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Preventing stroke, premature death and cognitive decline in a broader community of patients with atrial fibrillation (DaRe2THINK)

Submission date
02/02/2021

Recruitment status
Recruiting

Registration date
16/02/2021

Overall study status
Ongoing

Last Edited
29/01/2025

Condition category
Circulatory System

[X] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The DaRe2 approach (healthcare Data for pragmatic clinical Research in the NHS – primary 2 secondary) will test a new way of running trials which could improve the health and well-being of those treated by the NHS, whilst reducing the time needed from staff and patients to engage in research.
As an example of this new system, DaRe2THINK will target patients with Atrial fibrillation. AF is a common heart rhythm condition that leads to a high chance of stroke, frequent hospital admissions, a higher risk of cognitive decline and dementia. Blood thinning tablets (anticoagulants) greatly reduce the number of patients with AF that will suffer a stroke, but are usually only given to older patients or those with other health issues. This leaves patients younger than 65 years, and some patients aged 65-75 without treatment that could prevent these devastating complications.
A new class of blood thinning tablets are now widely used in the NHS which are more convenient for patients to take, and have a lower risk of bleeding than older treatments. These drugs could provide an effective way to prevent strokes, brain damage and dementia in later life for a broader group of patients, but this needs to be tested in a clinical trial.
DaRe2THINK will answer important questions for a growing number of patients with AF. The combination of information from the community as well as hospitals across the NHS will allow us to see whether these blood thinning tablets should be prescribed more widely. DaRe2THINK will allow us to develop and improve this new clinical trial system so that future research in the NHS will continue to benefit those patients most in need.

Who can participate?
Patients with atrial fibrillation aged 55 - 73 years.

What does the study involve?
The trial will include 3,000 patients from up to 600 GP surgeries across England. Each patient will be randomised to either continue their current treatment or start an additional blood thinning tablet. Patients will be followed up remotely to look at the difference in those who suffer from strokes, blood clots, heart attacks, or other problems with the blood vessels and dementia.

Patients will self-report their memory, reaction times and quality of life using simple questionnaires through their mobile phone or the internet, again without needing to revisit their doctor.

What are the possible benefits and risks of participating?
We already know that AF can lead to strokes and dementia. The risk of these problems increases as you get older. We also know that blood thinners are currently used in the NHS to prevent can prevent strokes in older patients., and now we need to test if using them in They could also be valuable in younger patients is helpful to prevent strokes, and blood clots, in particular 'micro-strokes' that can lead to dementia, but we need to test that this is the case. Your contribution is vital to helping future patients with AF receive the best treatment throughout the NHS and across the world. Blood thinning drugs do not cause bleeding, but if bleeding is caused by another factor e.g. a knock to the head, they can make the bleeding worse. The newer blood thinners (DOACs) are much safer than older treatments such as warfarin and are now the standard of care within the NHS. Apart from AF, doctors commonly use these drugs to treat blood clots in the leg or lung, and certain types of heart and blood diseases. If you start a blood thinner, you will need to take extra care in day-to-day activities (for example, making sure you don't fall or cut yourself shaving). Minor bleeding occurs in around 1 in 10 patients, but isn't usually a reason to stop treatment and can be prevented by placing pressure on cuts or holding down longer after blood tests. They are established drugs, and your GP is used to prescribing and monitoring their use. Major bleeding usually only happens when there is an unknown health condition like a stomach ulcer. If you hit your head or collapse on blood thinners, you should seek medical attention.

Where is the study run from?
Institute of Cardiovascular Science, University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
December 2020 to January 2031

Who is funding the study?
National Institute for Health Research (NIHR) Health Technology Assessment (UK)

Who is the main contact?
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Study website
http://www.bham.ac.uk/dare2think

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2020-005774-10

IRAS number
290420

ClinicalTrials.gov number
NCT04700826

Secondary identifying numbers
CPMS 48082, IRAS 290420

Study information

Scientific Title
Preventing stroke, premature death and cognitive decline in a broader community of patients with atrial fibrillation using healthcare data for pragmatic research: A randomised controlled trial

Acronym
DaRe2THINK

Study objectives
DaRe2THINK will test the hypothesis that Direct Oral Anticoagulants (DOACs) are effective and cost-effective in patients with AF at low or intermediate risk of stroke by using an ambitious and innovative data-enabled approach through the Clinical Practice Research Datalink (CPRD) in Primary Care General Practices across England

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/03/2021, North Eastern: Tyne and Wear South (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)207 104 8265; tyneandwearsouth.rec@hra.nhs.uk), ref: 21/NE/0021

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice

Study type(s)
Treatment

Participant information sheet
http://www.bham.ac.uk/dare2think

Health condition(s) or problem(s) studied
Atrial fibrillation

Interventions
Participants will be randomised to one of two groups in a 1:1 ratio by a computer generated algorithm:
Group 1: Standard of Care
Group 2: Direct Oral Anticoagulant (DOACs)

Follow-up takes place remotely through the extraction of participants' health records and remote completion of patient reported outcome questionnaires (every 6months) and cognitive function tests (every 12months) using their personal electronic device, up to 5 years.

Drugs used and dosage:
Apixaban 5mg twice daily, or 2.5mg twice daily if meeting criteria for reduced dose.
Dabigatran 150mg twice daily, or 110mg twice daily if meeting criteria for reduced dose.
Edoxaban 60mg once daily, or 30mg once daily if meeting criteria for reduced dose.
Rivaroxaban 20mg once daily, or 15mg once daily if meeting criteria for reduced dose.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
apixaban, dabigatran, edoxaban, rivaroxaban

Primary outcome measure
Time to first event of:
1. Cardiovascular mortality
2. Ischaemic cerebrovascular events (stroke and transient ischaemic attacks)
3. All thromboembolic events (including venous and arterial thromboembolism)
4. Myocardial infarction
5. Vascular dementia
Collected through yearly assessment of primary and secondary care records assessed at 5 years

Secondary outcome measures
1. Change in cognitive function using the UK Biobank fluid intelligence/reasoning test (mixed effects repeated measures analysis of information collected at baseline and yearly), with analysis at 5 years
2. Change in cognitive function using the UK Biobank trail making test (mixed effects repeated measures analysis of information collected at baseline and yearly), with analysis at 5 years
3. Change in cognitive function using the UK Biobank symbol digit substitution test (mixed effects repeated measures analysis of information collected at baseline and yearly), with analysis at 5 years
4. Change in cognitive function using the UK Biobank non-verbal fluid reasoning matrices test (mixed effects repeated measures analysis of information collected at baseline and yearly), with

analysis at 5 years
5. Incremental cost per quality-adjusted life-years gained from the healthcare perspective (collected through yearly assessment of primary and secondary care records) assessed at 5 years
6. Incremental cost per quality-adjusted life-years gained from the societal perspective assessed (collected through yearly assessment of primary and secondary care records) assessed at 5 years
7. Time to composite of major adverse cardiovascular events (non-fatal stroke, non-fatal myocardial infarction and cardiovascular death collected through yearly assessment of primary and secondary care records) assessed at 5 years
8. Time to any major bleeding or clinically-relevant non-major bleeding that requires hospitalisation (collected through yearly assessment of primary and secondary care records) assessed at 5 years
9. Time to minor bleeding that requires attention from primary care (any bleeding that leads to a primary care consultation) collected through yearly assessment of primary and secondary care records assessed at 5 years
10. Time to haemorrhagic stroke and other types of intracranial bleeding (collected through yearly assessment of primary and secondary care records) assessed at 5 years
11. Number of all-cause general practice visits (collected through yearly assessment of primary and secondary care records) assessed at 5 years
12. Number of all-cause hospital admissions (collected through yearly assessment of primary and secondary care records) assessed at 5 years
13. Duration of all-cause hospital admissions (collected through yearly assessment of primary and secondary care records) assessed at 5 years
14. Number of heart failure hospitalisations (collected through yearly assessment of primary and secondary care records) assessed at 5 years
15. Duration of heart failure hospitalisations (collected through yearly assessment of primary and secondary care records) assessed at 5 years
16. Time to all-cause mortality (collected through yearly assessment of primary and secondary care records) assessed at 5 years
17. Time to cardiovascular death (collected through yearly assessment of primary and secondary care records) assessed at 5 years
18. Change in patient-reported quality of life using the Euroqol five-dimensions five-level (EQ-5D-5L) summary index score (mixed-effects repeated measures analysis of 6-monthly assessment) assessed at 5 years; Range 0 = death to 1 = complete health
19. Change in patient-reported quality of life using the EQ-5D-5L visual analogue score (mixed effects repeated measures analysis of 6-monthly assessment) Range 0-100, with a higher score indicating better quality of life
20. Time to ischaemic cerebrovascular event (stroke and transient ischaemic attacks) collected through yearly assessment of primary and secondary care records and assessed at 5 years
21. Cumulative number of ischaemic cerebrovascular events (stroke and transient ischaemic attacks) collected through yearly assessment of primary and secondary care records and assessed at 5 years
22. Time to any thromboembolic event (including venous and arterial thromboembolism) collected through yearly assessment of primary and secondary care records and assessed at 5 years
23. Time to arterial thromboembolic (collected through yearly assessment of primary and secondary care records) assessed at 5 years
24. Time to venous thromboembolic event (collected through yearly assessment of primary and secondary care records) assessed at 5 years
25. Cumulative number of thromboembolic events (including venous and arterial thromboembolism) collected through yearly assessment of primary and secondary care records and assessed at 5 years
26. Time to myocardial infarction (collected through yearly assessment of primary and secondary

care records) assessed at 5 years
27. Cumulative number of myocardial infarctions (collected through yearly assessment of primary and secondary care records) assessed at 5 years
28. Time to vascular dementia (collected through yearly assessment of primary and secondary care records) assessed at 5 years

Other Outcome Measures:
29. Number/proportion of potential participants located by CPRD and notified to the lead NIHR Clinical Research Network (CRN) assessed at 5 years
30. Number/proportion of primary care practices that have completed sign-up processes assessed at 5 years
31. Number/proportion of patients eligible on automated screening that are successfully recruited assessed at 5 years
32. Rate of patient recruitment assessed at 5 years
33. Patient-reported compliance to DOAC therapy in the DOAC arm collected every 6months and assessed at 5 years
34. Repeat prescriptions obtained for DOAC therapy a (collected through yearly assessment of primary and secondary care records) assessed at 5 years
35. Missing data rates for 6-monthly patient-reported Euroqol five-dimensions five-level (EQ-5D-5L) summary index score, with death equivalent to a score of zero assessed at 5 years
36. Proportion of participant time-points with missing data for cognitive function using the UK Biobank fluid intelligence/reasoning test assessed at 5 years

Overall study start date
01/12/2020

Completion date
01/01/2031

Eligibility

Key inclusion criteria
Current inclusion criteria as of 19/06/2023:

1. Diagnosis of AF (previous, current or chronic)
2. Age at enrolment >=55 years to <=73 years

Previous inclusion criteria:

1. Diagnosis of AF (previous, current or chronic)
2. Age at enrolment >=60 years to <=73 years

Participant type(s)
Patient

Age group
Adult

Lower age limit

55 Years

Upper age limit
73 Years

Sex
Both

Target number of participants
Planned Sample Size: 3,000; UK Sample Size: 3,000

Key exclusion criteria
Current exclusion criteria as of 01/11/2022:

Participant exclusion criteria based on coding in the Primary Care record:
1. Prior documented stroke, transient ischaemic attack or systemic thromboembolism.
2. Combination of multiple known risk factors for stroke where oral anticoagulation would ordinarily be started, including: Heart failure; Hypertension; Age 65 years or older; Diabetes mellitus; Previous myocardial infarction, peripheral artery disease or aortic plaque; and/or Female gender.
3. Any prior history of intracranial bleeding.
4. Prior major bleeding requiring hospitalisation in the last 3 years.
5. Condition that poses a significant risk for bleeding (within 12 months) including gastrointestinal ulceration, brain/spinal/ophthalmic injury or surgery, arteriovenous malformations or vascular aneurysms, major intraspinal or intracerebral vascular abnormalities, hepatic disease associated with coagulopathy, known or suspected oesophageal varices, and cancers with high bleeding risk.
6. Estimated glomerular filtration rate <30 mL/min/1.73m² measured within the last 12 months.
7. Patients receiving systemic treatment with azole-antimycotics within the last 3 months (ketoconazole, itraconazole, voriconazole and posaconazole).
8. Documented diagnosis of dementia.
9. Hypersensitivity or known intolerance to direct oral anticoagulants.

Participant exclusion criteria based on review by Primary Care staff:
1. Currently receiving an anticoagulant.
2. Any clinical indication for anticoagulation.
3. Active clinically-significant bleeding.
4. Life expectancy estimated <2 years.
5. Participant unable or unwilling to provide informed consent for access and linkage of past and future electronic healthcare records.
6. Currently participating in another clinical trial.
7. Women of childbearing potential.

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Previous exclusion criteria as of 21/09/2021:

1. Existing use of an anticoagulant.
2. Another clinical indication for anticoagulation.
3. Hypersensitivity or known intolerance to direct oral anticoagulants.
4. Prior documented stroke, transient ischaemic attack or thromboembolism.

5. Two or more CHA2DS2-VASc one-point risk factors indicating a risk of stroke or thromboembolism: Heart failure, Hypertension; Age 65 years or older; Diabetes mellitus; Previous myocardial infarction, peripheral artery disease or aortic plaque; and/or Female gender (if in the presence of other risk factors).
6. Active clinically-significant bleeding.
7. Prior major bleeding, defined as any intracranial bleed, or bleeding that resulted in a drop in haemoglobin ≥2g/dL, required hospitalisation or transfusion.
8. Condition that poses a significant risk for bleeding (within 12 months) including gastrointestinal ulceration, brain/spinal/ophthalmic injury or surgery, arteriovenous malformations or vascular aneurysms, major intraspinal or intracerebral vascular abnormalities, hepatic disease associated with coagulopathy, known or suspected oesophageal varices, and cancer with high bleeding risk.
9. Estimated glomerular filtration rate <30 mL/min/1.73m2 measured within the last 12 months.
10. Patients receiving systemic treatment with azole-antimycotics within the last 3 months (ketoconazole, itraconazole, voriconazole and posaconazole).
11. Current diagnosis of dementia.
12. Life expectancy <2 years.
13. Unable or unwilling to provide informed consent for access and linkage of past and future electronic healthcare records.
14. Currently participating in another clinical trial.

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Previous exclusion criteria:

1. Existing use of an anticoagulant
2. Another clinical indication for anticoagulation
3. Hypersensitivity or known intolerance to direct oral anticoagulants
4. Prior documented stroke, transient ischaemic attack or thromboembolism
5. Two or more CHA2DS2-VASc one-point risk factors: Heart failure Hypertension; Age 65 years or older; Diabetes mellitus; Previous myocardial infarction, peripheral artery disease or aortic plaque; and/or Female gender
6. Active clinically-significant bleeding
7. Prior major bleeding, defined as any intracranial bleed, or bleeding that resulted in a drop in haemoglobin ≥2g/dL, required hospitalisation or transfusion
8. Condition that poses a significant risk for bleeding (within 12 months) including gastrointestinal ulceration, brain/spinal/ophthalmic injury or surgery, arteriovenous malformations or vascular aneurysms, major intraspinal or intracerebral vascular abnormalities, hepatic disease associated with coagulopathy, known or suspected oesophageal varices, and cancer with high bleeding risk
9. Estimated glomerular filtration rate <30 mL/min/1.73m2 measured within the last 12 months
10. Patients receiving systemic treatment with azole-antimycotics within the last 3 months (ketoconazole, itraconazole, voriconazole and posaconazole)
11. Current diagnosis of dementia
12. Life expectancy <2 years
13. Unable or unwilling to provide informed consent for access and linkage of past and future electronic healthcare records

Date of first enrolment
01/06/2021

Date of final enrolment

01/12/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospitals Birmingham NHS Foundation Trust (and around 600 primary care practices across England)
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
NIHR CRN: West Midlands
James House
Newport Road
Albrighton
United Kingdom
WV7 3FA

Study participating centre
NIHR CRN: North East and North Cumbria
Regent Point
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United Kingdom
NE3 3HD

Study participating centre
NIHR CRN: North West Coast
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
NIHR CRN: Yorkshire and Humber
8 Beech Hill Road
Sheffield
United Kingdom
S10 2SB

Study participating centre
NIHR CRN: Greater Manchester
2nd Floor
Citylabs
Manchester
United Kingdom
M13 9NQ

Study participating centre
NIHR CRN: East Midlands
Knighton Street Outpatients
1st Floor
Leicester
United Kingdom
LE1 5WW

Study participating centre
NIHR CRN: West of England
Whitefriars
Lewins Mead
Bristol
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BS1 2NT

Study participating centre
John Radcliffe Hospital
NIHR CRN: Thames Valley and South Midlands
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre

NIHR CRN: Eastern
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Sponsor type
University/education

Website
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ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR130280

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2031

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 5.0	24/07/2023	21/12/2023	No	No