

The AHSN Network AF Community

Going Further and Faster to Prevent Strokes with AHSNs

Heart Rhythm Congress Symposium

12 October 2016

Developing a Genotype Guided dosing service in the North West Coast region

Dr Julia Reynolds, Innovation Agency

Why did we do it?

- Increases time in therapeutic range
- Potentially less clinic visits
- Interest in our region in point of care testing and genotype
- Algorithm in addition to the test
- *CYP2C9*2*, *CYP2C9*3* & *VKORC1*
- Examining **feasibility** of it in clinic



The NEW ENGLAND
JOURNAL of MEDICINE

HOME	ARTICLES & MULTIMEDIA ▾	ISSUES ▾	SPECIALTIES & TOPICS ▾	FOR AUTHORS ▾	CME ▸
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ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin

Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian B. Leathart, M.Phil., Hugo Kohnke, M.Sc., Anke H. Maitland-van der Zee, Pharm.D., Ph.D., Paula R. Williamson, Ph.D., Ann K. Daly, Ph.D., Peter Avery, Ph.D., Farhad Kamali, Ph.D., and Mia Wadelius, M.D., Ph.D., for the EU-PACT Group*

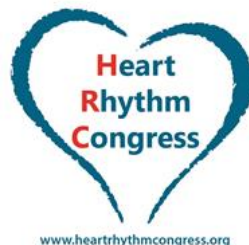
N Engl J Med 2013; 369:2294-2303 | December 12, 2013 | DOI: 10.1056/NEJMoa1311386



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How did we do it?

- Started the project in September 2014
- Challenges with the equipment (Oct-March 2015). Extensive testing, adjustment of software etc.
- Negotiation of Trust governance
- Funding – CLAHRC & AHSN
- Discussion with clinical teams challenged for space/time/training
- Implementation study collecting data which would not otherwise be collected
- Information governance
- Sample storage, tissue transfer agreements etc.
- QA
- Not a research project!!
- Timings – test takes 50 minutes.



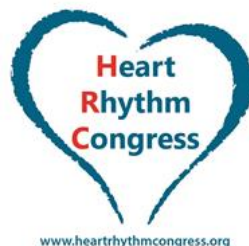
Nurses Janet and Claire with patient Paul



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Things to consider

- Do we need more research?
- Issues with non-white European populations
- Time for tests and clinic space
- More patients taking DOACs
- Consent to store samples/tissue
- Over 50 patients have taken it up
- Aim for 300
- Comparative arm
- Recruitment and new care models mean it is not feasible in some areas



Successes on the road to reducing strokes.

How Academic Health Science Networks collaborate with partner organisations to reduce AF related Strokes

The Greater Manchester Data Landscape Tool

Andy Ortowski, Greater Manchester AHSN

Greater Manchester AHSN



14
Commissioners

500
GP
Practices

12
Local
Authorities

4
Universities



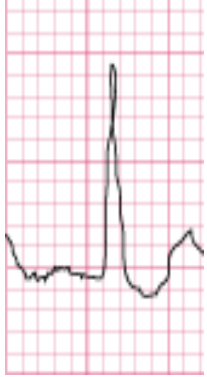
1 Ambulance Service

16
Provider
Organisations



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Stroke prevention in AF – A pathway of missed opportunities



NICE National Institute for
Health and Care Excellence

- Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and estimates suggest its prevalence is increasing
- If left untreated, AF increases the risk of stroke five-fold
- AF-related strokes are often more severe with higher morbidity and mortality, but are also preventable with effective management
- Public Health England (PHE) estimate the average cost/stroke at £24,000
- Societal costs of stroke in the UK are estimated at £8bn/year
- NICE Guidelines identified that over 50% of patients with known AF were not on effective medication
- Better management of AF-related stroke could save the NHS £95 million a year

Engage...



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NICE CG180 (2014) – Improving stroke prevention in AF

- NICE CG180 guidelines provide key markers of care and quality recommendations:
 - *Offer anticoagulation to people with a CHA_2DS_2 -VASc score of 2 or above, taking bleeding risk into account*
 - *Consider anticoagulation for men with a CHA_2DS_2 -VASc of 1*
 - *Calculate time in therapeutic range (TTR) at each visit*
 - *Do not offer aspirin monotherapy*

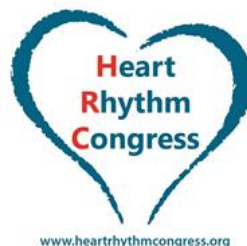
NICE National Institute for
Health and Care Excellence

Atrial fibrillation: management

Clinical guideline

Published: 18 June 2014

[nice.org.uk/guidance/cg180](https://www.nice.org.uk/guidance/cg180)

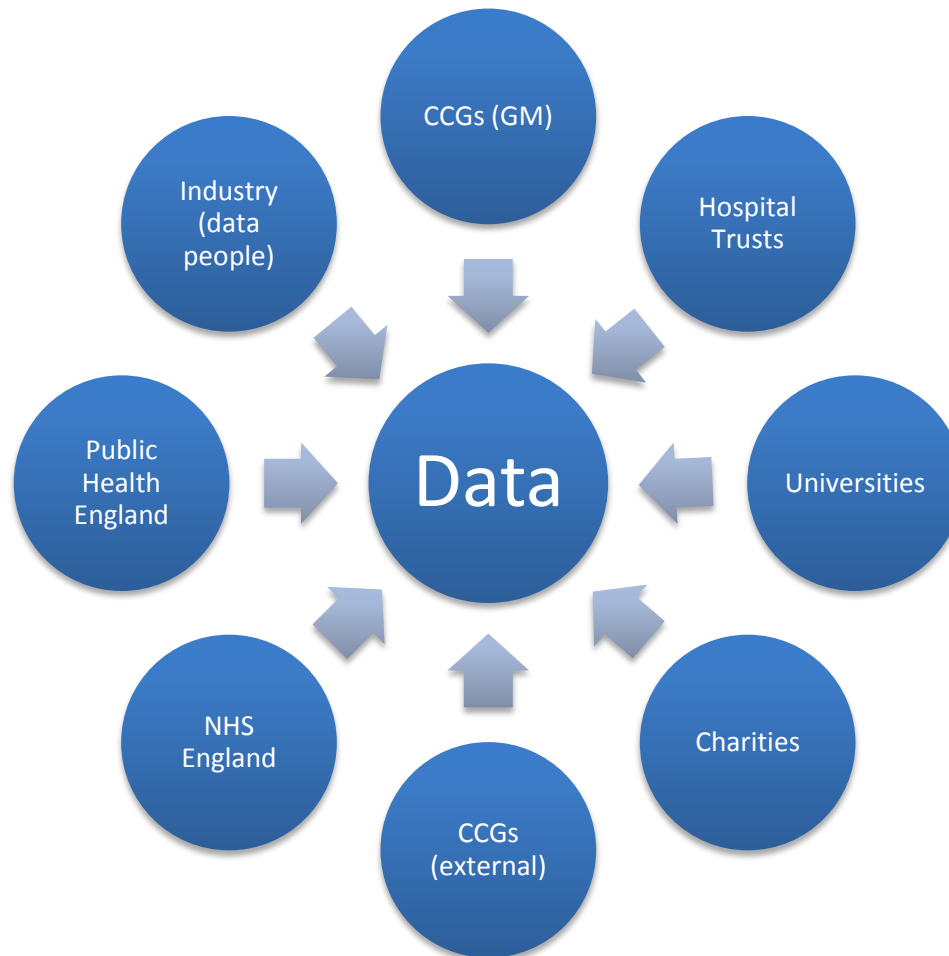


The same but different...



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Collaboration



CG180 and what the public data sets can show you

CG180 Guidance

Progression to stroke

Review stroke risk when patients reach 65 years old

Review stroke and bleeding risks annually

HES
SSNAP
GRASP-AF

1.1 Diagnosis and assessment

Men are more commonly affected than women; increasing prevalence with age

Most common arrhythmia in people ≥ 75 years; 15% prevalence

NCVIN
QOF

1.4 Assessment of stroke and bleeding risks

Use CHA₂DS₂-VASc stroke risk score

Use the HAS-BLED to assess risk of bleeding

NCVIN
QOF

1.5 Interventions to prevent stroke

Consider OAC for men with a CHA₂DS₂-VASc of 1

Offer OAC to people with a CHA₂DS₂-VASc of >2

SSNAP
QOF AF004/5
GRASP-AF

1.5.1 Assessing anticoagulation control with VKA

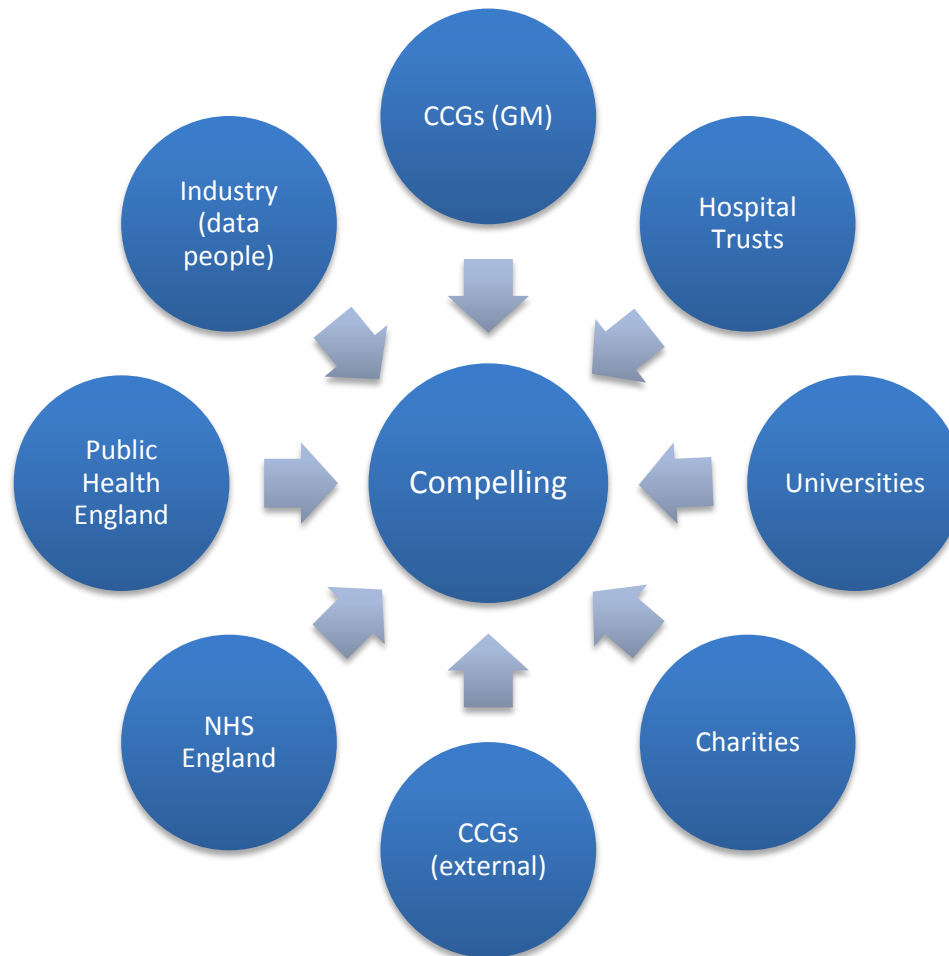
Calculate TTR at each visit
Take into account factors that may contribute to poor control
Consider combination therapy

TTR

Key Datasets



Collaboration



Stroke & Atrial Fibrillation

INSIGHTS

The Greater Manchester Academic Health Science Network (GM AHSN) consists of membership organisations such as CCGs, provider trusts and universities as well as partners in research, technology and industry. By spreading learning, leadership and innovation we will deliver significant improvement to the health of the population, engineer real opportunities for wealth creation and build new relationships with the industry.

Under our 5-year license from the Treasury, the National Commissioning Board requires us to systematically implement and measure best practice in NICE guidance and the six High Impact Innovations described in Innovation Health and Wealth.

In our suite of CVD work, we are prioritising the adoption of NICE guideline CG180 The management of Atrial Fibrillation (AF). The following information will support our members understanding of the challenges in this pathway and the opportunities to prevent AF related stroke.



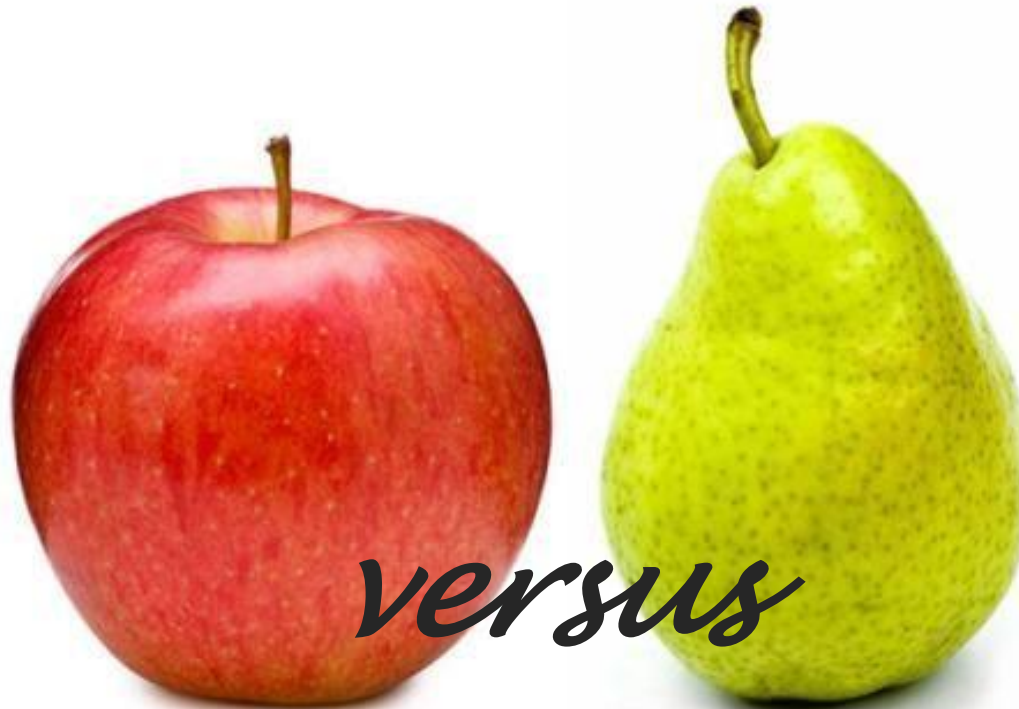
How do you benchmark with fair comparisons?

HES

SSNAP

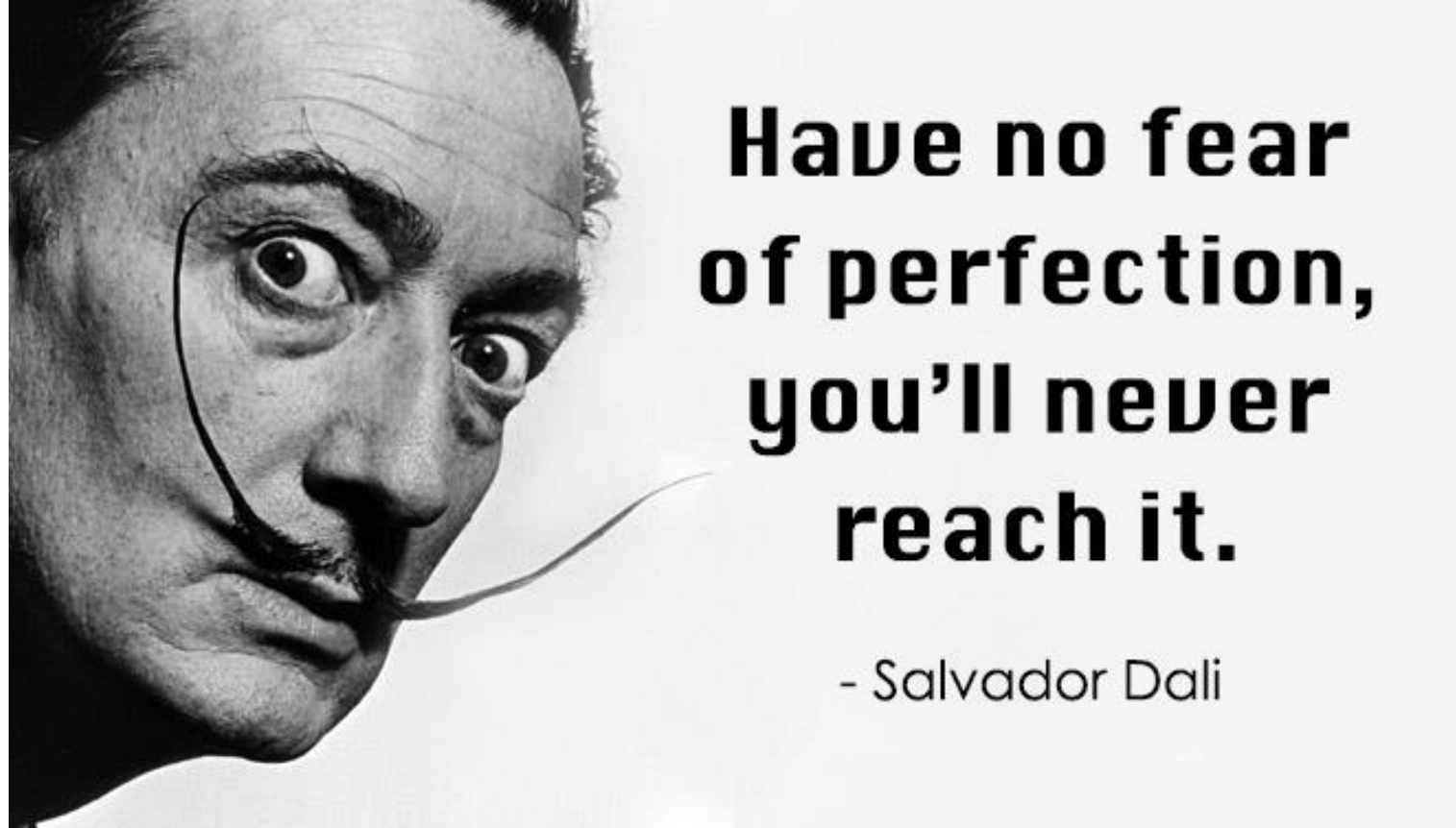
QOF

GRASP-AF



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We continue to collaborate...



Any Questions?



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*The***AHSN***Network*

Collaborating for the Future

Sarah White, Stephen Ray
West of England Academic Health Science Network

Let's Talk DWAC



Phase 1 – The Pilot

Aim: To Optimise
Anticoagulation for AF
patients

Evaluation of results

The Beginnings of Collaboration

- Clear evidence base – NICE CG180
- Engaged early with industry partners
 - Boehringer Ingelheim
 - Pfizer
 - Bayer
 - Daiichi Sankyo



Financial Collaboration



- Medical and Educational Grants and Services
 - BI
 - Bayer
- Supported various outputs; meetings, resources, training events
- DWAC is starting to take shape...

Scaling up the Collaboration

Phase 1 is a success;

Engaging Other Stakeholders
CCG

Development of resources with patients

Plan training - Pharmacists/GP's

ICS and data requirements

Communications strategy

Relationship management

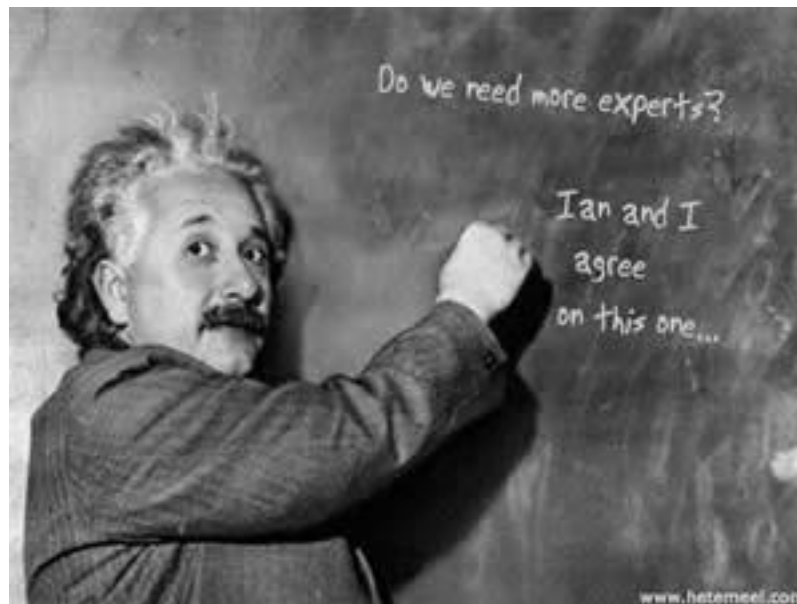


New Year 2015

- Joint Working Agreement agreed for Phase 1
- Seconded team members
- To be based in our office
- Work alongside the QI team
- QI capacity increased



We're going to need a
bigger team...



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Phase 2 – The changing face of Collaboration

- Emergent team processes
- Culture clash
- Steep learning curve
- Quality Improvement Support Team
- New team member



How did it work out?

- Seconded for nearly two years
- Fully embedded team members
- Capacity to roll DWAC out at scale realised
- QI learning in situ
- 52 GP practices in Glos have received face to face support
- Partnership between AHSN and Bayer strengthened
- Skills shared
- Worked closely with other partners



Hello, We're

AWESOME

How can we help you?



What did we gain from Collaboration?

- People who were invested in the project
- Different 'voices'
- A flexible, mobile team
- Capacity to support GP practices
- QI learning and experience
- Lessons learnt first hand
- Success in Phase 2
- Team work
- Support
- Access to expertise
- Nominated for PF Award



What about Bayer...?

Catalyst for partnership working approach and support credibility as a trusted partner

Increase in the focus from medical and legal departments to support the Bayer approach

Other AHSNs and CCGs wanting to work with Bayer on iterations of DWAC

Other departments within Bayer looking to do more JW with hospital trusts/networks/CCGs in the therapy areas of ophthalmology and cancer

A greater understanding of the issues faced by the NHS and how we can help

The building of trust and the increase of the enjoyment which goes with this type of Joint Working



And the future? Collaborate to Innovate

WEAHSN evaluating the impact of QIST

“It was unobtrusive and useful”

“I was skeptical at the start but enjoyed the project and found QIST very supportive and helpful”

“Keep the good work up”

“QIST support was invaluable”



Realist Evaluation

There is a need for leadership and overall management of the project to achieve the programme theory. Within this project the leadership and management of the overall project and its completion was largely contributed to the role taken by the AHSN QI team, and the provision of management resources to support

University of the West of England, Realist Evaluation of DWAC Phase 2



Future WEAHSN Collaborations

Joint Working Model good example of how collaboration can work

Working with Pfizer around STP's Emergent projects – Escape Pain, Heart Failure, Diabetes – industry involvement

Enterprise and Translation team collaborating with social enterprise groups and industry partners





Detecting AF

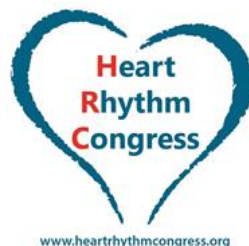
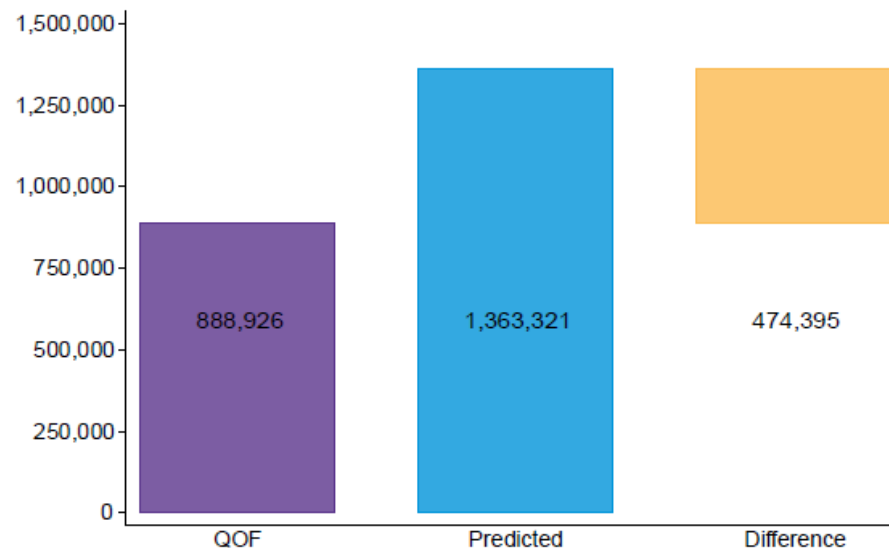
Sadia Khan, AHSN / HRC 2016

There are 1.4 million people with AF in the UK

Detection of AF in England

Source: QOF 2013/14; NCVIN 2015

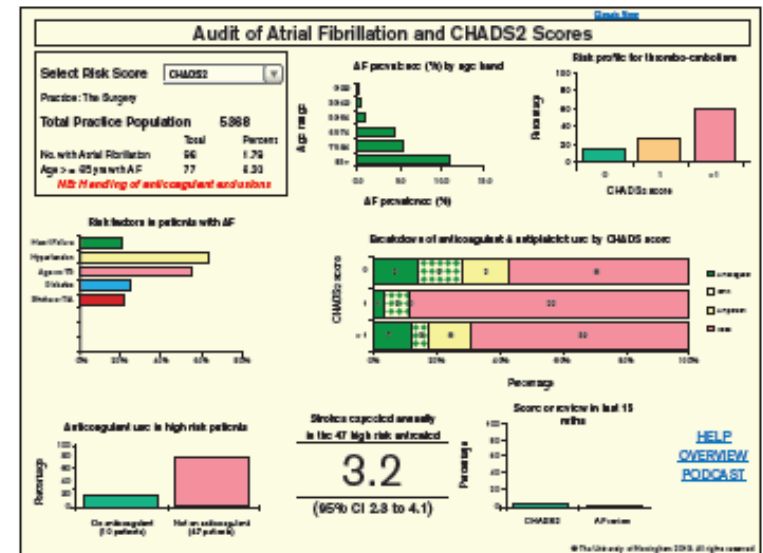
1.4 million people in England are estimated to have atrial fibrillation (AF) (2.4% of the adult population).



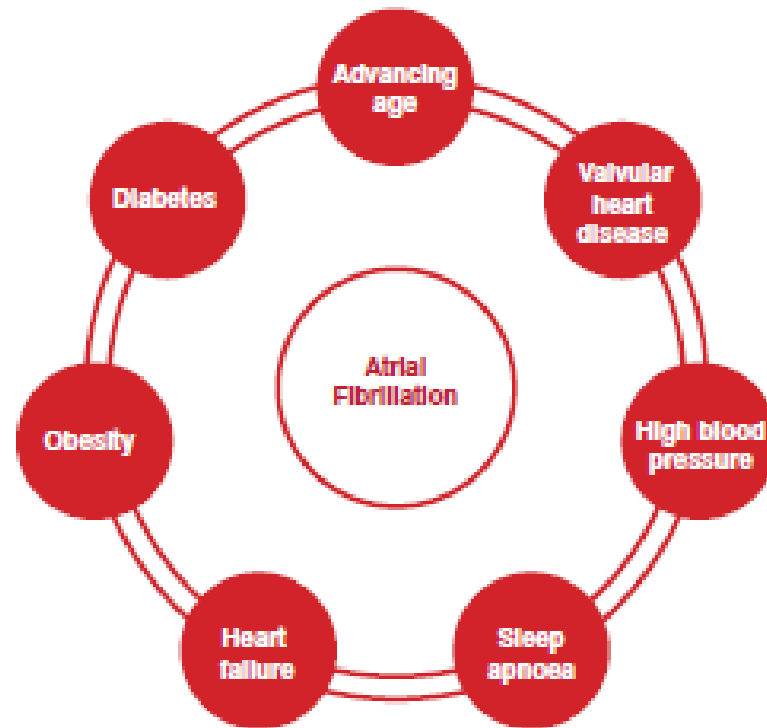
Source : Stroke Association

The 'missing'

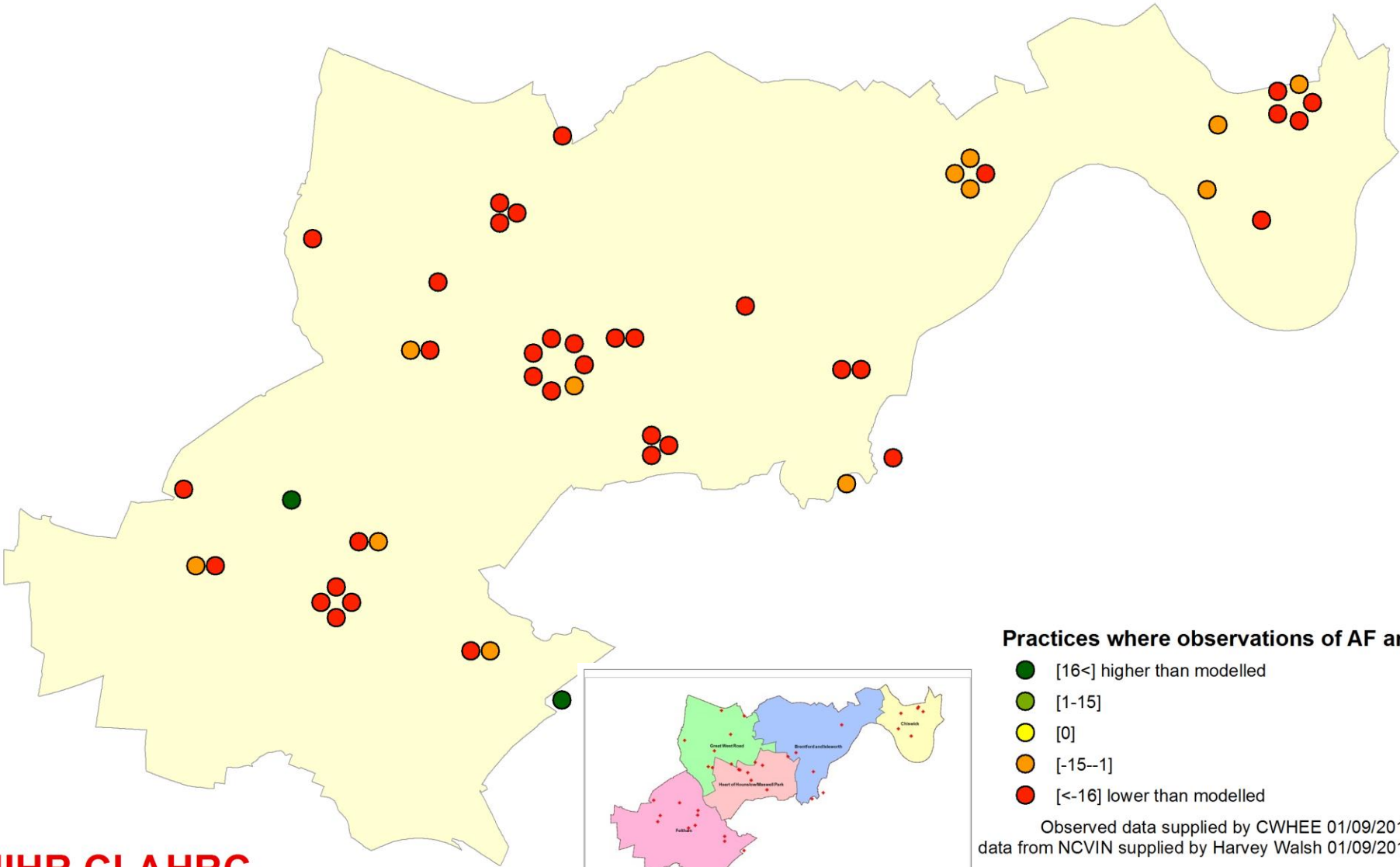
- May not really be missing
 - Clinical coding
 - Transfer of information between settings / systems



The 'missing'



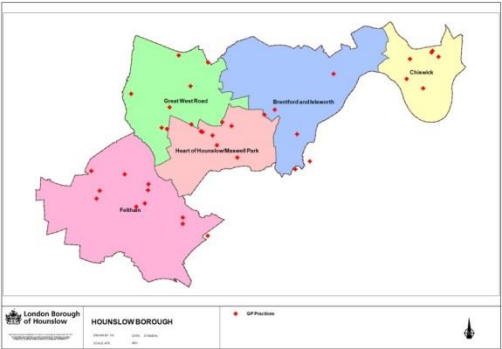
Modelled AF in Hounslow Practices



Practices where observations of AF are

- [16<] higher than modelled
- [1-15]
- [0]
- [-15--1]
- [<-16] lower than modelled

Observed data supplied by CWHEE 01/09/2016
data from NCVIN supplied by Harvey Walsh 01/09/2016



FACT: 1 in 4 of us will develop atrial fibrillation,
a leading cause of stroke.

a simple

pulse check

can save your life.

Know Your Pulse in four steps

- 1** To assess your resting pulse rate in your wrist, sit down for 5 minutes (relax). Remember that any stimulus taken before the reading will affect the rate (such as caffeine or nicotine). You will need a watch or clock with a second hand.
- 2** Take off your watch and hold your left or right hand out with your palm facing up and your elbow slightly bent.
- 3** With your other hand, place your index and middle fingers on your wrist, at the base of your thumb. Your fingers should sit between the bones on the edge of your wrist (and the string/band attached to your thumb (as shown in the image). You may need to move your fingers around a little to find the pulse. Breathe firm pressure on your wrist with your fingers in order to feel your pulse.
- 4** Count for 30 seconds, and multiply by 2 to get your heart rate in beats per minute. If your heart rhythm is irregular, you should count for 1 minute and do not multiply.

Record your pulse here

Day	Rate	Activity
1		
2		
3		
4		
5		
6		
7		

Sensitivity 87 %, specificity 81% - SAFE study 2005

<http://www.youtube.com/embed/ZvkIMdF7M20?rel=0>



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Cameroon's Cardiopad inventor wins African engineering award

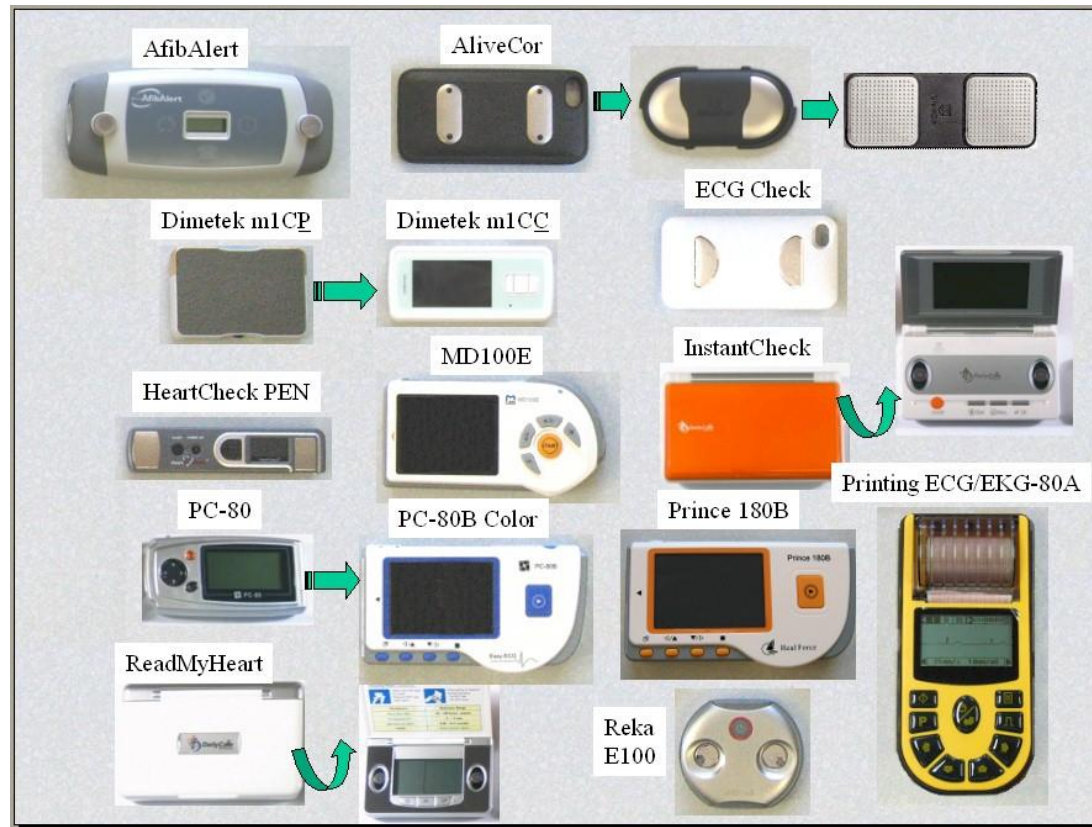
Question . How many cardiologists are there in Cameroon?
Clue- 20 million population



BBC news May 2016



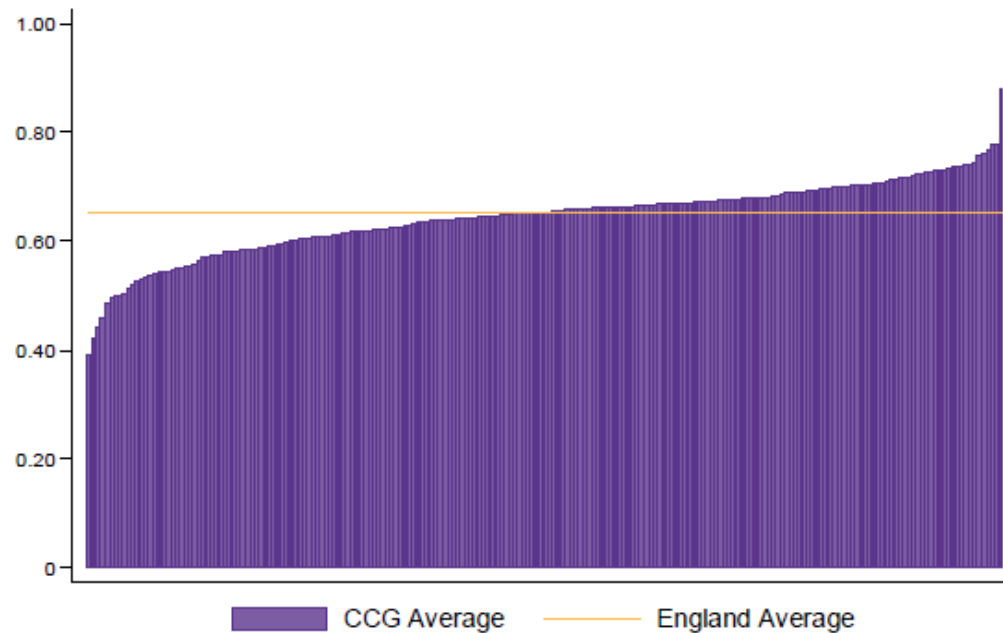
Technology to the rescue?



Undiagnosed AF in England

Source: QOF 2013/14; NCVIN 2015

There is significant variation between practices in the proportion of their patients with AF who remain undiagnosed.



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NIHR CLAHRC
Northwest London

NHS
Hounslow
Clinical Commissioning Group

Thank you for listening

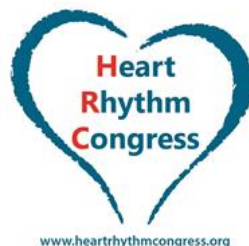


Outreach services and Virtual Clinics

Helen Williams, Consultant Cardiovascular Pharmacist
Sharron Gordon, Pharmacist Consultant Specialist
Anticoagulation

Declarations of Interest (Sharron)

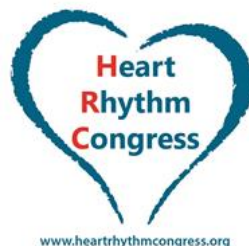
- Managing director of Sharron Gordon Ltd
- Consultancy for DS, BMS-Pfizer, Bayer
- Presentations for BI, Bayer, BMS-Pfizer.
- Sponsored for conferences from DS & Bayer.
- Educational grants from DS & Bayer to develop support for patient care.



Wessex AF programme

All activity to reduce AF related stroke aims to deliver improvements in Detection, Protection (anticoagulation) and Perfection (counselling and long term adherence). We are working on;

- CCG level data
- An NMS referral card project
- A video counselling tool.
- Education and training.
- Supporting an advisory network.
- Using devices to increase identification.
- Supporting the development of outreach clinics.



Outreach Clinics

Objective: To support audit of the practice using PRIMIS tools (GRASP AF and Warfarin patient safety tool (WPST). To support practitioner learning. To review patients and ensure follow up by community pharmacists to support safety and adherence.

<http://wessexahsn.org.uk/projects/110/optimising-anticoagulation-in-atrial-fibrillation>





Plenary Discussion

Struggle and Stumble, the difficult path to adopting innovation

Personalisation of anticoagulation using Genomics

Sir John Burn MD

FRCP FRCPE FRCPCH FRCOG FMedSci

Professor of Clinical Genetics, Newcastle University

Hon Consultant, Newcastle Hospitals NHS FT

Non-Executive Director NHS England

Chair QuantuMDx group Ltd



Personalisation of anticoagulation using Genomics

Heart Rhythm Congress
Birmingham

Sir John Burn MD

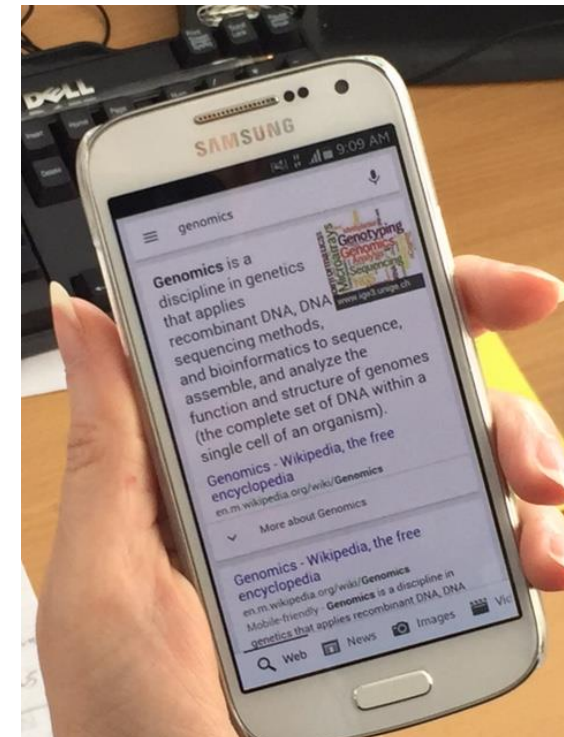
FRCP FRCPE FRCPCH FRCOG FMedSci

Professor of Clinical Genetics, Newcastle University

Hon Consultant, Newcastle Hospitals NHS FT

Non-Executive Director NHS England

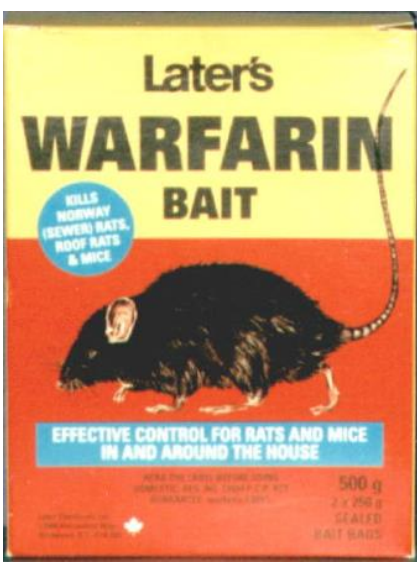
Chair QuantuMDx group Ltd



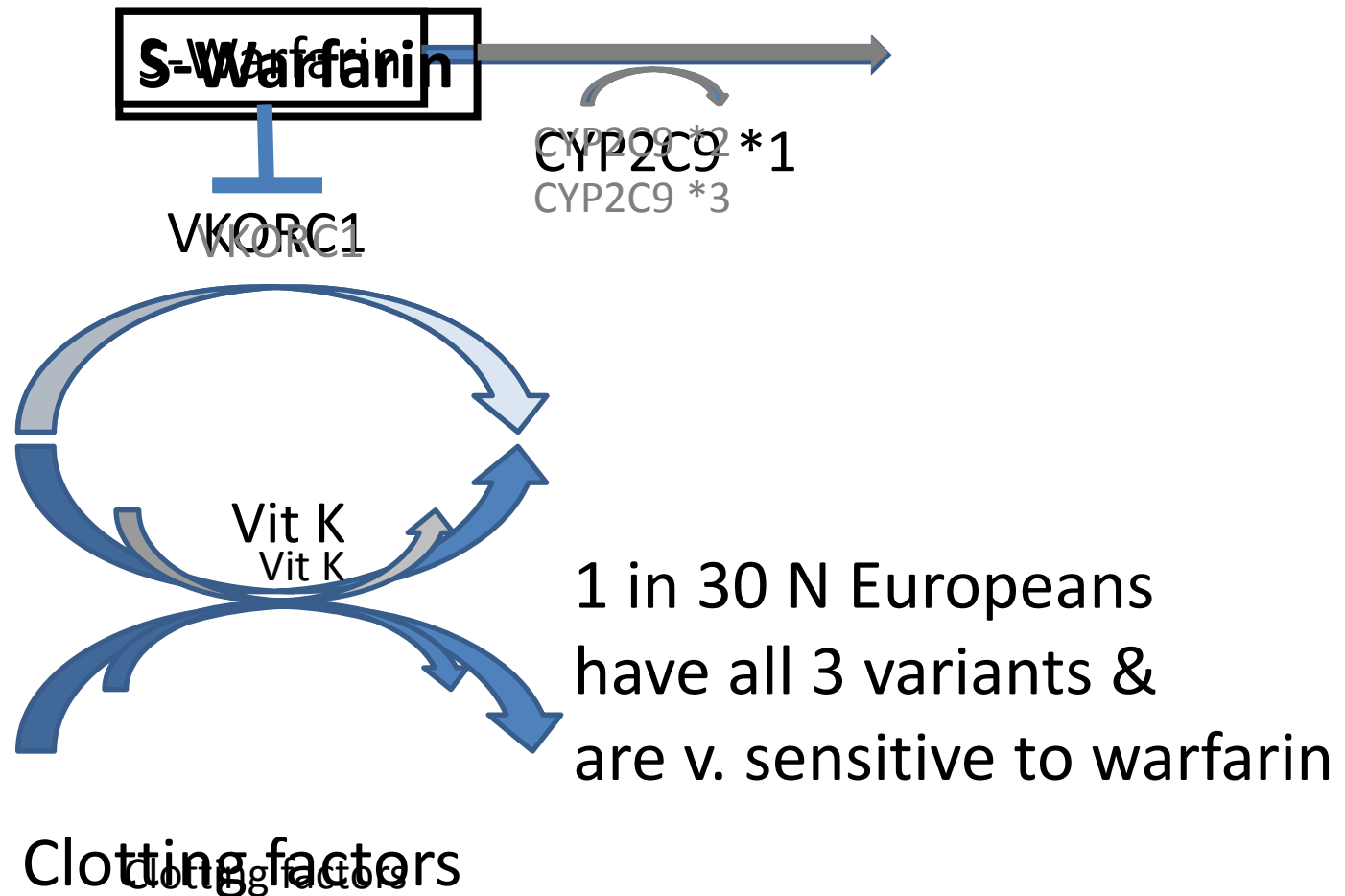


DOACs

**Personalised
Warfarin use**



Why people vary in their response to warfarin

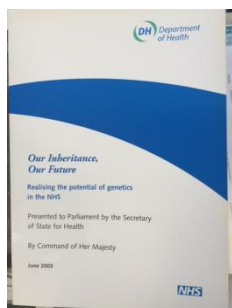


[Aithal GP¹](#), [Day CP](#), [Kesteven PJ](#), [Daly AK](#)

Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. [Lancet](#). 1999 Feb 27;353(9154):717-9.

The odds ratio for individuals with a low warfarin dose requirement having one or more CYP2C9 variant alleles compared with the normal population was 6.21 (95% CI 2.48-15.6).

Patients in the low-dose group were more likely to have difficulties at the time of induction of warfarin therapy (5.97 [2.26-15.82]) and have increased risk of major bleeding complications (rate ratio 3.68 [1.43-9.50]) when compared with randomly selected clinic controls.



Our Inheritance, Our Future

Realising the potential of genetics in the NHS

White Paper presented to Parliament June 2003

A Patient now

Mary, 58, AF, GP prescribes warfarin, misses apts., collapse, severe internal bleeding, lucky to survive...

“In the future

.....Mary is one of the 4-5% who metabolise warfarin slowly.....Mary's GP does a quick pharmacogenetic test using special equipment in the surgery.....starts on lower, safer dose of warfarin... suited to personal genetic makeup”

Born April 2014

QuantuMDx disposable
gene test

*lyse, extract, amplify and
analyse in under 20
minutes*

DNA
extraction

Nanowire
chip

Detector

PCR Chip

PCR

QuantuMDx



Genotype guided warfarin dosing in NHS



Harsh Sheth Farhad Kamali Ann Daly Liz Kendrick John Hanley

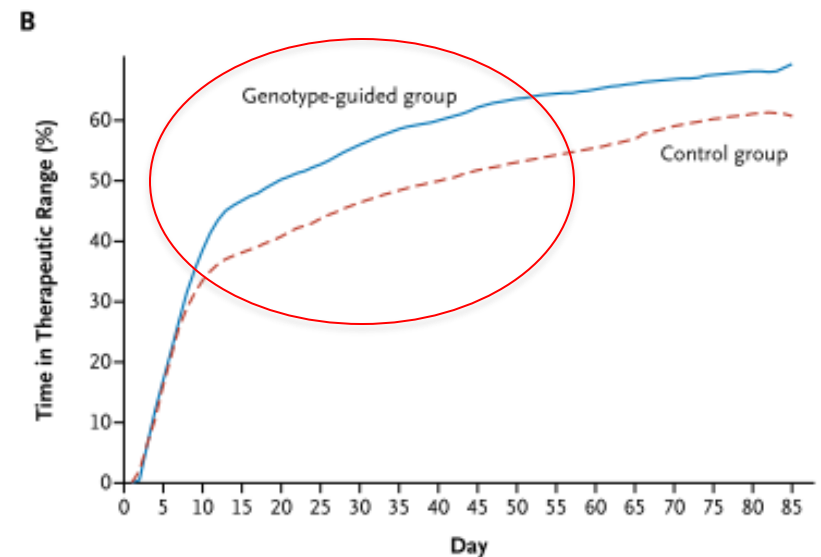
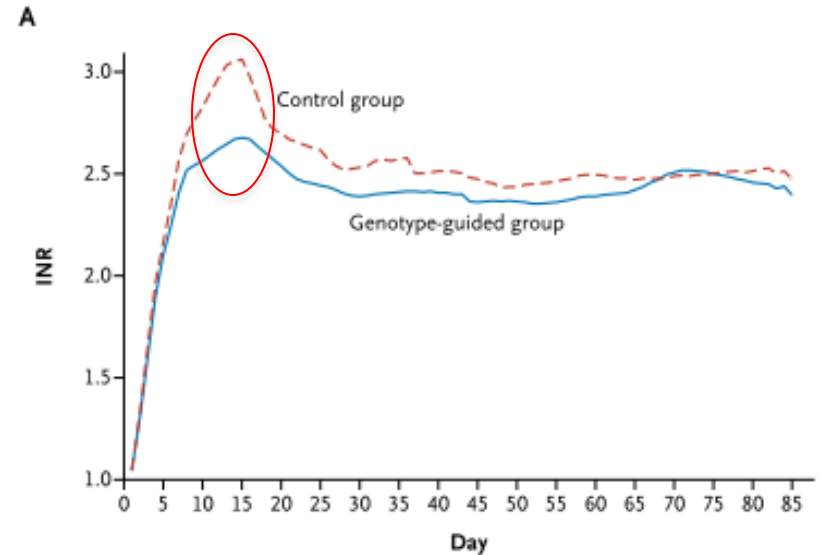
In a multi centre trial involving Newcastle, genotype guided dosing resulted in participants reaching the therapeutic window earlier and with fewer episodes of over dosing

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin

Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian B. Leathart, M.Phil., Hugo Kohnke, M.Sc., Anke H. Maitland-van der Zee, Pharm.D., Ph.D., Paula R. Williamson, Ph.D., Ann K. Daly, Ph.D., Peter Avery, Ph.D., Farhad Kamali, Ph.D., and Mia Wadelius, M.D., Ph.D., for the EU-PACT Group*

Pirmohamed M et al, New England Journal of Medicine 2013



ParaDNA for rapid diagnostics

One sample, up to 16 different genetic analyses, results under one hour (sample, seal and test)



Field Intelligence Unit
(onboard computer and
batteries – 4
independent samples)



Screening Unit
(laptop controlled and
mains powered- 4
independent samples)



One independent
amplification head (SHUbox:
laptop controlled and mains
powered)

NICE guidelines (2014)

Guidelines for warfarin:

Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:

- 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months
- 2 INR values less than 1.5 within the past 6 months
- TTR less than 65%. [new 2014]

Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences. [new 2014]

Missed mentioning the 2013 EU-PACT study which showed superior anti-coagulation control with genotyping.



BMJ 2016;354:i5187 doi: 10.1136/bmj.i5187 (Published 28 September 2016)

Page 1 of 2



click for updates

EDITORIALS

Novel oral anticoagulants for atrial fibrillation

Patients must live with uncertainty until we have independent scrutiny of key trial data

Kamal R Mahtani *deputy director*, Carl Heneghan *director*

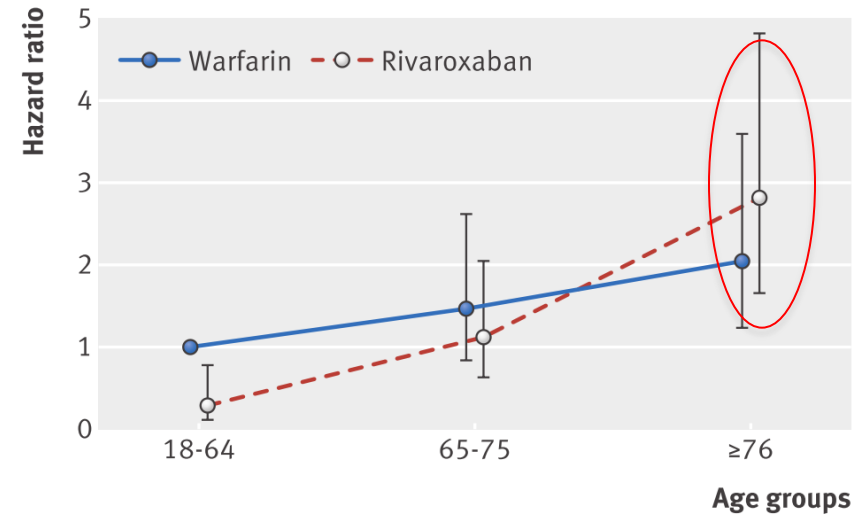
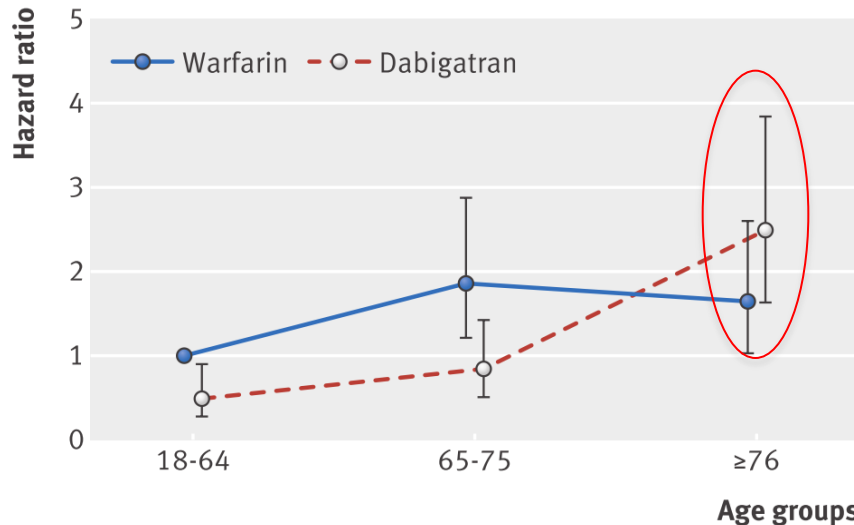
Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

In 2014 NICE approved Dabigotran and Rivaroxaban as alternatives to warfarin

NICE. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. Technology appraisal guidance TA249. 2012. <https://www.nice.org.uk/guidance/ta249/chapter/4-Consideration-of-the-evidence>

NICE. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. Technology appraisal guidance TA256. 2012. <https://www.nice.org.uk/guidance/ta256/chapter/4-consideration-of-the-evidence>

Bleeding risk of DOACs in general population



Trend for a increase in bleeding risk with increase in age for DOACs compared to warfarin

Ximelagatran & warfarin in vitamin K deficient rats

Kamali F, Wood P Ward A

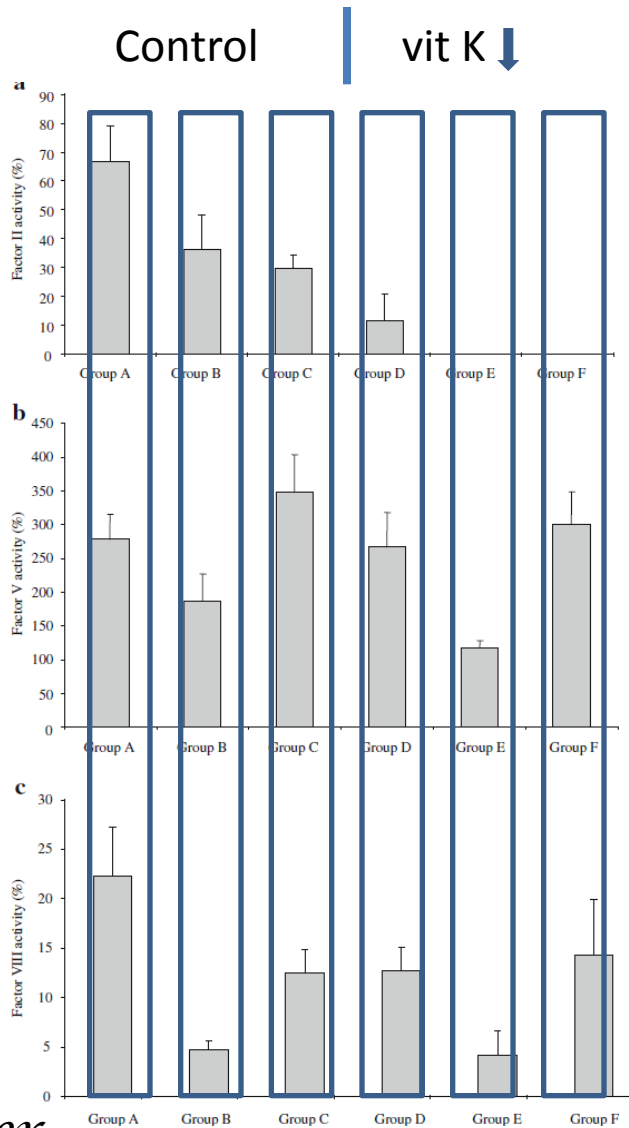
Ann Haematol 2009;88:141-9

Factor II

Factor V

Factor VIII

Anticoagulant activity of both significantly greater in rats with vitamin K deficiency



X

W

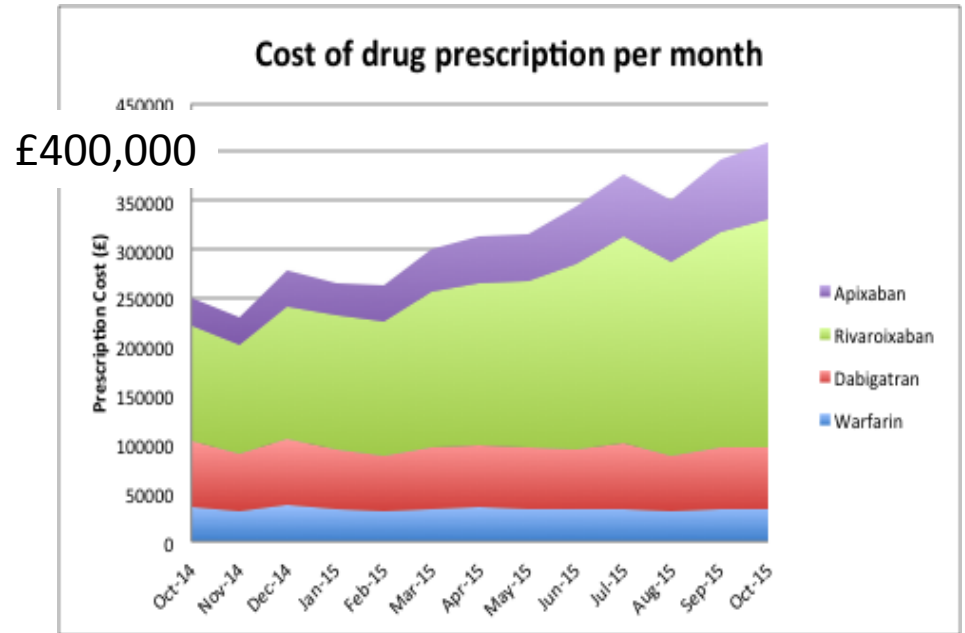
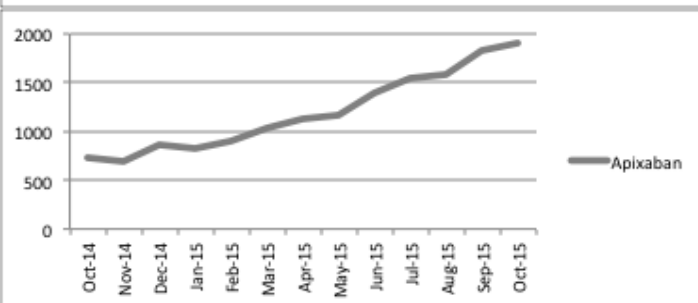
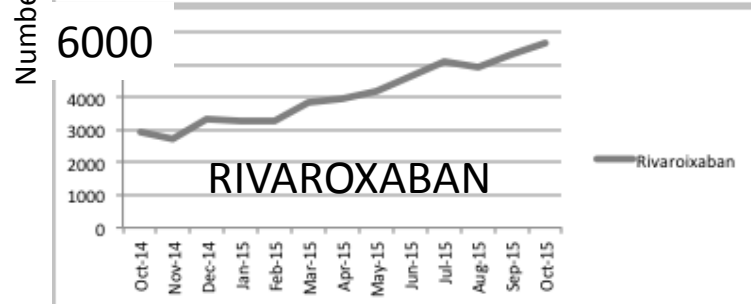
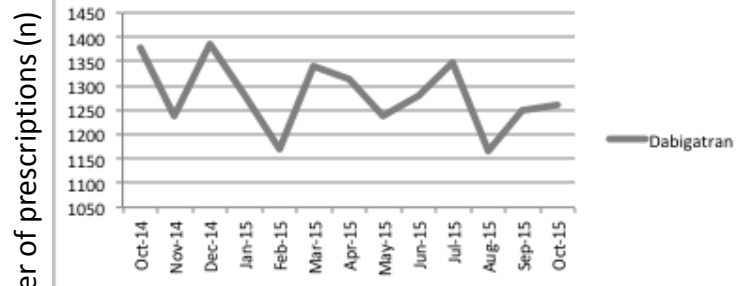
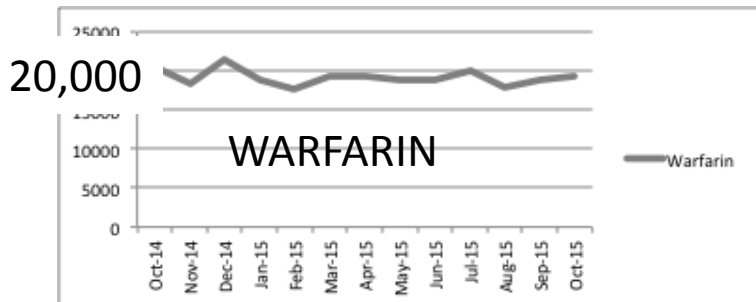
X

W

Factor Xa Inhibitor Antidote (Andexanet Alfa)

- Andexanet Alfa completed Phase III trials (ANNEXA-R and ANNEXA-A; Siegal et al. NEJM 2015)
- Anticoagulation activity reversed 2-5 minutes after administration; no clinical toxic effects observed
- Cost £2500 per use

Prescription trend by GP practices in Newcastle area 2014-15



GPs spending 25x per patient more on NOACs prescription compared to warfarin

Expenditure on anti-coagulants rose by £100 million across England in the year to November 2015 for no proven health gain



technologies such as those that provide rapid and real time results and those that can be used at the point of care. Patients and health professionals can make shared decisions about medicines and adjust dosing in real time.

Targeted and personalised interventions

Personalised medicine offers the opportunity to move away from 'trial-and-error' prescribing to optimal therapy first time round.

Currently key pharmaceutical interventions are effective in only 30-60% of patients due to differences in the way an individual responds to and metabolises medicines. Knowledge of the genetic variants responsible for individual drug response can be used to create an individual's 'pharmacogenomic' profile, identifying optimal treatment.

We are already beginning to see the development of simple point of care tests, based on genomic knowledge, which enable clinicians in a wide variety of settings to identify the best therapy. This marks the beginning of an end to the frustrating and costly practice of 'trial-and-error' prescribing. The development and regulatory approval of so called companion diagnostics - a diagnostic test, device or imaging tool used as a companion to a therapeutic drug - is already making this a reality.

Warfarin

Warfarin is a common and effective treatment to prevent blood clots, but patients show a 40-fold difference in dose needed. The current 'trial and error' approach to discover the right dose for an individual means some suffer significant problems as their treatment is worked out. Appropriate testing can be used so people get the right dose sooner – cutting side-effects and improving outcomes.

Variant allele(s) found in hospital patients on warfarin with high INR

Patient ID	INR	CYP2C9*2	CYP2C9*3	VKORC1
HH178832	1.9	*1/*1	*1/*1	G/G
HH488300	11.6	*1/*1	*1/*3	G/G
HH128895	4.8	*1/*2	*1/*1	G/G
HH179506	6.9	*1/*1	*1/*1	G/A
HH488643	11.7	*1/*1	*1/*1	G/A
HH181351	5.7	*1/*1	*1/*3	G/A
HH181710	8.7	*1/*2	*1/*3	A/A
HH184650	5.4	*1/*2	*1/*1	G/A
HH184832	5.1	*1/*2	*1/*1	G/A
HH185754	9.6	*1/*1	*1/*1	G/A
HR192035	8.4	*1/*1	*1/*1	G/A

*Genotyping could have help predict patients difficult to stabilize on warfarin
they could switch to DOACs or be offered self testing*

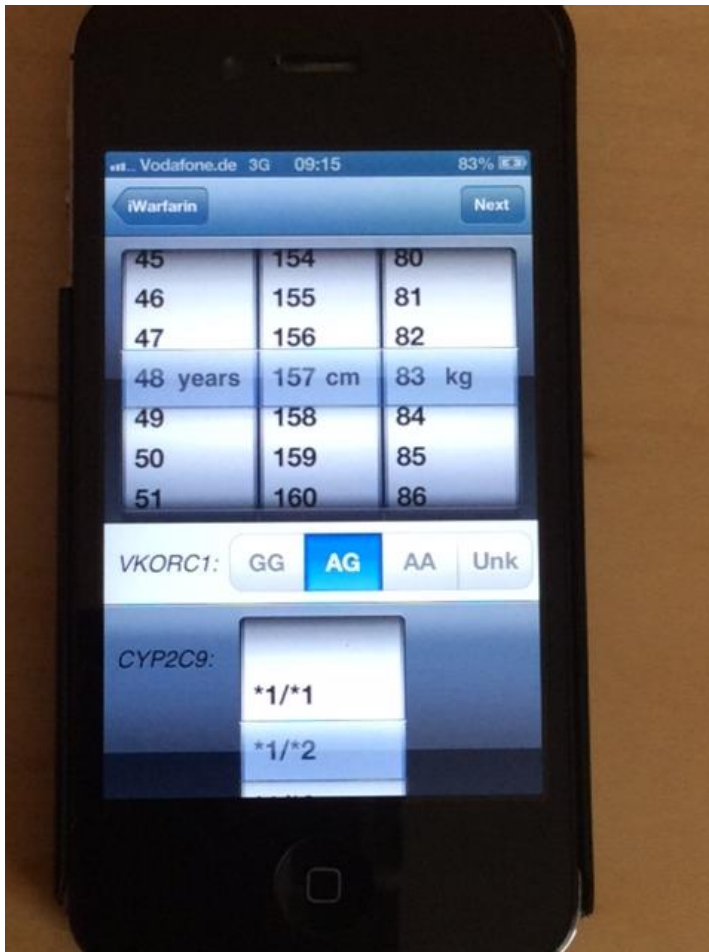
How it works



Routing of patients to warfarin/ DOAC based on genotype

		CYP2C9					
		*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
VKORC1	G/G	6mg, 24%	5mg, 7%	4mg, 4%	4mg, 1%	3mg, 0.5%	2mg, 0.1%
	G/A	4mg, 31%	4mg, 8%	3mg, 6%	3mg, 1%	2mg, 1%	1mg, 0.2%
	A/A	3mg, 13%	2mg, 3%	2mg, 2%	2mg, 0.2%	1mg, 0.3%	1mg, 0.1%

Reduced bleeding with endoxaban in sensitive and highly sensitive responders compared to warfarin (low dose P=0.0036; high dose P=0.0066)



Telephone apps already exist to calculate optimal dose.

All that is needed is the bedside device

Summary

- The clinical case for warfarin and DOACs is finely balanced
- Three variants affecting warfarin metabolism and vitamin K activation cause major variation in response
- Genotyping and self testing can make warfarin the better option for most people
- DNA testing can now be offered in the clinic
- Major financial savings are available if we can adapt our clinical practice



Debate: Does Warfarin's Legacy Live on?

Ask an AHSN: How do we go further and faster to prevent AF related stroke?

Summary & Close