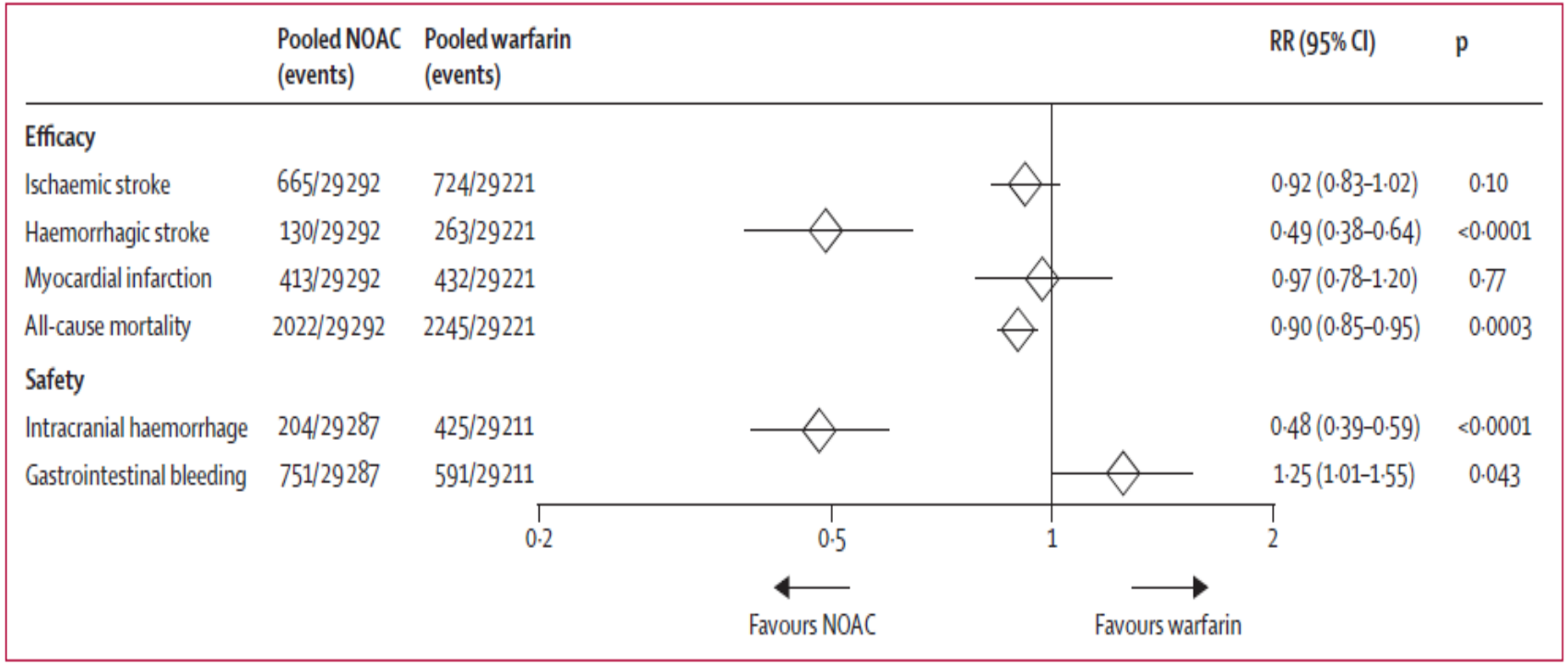


New oral anticoagulants significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0·81, 95% CI 0·73–0·91; p<0·0001), mainly driven by a reduction in haemorrhagic stroke (0·49, 0·38–0·64; p<0·0001).

No head to head randomized clinical studies between NOACs currently exist.

Lancet 2014; 383: 955-62

Atrial Fibrillation – Efficacy and Safety



New oral anticoagulants also significantly reduced all-cause mortality (0·90, 0·85–0·95; p=0·0003) and intracranial haemorrhage (0·48, 0·39–0·59; p<0·0001), but increased gastrointestinal bleeding (1·25, 1·01–1·55; p=0·04)
No head to head randomized clinical studies between NOACs currently exist.

Lancet 2014; 383: 955-62

THE NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

SHATTUCK LECTURE

Clinical Research to Clinical Practice — Lost in Translation?

Claude Lenfant, M.D.

Practice is science touched with emotion.

Confessio Medici
Stephen Paget, 1909

From the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md., and the Department of Health and Human Services, Washington, D.C. Address reprint requests to Dr. Lenfant at the National Heart, Lung, and Blood Institute, National Institutes of Health, 9000 Rockville Pike, Bldg. 31, Room 5A52, Bethesda, MD 20892.

N Engl J Med 2003;349:868-74.

DURING THE 20TH CENTURY, ENORMOUS PROGRESS WAS MADE IN IMproving the health and therefore the life span of all Americans. The average life expectancy at birth increased by nearly 30 years between 1900 and 2000. Although the largest gains were made in the early part of the century, we still managed to add another 1.5 years between 1990 and 2000.

Much of our continued success in extending life expectancy over the past several decades is almost certainly due to research supported by the National Institutes of Health (NIH) and generously funded by the American public. NIH-supported research has not only made possible the development of new and improved treatments for a wide range of human diseases; it has also provided the knowledge of disease risk factors needed to formulate effective approaches to prevent them. For example, research supported by the National Heart, Lung, and Blood Institute has identified important cardiovascular risk factors, has established the effectiveness of approaches to prevent or control them, and has assessed the effectiveness of treatment interventions for established disease.

As director of the National Heart, Lung, and Blood Institute, I am especially gratified to be able to point out that the lion's share of our recent gains in life expectancy in the United States has come from reductions in rates of death from heart disease and stroke. According to data provided by the National Center for Health Statistics, life expectancy increased by six years between 1970 and 2000, and nearly two thirds of that increase can be attributed to reductions in mortality due to cardiovascular disease (Fig. 1). And although primary prevention has played an important part in the reductions, it appears, at least for coronary heart disease, that secondary prevention and other treatments have had a significantly greater effect. According to one analysis of the decline in mortality due to coronary heart disease that occurred between 1980 and 1990, the reduction was due largely to secondary prevention and other improvements in treatment, with primary prevention accounting for only one quarter of the decline.[1]

Still, one might question whether we have enjoyed the maximal return on the more than $250 billion that this country has invested in the NIH since 1950. Consider that in 2000 the life expectancy at birth for men and women in the United States lagged behind that of 22 other countries, ranging from Japan to Israel and including Canada and most of western Europe. If we view the longevity of citizens in our sister nations as an indication of what is possible in the modern world, then we must question why our reality is falling short. Some may believe that the difference between life expectancy in the United States and that in other economically developed countries is largely a manifestation of societal differences. I, however, believe the answer is this: we in the United

NEJM 2003

Randomized clinical trials vs Real Life Studies:

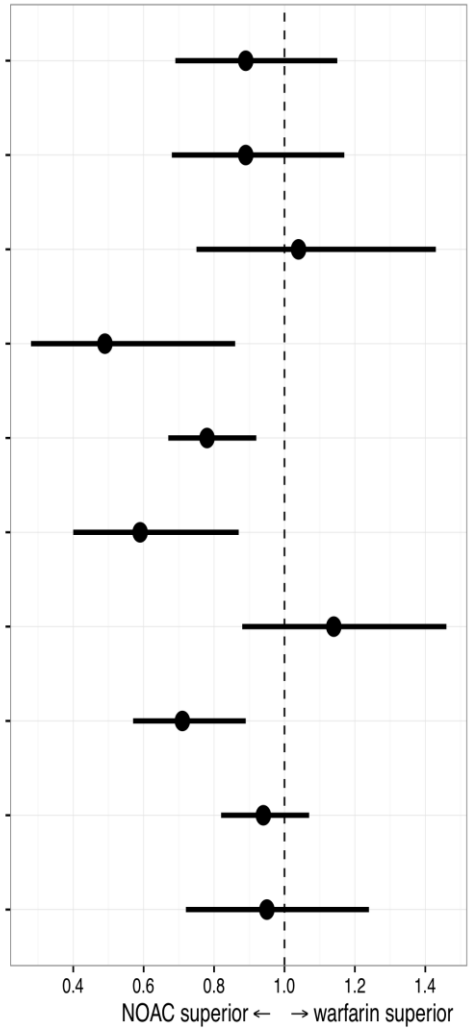
WHAT DOES REAL WORLD EVIDENCE OFFER IN COMPARISON TO CONVENTIONAL RANDOMISED CONTROLLED TRIALS?

RCTs		RWE
Prospective data collection		**Prospective and/or retrospective data collection**
Limited segment of the population is eligible for inclusion		**Broader and more representative of the patient population**
Good patient adherence and compliance		**Real world patient adherence and compliance**
Important for demonstrating efficacy and safety for drug licensing		**Demonstrates the benefits of a drug in everyday clinical practice**
Limited ability to investigate costs		**Ideal for showing value within local health economy**

Non-vitamin K Oral Anticoagulants are Non-inferior for Stroke Prevention but Cause Fewer Major Bleedings than Well-managed Warfarin With Time In Therapeutic Range 70% or Higher In Sweden

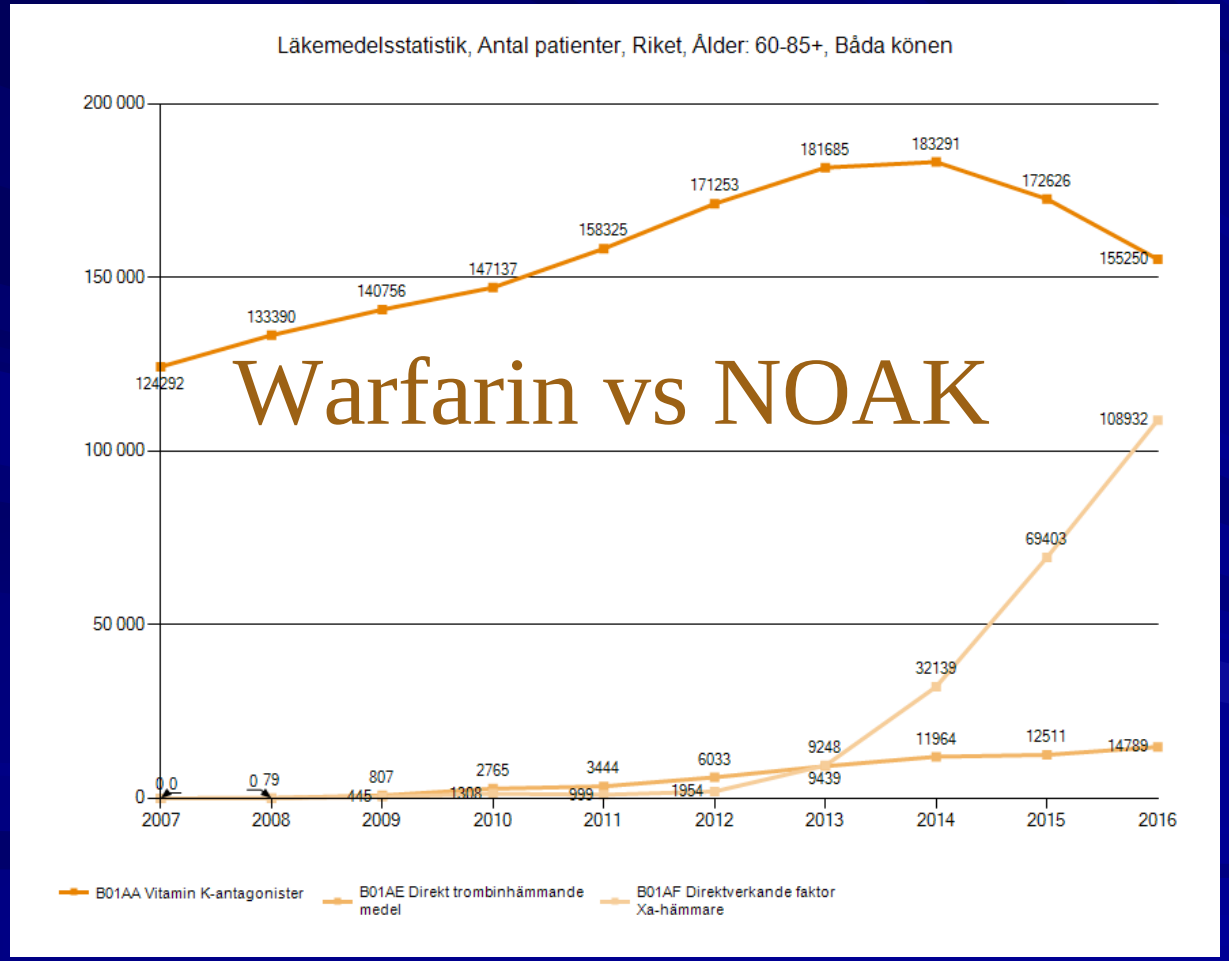
Vilhelm Sjögren, Björn Byström, Bo Norrving, Jonas Oldgren, Henrik Renlund, Peter J. Svensson, Anders Själander

Results



	Annual incidence NOACs	Annual incidence Warfarin	HR (95% CI)	p
All-cause stroke and systemic embolism	1.35	1.58	0.89 (0.69–1.15)	0.36
All-cause stroke	1.21	1.40	0.89 (0.68–1.17)	0.41
Ischemic stroke	1.04	1.03	1.04 (0.75–1.43)	0.83
Hemorrhagic stroke	0.16	0.35	0.49 (0.28–0.86)	*0.01*
Major bleeding	2.76	3.61	0.78 (0.67–0.92)	*0.003*
Intracranial bleeding	0.40	0.69	0.59 (0.40–0.87)	*0.008*
Gastrointestinal bleeding	1.26	1.14	1.14 (0.88–1.46)	0.32
Other bleeding	1.45	2.08	0.71 (0.57–0.89)	*0.003*
All-cause mortality	4.21	4.66	0.94 (0.82–1.07)	0.33
Myocardial infarction	1.25	1.45	0.95 (0.72–1.24)	0.68

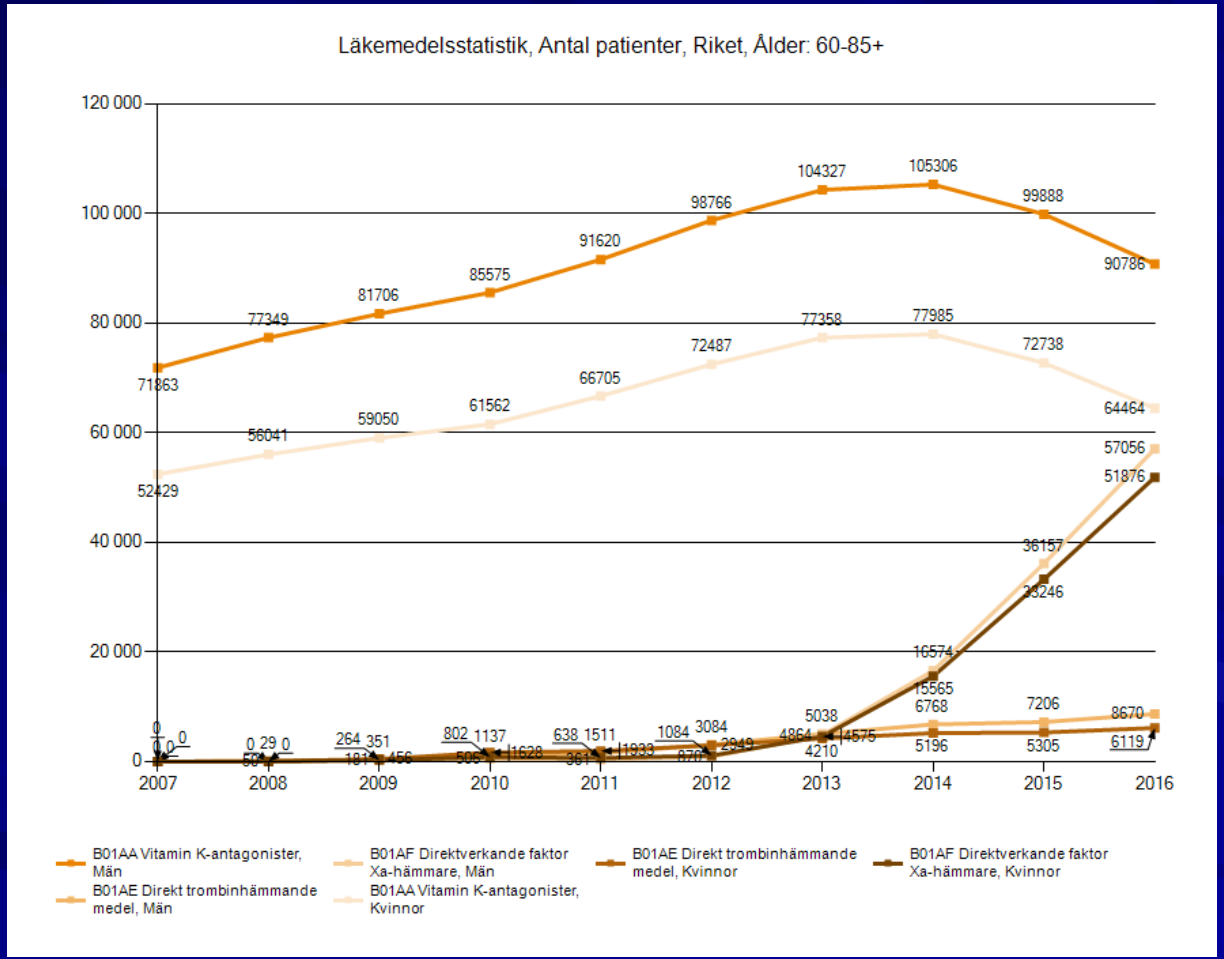
Warfarin vs NOAK



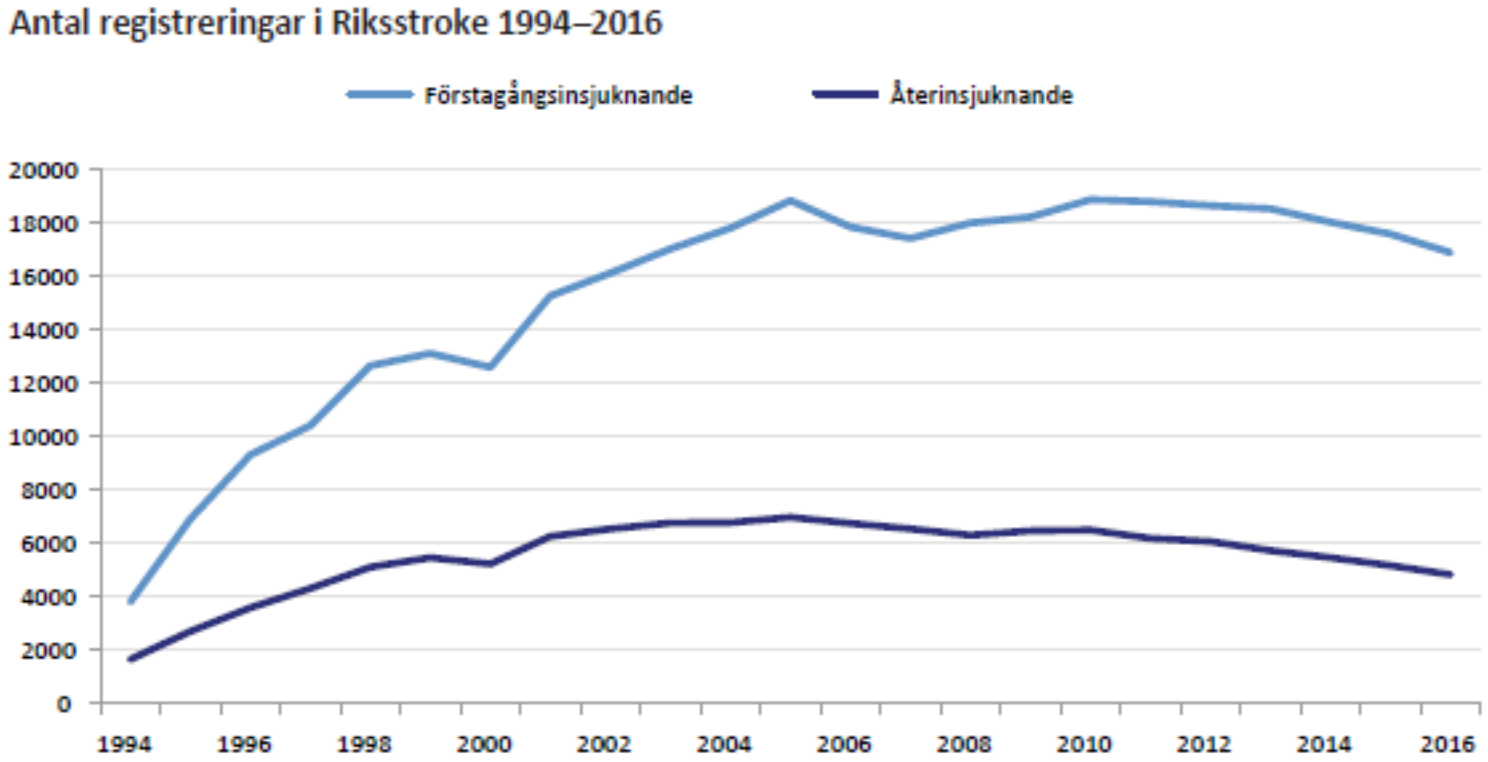
Warfarin vs NOAK

Socialstyrelsen november 2017

Warfarin vs NOAK och kön

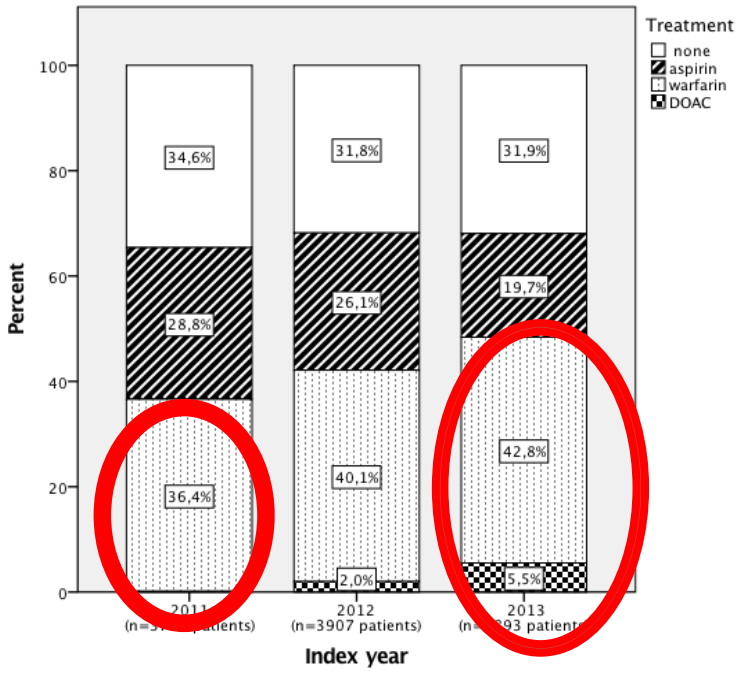


Socialstyrelsen november 2017



Figur 7. Figuren visar antalet registreringar i Riksstroke 1994–2016, uppdelad på förstagångs- och återinsjuknanden.

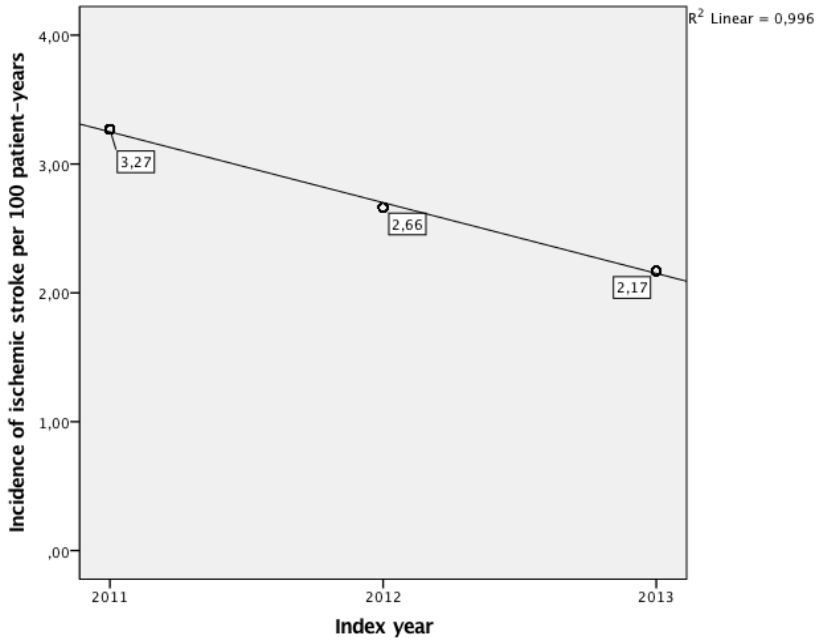
Oral anticoagulants in Skane 2011-2013



- OAC increases from 36% to 48%
- Aspirine have decline from 29% to 20%

Presented at Kardiovaskulära vårmötet 2017

Incidence of ischemic stroke 2011-2013 in Skane



Incidenc of ischemic stroke has decline from 3,27 to 2,17 case / 100 patient-year

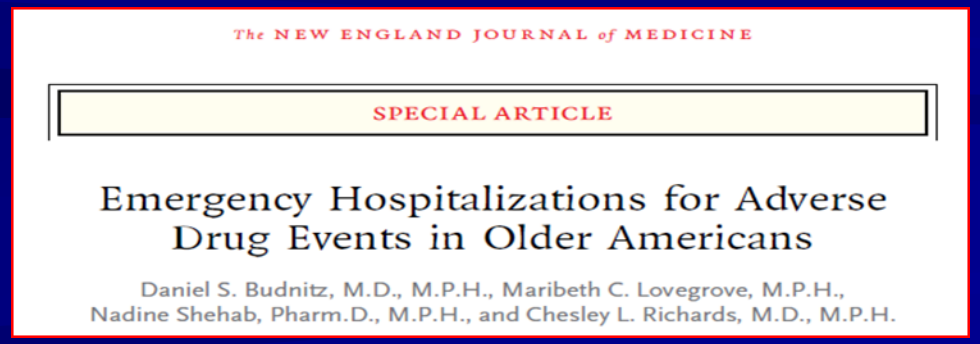
Presented at Kardiovaskulära vårmötet 2017

LUND UNIVERSITY

Emergency Hospitalization for Adverse Drug Events in Older Americans

- Annual National Estimate of Hospitalisation N=99.628
- Hematologic agents 42% (warfarin)
- Endocrin agents 23 % (insulin)
- Cardiovascular 10 % (oral anti platlets agents)

- Warfarin; GIH 41%, ICH 6,0%, Other 53%



NEJM 2011; 365; 2002

AK-beh och hospitalisering i NOAK-eran

JAMA | Original Investigation

US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014

Nadine Shehab, PharmD, MPH; Maribeth C. Lovegrove, MPH; Andrew I. Geller, MD; Kathleen O. Rose, BSN; Nina J. Weidle, PharmD; Daniel S. Budnitz, MD, MPH

Table 2. US Emergency Department (ED) Visits for Adverse Drug Events (ADEs) by Drug Class, 2013-2014[a]

Drug Class	ED Visits for ADEs		ED Visits for ADEs Resulting in Hospitalization[b]	
	No. of Cases	National Estimate, % (95% CI)[c]	No. of Cases Hospitalized	National Estimate, % Hospitalized (95% CI)[c]
Hematologic Agents				
Anticoagulants	7211	17.6 (14.1-21.0)	3691	48.8 (42.0-55.5)
Vitamin K antagonists (warfarin)	6179	15.1 (12.3-17.9)	3156	48.5 (41.8-55.1)
Factor Xa inhibitors	580	1.4 (0.9-2.0)	300	50.4 (43.0-57.8)
Unfractionated and low-molecular-weight heparins	450	0.8 (0.6-1.1)	224	46.5 (38.7-54.4)
Direct thrombin inhibitors (oral)	173	0.5 (0.2-0.7)	107	63.8 (49.8-77.8)
Antiplatelets	2656	6.6 (4.7-8.5)	1312	44.4 (35.7-53.2)
Platelet $P2Y_{12}$ receptor antagonists[d]	1837	4.6 (3.0-6.2)	942	47.8 (37.7-57.9)
Aspirin with or without dipyridamole	1545	3.6 (2.2-5.0)	753	41.2 (32.6-49.8)

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Årsrapport för biverkningar 2016

Enheten för läkemedelssäkerhet 2017-06-16

Tabell 2. De vanligast förekommande substanserna i allvarliga biverkningsrapporter från hälso- och sjukvården och de vanligaste biverkningarna i de rapporterna.

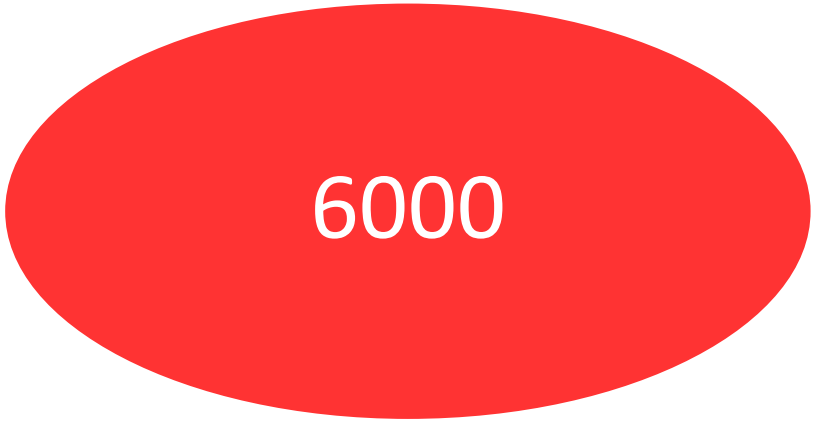
Läkemedelssubstans (ATC-kod)* Biverkningar (antal)**	Antal rapporter
warfarin (B01AA03)	162
förhöjt INR (45), cerebral blödning (34)	
apixaban (B01AF02)	143
läkemedel utan effekt (23), cerebral blödning (21)	
rivaroxaban (B01AF01)	139
cerebral blödning (16), näsblödning (16)	
paracetamol (N02BE01)	103
förgiftning (91), förhöjd koncentration (71), överdos (71)	
enalapril (C09AA02)	69
angioödem (36), akut njurskada (5)	
intrauterint preventivmedel med gestagen (G02BA03)	62
graviditet (31), ektopisk graviditet (21)	
infliximab (L04AB02)	48
anafylaktisk reaktion (5) överkänslighet (5)	
vaccin mot difteri, H. influenzae B, kikhosta, polio, stelkramp och hepatit B (J07CA09)	44
feber (10), muskelslapphet (5)	
vaccin mot influensavirus (J07BB02)	43
narkolepsi (19), kataplexi (10)	
rituximab (L01XC02)	43
agranulocytos (7) neutropeni (5)	

* Tabellen visar de mest rapporterade substanserna enligt ATC-kod. ** Tabellen visar de två vanligast förekommande biverkningarna och varje rapport kan innehålla flera biverkningsdiagnoser/symtom

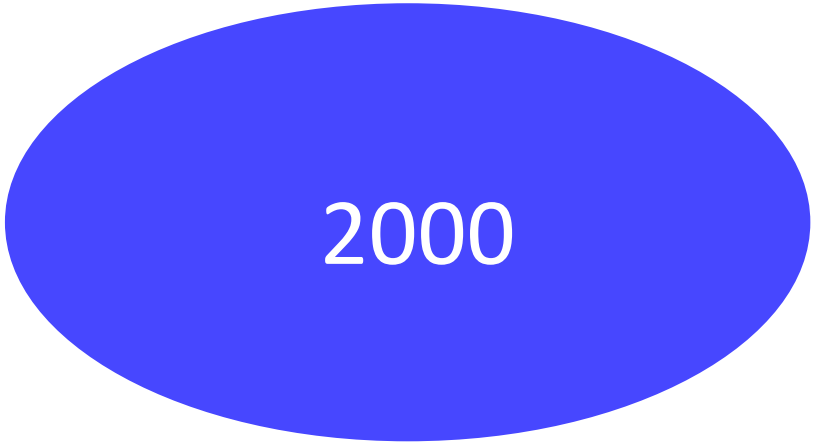
Läkemedelsverket 2017

Oral antikoagulation i Sverige, stroke, blödning och akut kirurgi

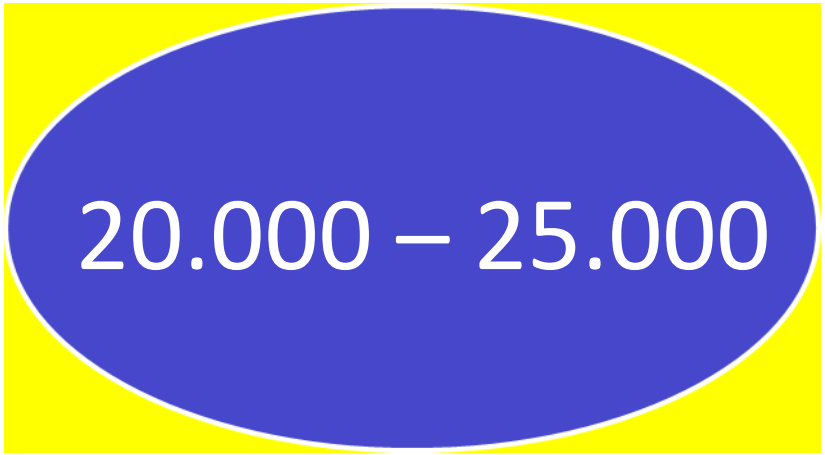
Kommer behöva akut kirurgi under AK-beh



Kommer blöda under AK-beh



Kommer få stroke trots AK-beh



Kommer ej att få trombos

Prevalens 3% = 300 000 patienter i Sverige med FF-diagnos. 70 % är AK-beh

Följsamhet till OAC

- The overall persistence with any OAC was 88.2% (CI 87.5-88.9) at 1 year and 82.9% (CI 81.8-83.9) at 2 years.

- Conclusion
- After 2 years, the persistence with any anticoagulant treatment was high in patients with non-valvular AF.

Forslund T et al. Eur J Clin Pharmacol2016 Mar;72(3):329-38

LUNDS UNIVERSITET

Antikoagulantiabehandling vid förmaksflimmer – behandlingsrekommendation

Huvudbudskap

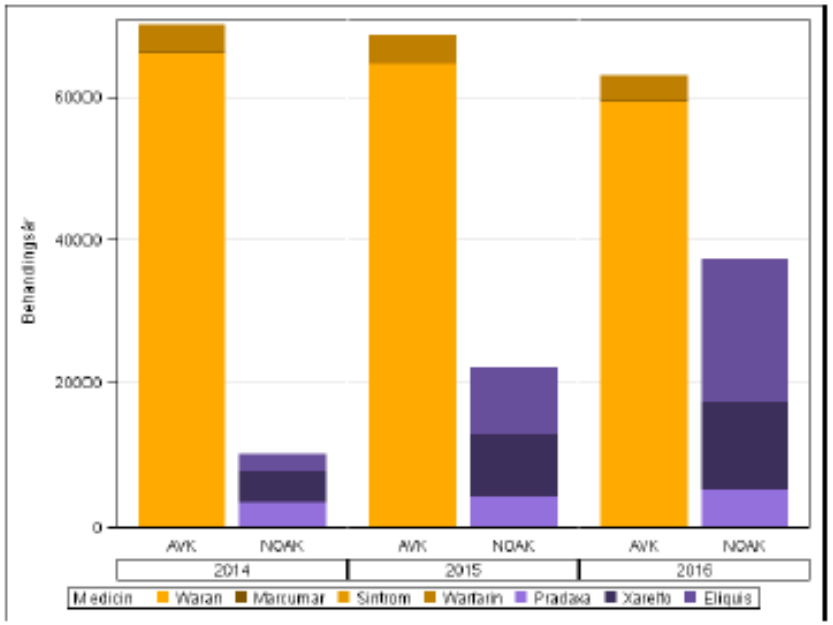
- Alla patienter med förmaksflimmer och förhöjd risk för ischemisk stroke bör få behandling med OAK (orala antikoagulantia), det vill säga NOAK (Non-vitamin K Orala AntiKoagulantia) eller warfarin. Riskvärdering med CHA_2DS_2-VASc syftar primärt till att identifiera patienter som har så låg risk för ischemisk stroke att behandling med antikoagulantia bör avstås, och beslutet ska omprövas vid regelbundna kliniska kontroller.
- Vid nyinsättning av orala antikoagulantia till patienter med förmaksflimmer rekommenderas NOAK före warfarin på grund av visad lägre dödlighet och minskad risk för allvarliga blödningar, inkluderande hjärnblödning. Undantag är patienter med mekanisk klaff, minst måttlig mitralisstenos eller allvarligt nedsatt njurfunktion, där endast warfarin ska användas.
- Trombocythämning ska inte användas som strokeskydd vid förmaksflimmer. Trombocythämmare ger ett avsevärt sämre skydd än orala antikoagulantia mot ischemisk stroke och har lika hög blödningsrisk.
- Under pågående eller planerad graviditet är NOAK och warfarin kontraindicerade eller ej rekommenderade. Under amning kan warfarin användas, medan NOAK är kontraindicerade.
- All oral antikoagulantiabehandling (NOAK och warfarin) kräver regelbunden klinisk uppföljning. Denna bör inkludera genomgång av allmän hälsosituation med bedömning av riskfaktorer för stroke och blödning, kontroll av blodtryck, blodstatus och uppskattad njurfunktion, samt genomgång av övrig medicinering med risk för interaktioner, patientens följsamhet till behandlingen, eventuella biverkningar och övriga sjukdomar.
- Vid allvarlig blödning eller inför invasiv åtgärd med hög blödningsrisk, där det inte finns tid att avvakta den avklingande effekten av OAK, kan den antikoagulerande effekten reverseras. För den direkta trombinhämmaren dabigatran finns specifik antidot, och för faktor Xa-hämmarna finns viss klinisk erfarenhet och viss dokumentation avseende reversering med protrombinkomplexkoncentrat. Warfarin reverseras i akuta fall med protrombinkomplexkoncentrat och K-vitamin intravenöst.
- Vid kortvarigt uppehåll av antikoagulation i samband med kirurgi/invasiva åtgärder hos patienter med NOAK eller warfarin som strokeprofylax vid förmaksflimmer, rekommenderas inte rutinmässig överbryggande behandling med lågmolekylärt heparin (LMH).
- Inför blodiga standardingrepp i munhålan (tandextraktioner, implantatoperationer, biopsier) bör NOAK eller warfarin i normalfallet inte sättas ut. Eventuell blödning ska istället åtgärdas med lokalt hemostatikum, suturering och tranexamsyra lokalt. Mer omfattande ingrepp bör handläggas av tandläkare med kunskap och rutiner för hanterande av eventuella blödningskomplikationer.
- Inför elektiv elkonvertering eller flimmerablation ska alla patienter förbehandlas minst tre veckor med ett OAK. Detta gäller även patienter utan riskfaktorer för ischemisk stroke. För patienter med riskfaktorer för ischemisk stroke ska behandling fortgå tills vidare, även efter omslag till sinusrytm. För patienter utan riskfaktorer för stroke ska behandling fortgå minst fyra veckor efter elkonvertering och två månader efter ablation.

Prognos

NOAK ökar warfarin minskar

- Med den ökningstakt som NOAK uppvisar kommer sannolikt inom några år NOAK att användas av mer än 85% av patienterna med rätt indikation för Orala Antikoagulantia

Auriculas årsrapport 2016



Figur 12: Behandlingsår per medicinop

Figuren visar att nya orala antikoagulantia ökar. Under 2016 motsvarar NOAK knappt 40% av alla behandlingsår.

NOAC från Dagens Medicin 2010

- **MÖJLIGHETER**
- Enklare
- Mindre interaktioner
- Livskvalité
- Fler patienter
- Mer alternativ
- Elkonvertering
- Mindre CNS blödning

- **PROBLEM**
- Följsamhet
- Njurar
- ”Real life”
- Antidot
- Ekonomi
- Uppföljning
- Mer GI blödning

Hur gick implementeringen av NOAK i Sverige Egna reflektioner

- Bra förarbete
- God information – men mycket mer behövs
- AK –mottagningen – behövs troligen i framtiden – form?
- Nya indikationer på väg in tex barn, profylax kirurgi-medicin, onkologi……..
- Önsketänkande Head to Head studie NOAK – skulle vara möjlig i Sverige!!!!!

AK mottagningen i framtiden!

- AK –mottagningen – behövs troligen i framtiden – form?
- Hur skall AK vården organiseras?
- Uppföljning av NOAK????
- Warfarin för vem och vem sköter det???
- Kunskap – jmf med tex iv heparin!!!!!

TACK