The acute management of intracerebral haemorrhage

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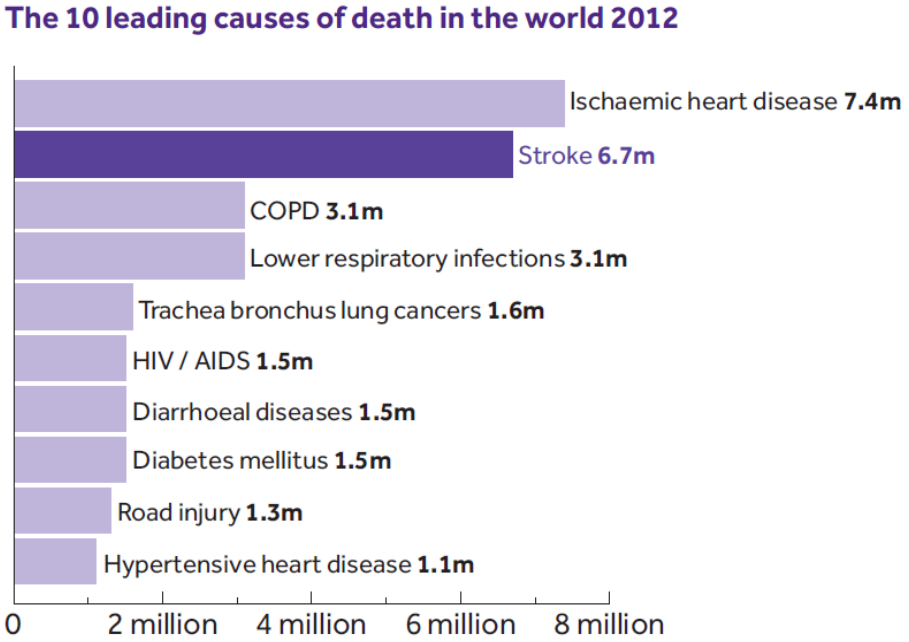
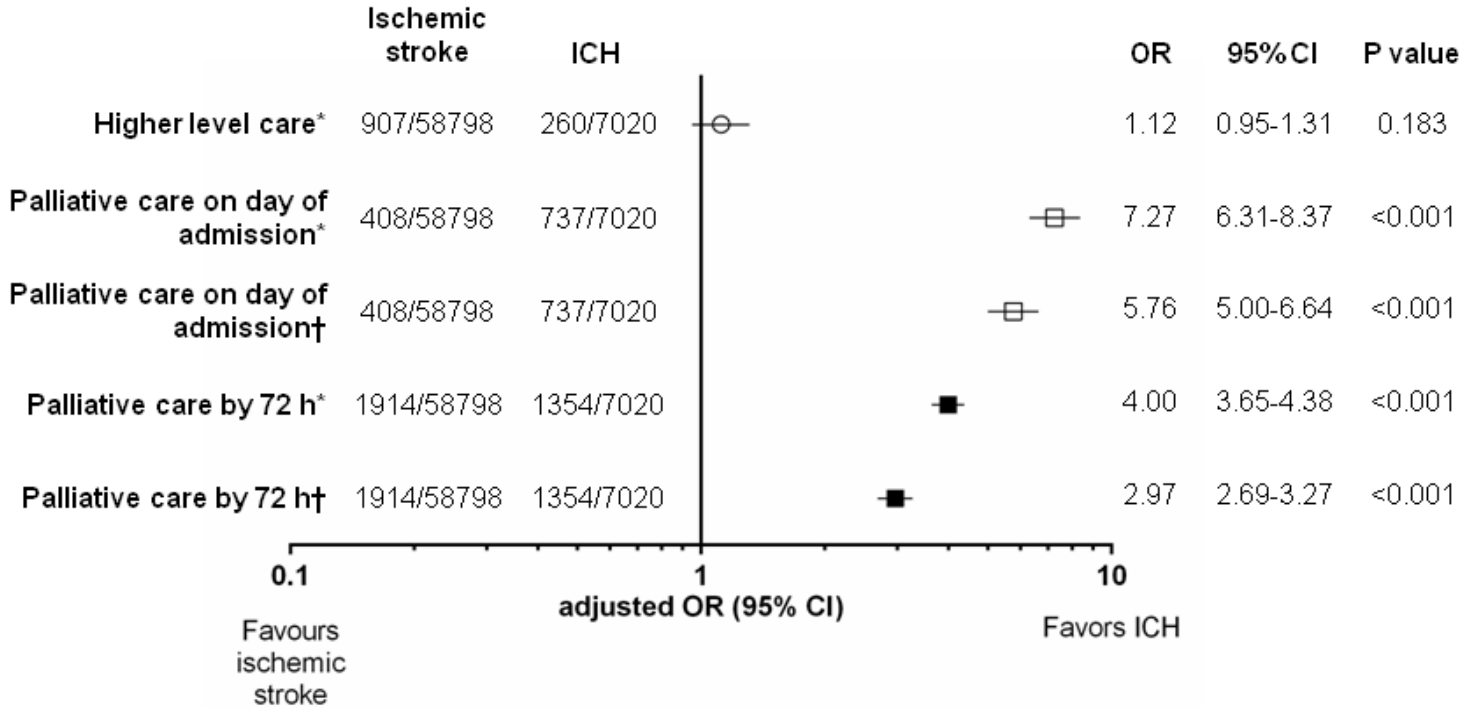
Intracerebral haemorrhage

- **Common health problem**
  - Causes 10-15% of strokes
  - More common in Asian populations
- **Poor patient outcomes**
  - Case fatality 30-40% at 1 month
  - Causes 5.8% of *all* global deaths (*vs.* 6.0% for ischaemic stroke)
  - Only 20% regain independence
  - Little improvement in outcomes over last 30 years



Evidence of nihilism in ICH?



*Adjusted for sex, age, premorbid mRS, comorbidities of congestive heart failure, hypertension, AF, and diabetes, previous stroke/TIA, Level of consciousness, and 'out of hours'. † also adjusted for early neurological deterioration (drop in NIHSS 1a of 1 or more in first week).

Parry-Jones et al (2016) *Int J Stroke* 11:321-31

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The acute management of intracerebral haemorrhage part 1

Hyperacute management: what to do?

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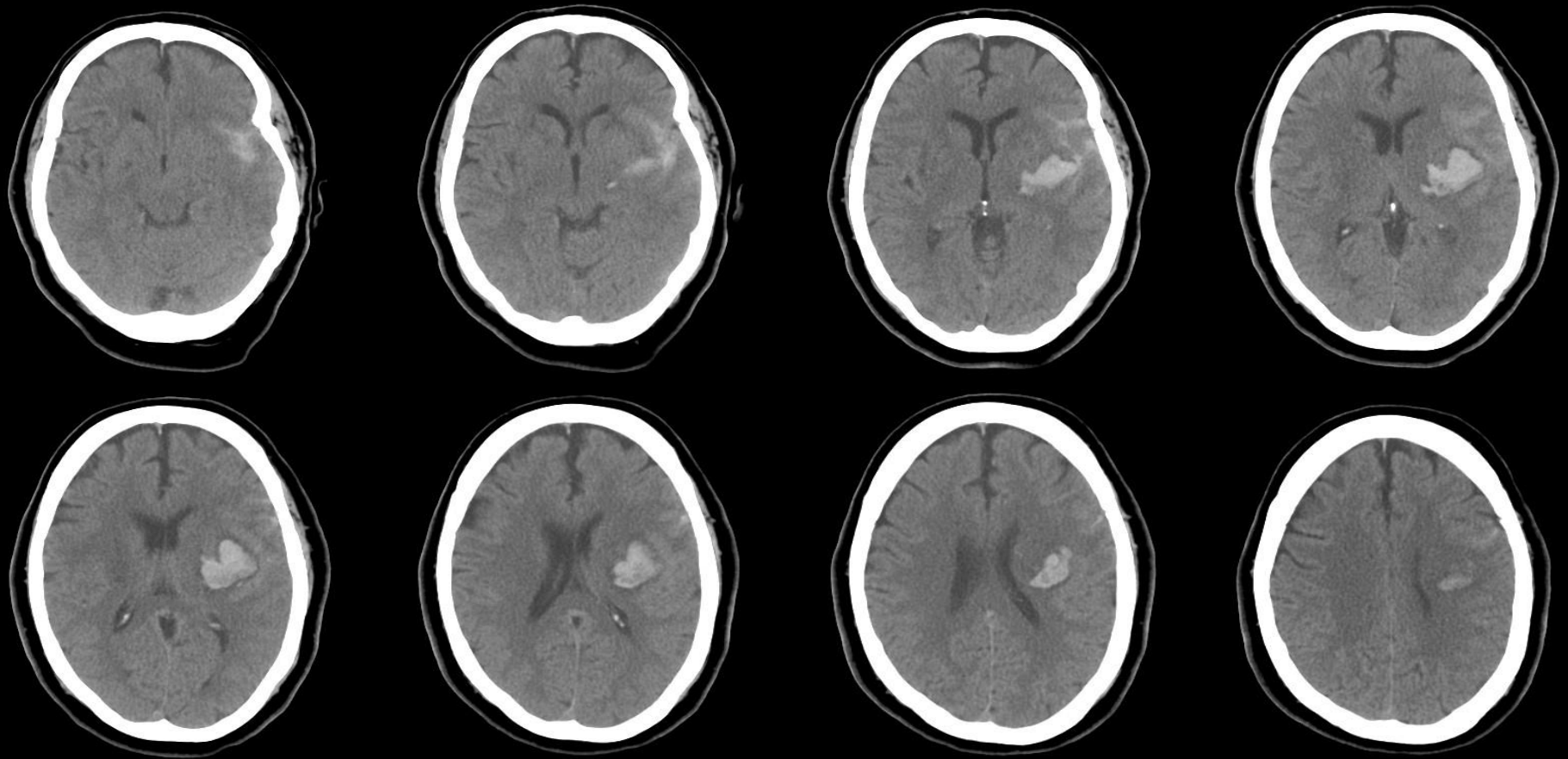
An illustrative case….

- 69 year-old female
- Chronic hypertension, atrial fibrillation
- DH: Perindopril, warfarin (INR target range 2-3)
- Baseline function normal (mRS = 0)
- Sudden onset slurred speech and right-sided weakness at 08:00
- Examination on arrival (09:00):
  - GCS E3 M6 V5 – 14/15
  - Severe R-sided weakness
  - NIHSS 12
  - BP 189/110

CT brain at 09:23 - 1.5 h post-onset



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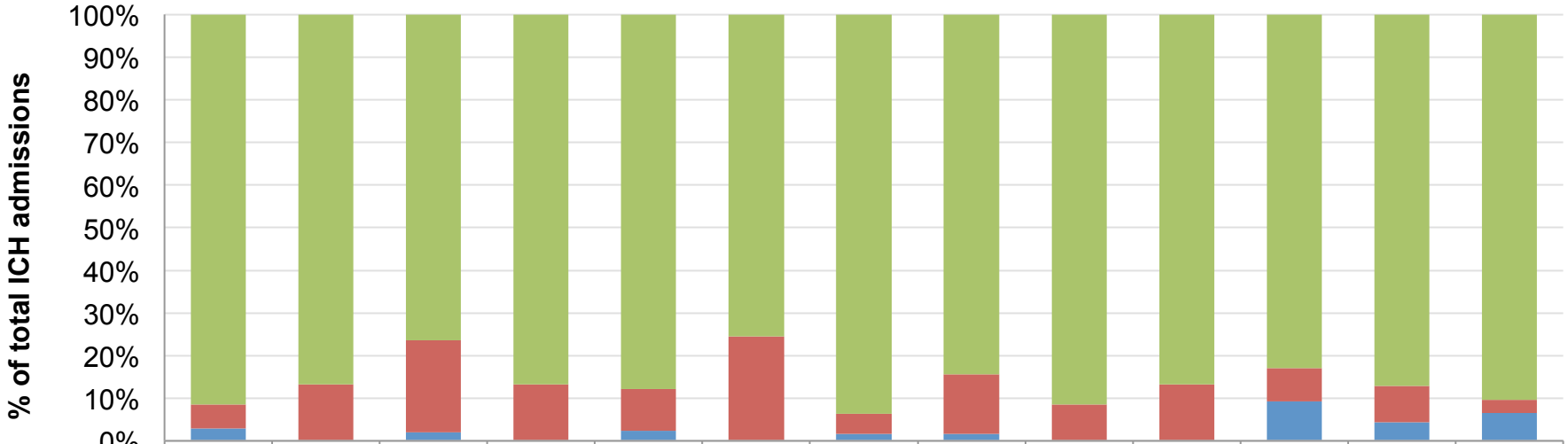
Anticoagulants – recent Salford audit data



	Q3 2013	Q4 2013	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016
No anticoag	32	39	39	39	36	43	59	49	65	72	63	61	28
VKA	2	6	11	6	4	14	3	8	6	11	6	6	1
DOAC	1	0	1	0	1	0	1	1	0	0	7	3	2

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VKA-ICH vs. DOAC-ICH

International, multicentre pooled analysis

13 centres – Europe, Asia, North America

500 patients (97 DOAC-ICH; 403 VKA-ICH)

Variable	DOAC-ICH (n=97)	VKA-ICH (n=403)
Age	80 (74-85)	80 (72-85)
GCS	14 (12-15)	15 (13-15)
ICH vol	14.4 (3.6-38.4)	10.6 (4.0-27.9)
IVH	42 (43)	146 (36)
Pre-mRS	1 (0 to 3)	0 (0 to 2)

Wilson *et al*, *Neurology*, 2017

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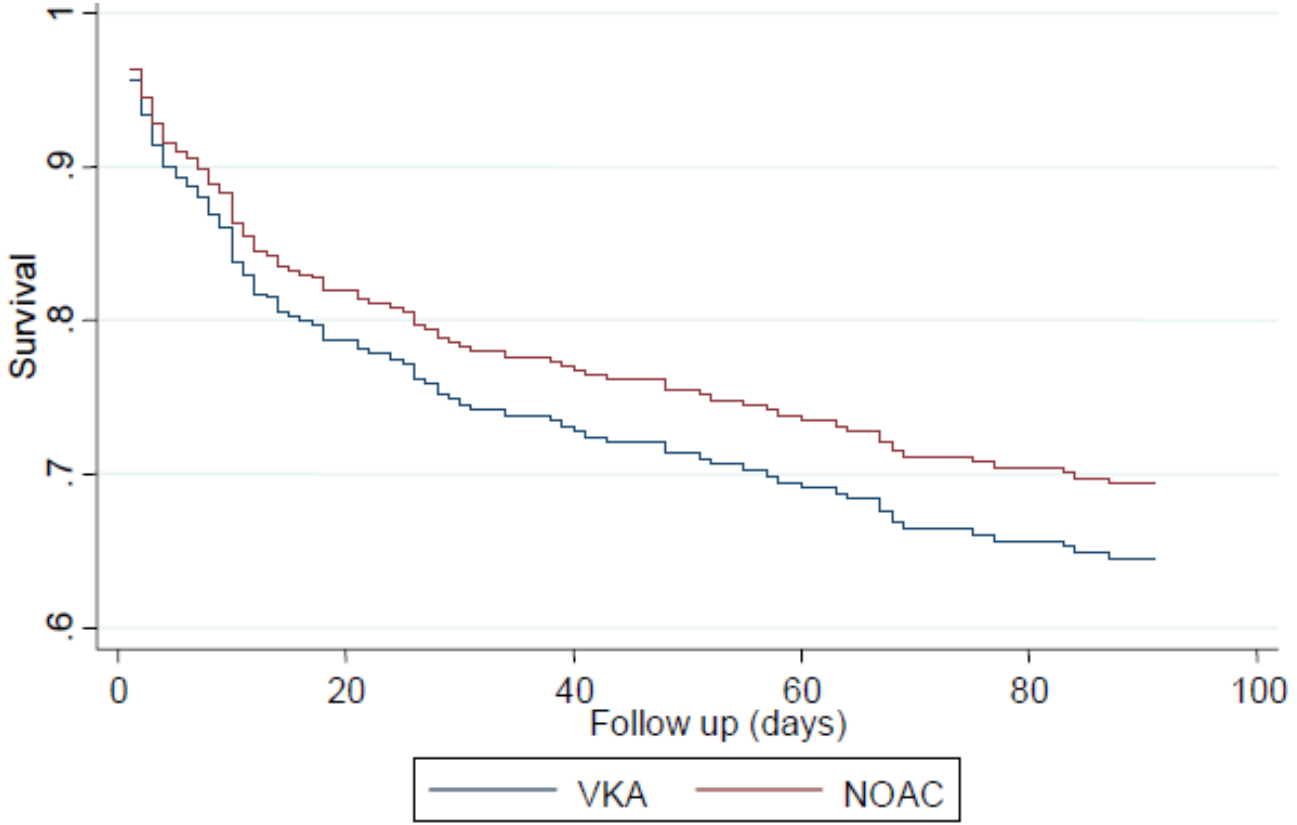
VKA-ICH vs. DOAC-ICH



Wilson *et al*, *Neurology*, 2017, *In press*

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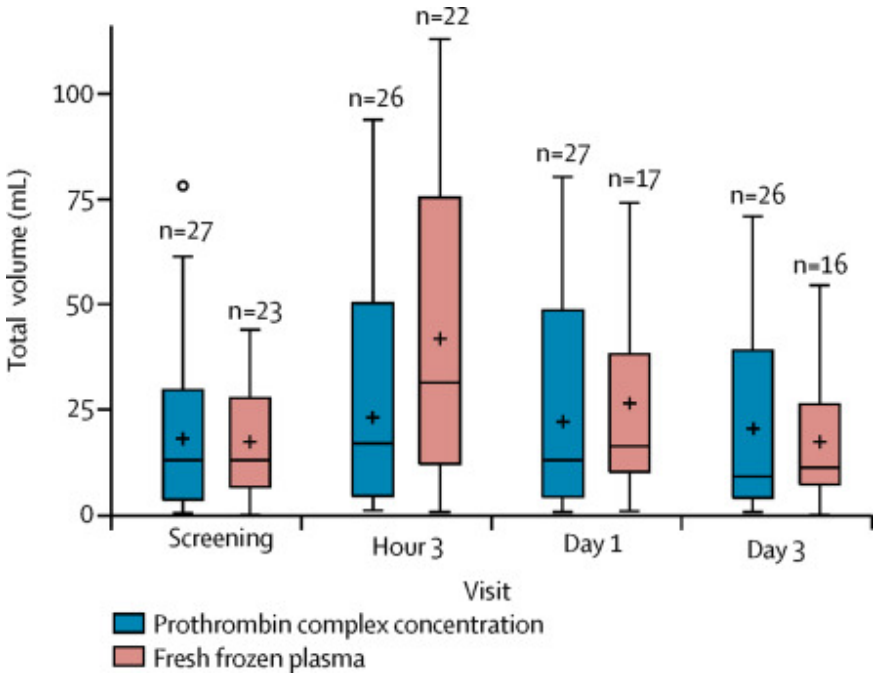
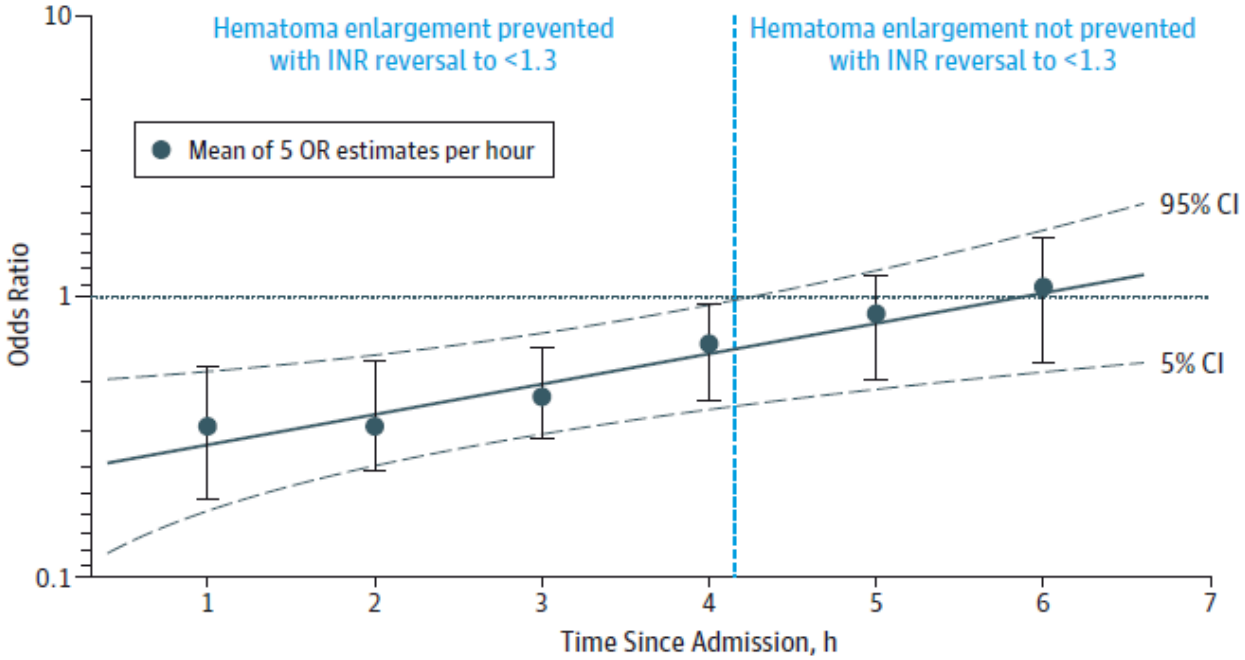
VKA-ICH: INCH trial

- Randomised, open-label, blinded-endpoint trial
- Within 12 h of onset, INR ≥ 2
- 20 mL/kg FFP vs. 30 IU/kg 4F PCC
- 23 FFP & 27 PCC treated
- Outcomes:
  - INR<1.3 by 3h: 9% FFP vs. 67% PCC
  - 90d mortality: 35% FFP vs. 19% PCC
  - Increased expansion with FFP



Steiner *et al. Lancet Neurol*, 2016:15,566–73.

VKA-ICH: ‘Time is brain’



Patients with hematoma enlargement, shown as No./No. achieving INR (%)						
INR <1.3	5/26 (19.2)	9/51 (17.6)	14/73 (19.2)	15/67 (22.4)	7/22 (31.8)	9/25 (36.0)
INR ≥1.3	6/17 (35.3)	11/30 (36.7)	25/64 (39.1)	27/64 (42.2)	11/28 (39.3)	13/29 (44.8)

Kuramatsu et al. (2015) *JAMA* 313: 824-36.

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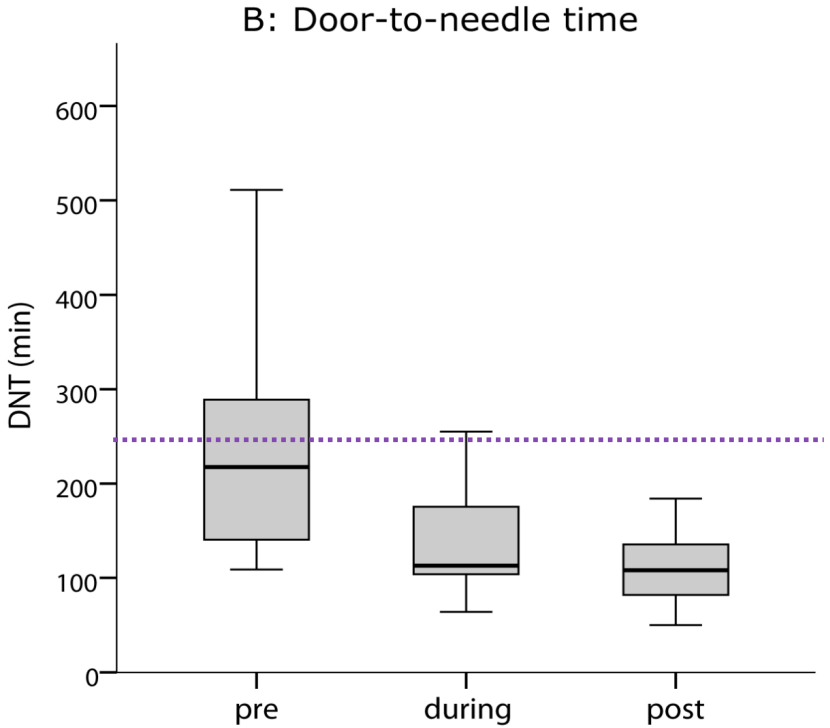
VKA-ICH: Improving door-to-needle times

Three key changes:

1. PCC stock in the ED
2. Point-of-care INR device
3. Standard protocol to deliver PCC without Haematology referral for every case



Parry-Jones (2015) *BMJ Qual Improv Rep* 8

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DOAC-ICH

Drug	Half life	Mode of action	Coagulation tests
Dabigatran	12-17 h	Direct thrombin (II)	**aPTT, TT**
Rivaroxaban	7-11 h	Factor Xa	**PT**, anti Xa
Apixaban	8-15 h	Factor Xa	anti Xa
Edoxaban	10-14 h	Factor Xa	**PT**, anti Xa

Options for reversal:

- PCC (3-factor, 4-factor)
- Idarucizumab (for dabigatran)
- *Andexanet alpha (for Xa inhibitors) – *not yet available*

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DOAC-ICH: current guidelines

What do the guidelines say?

- RCP (2016): idarucizumab for dabigatran; 4F PCC for others
- AHA/ASA (2015): PCC or rFVIIa 'might be considered'; Activated charcoal might be used if <2 h since last dose; Haemodialysis for dabigatran.
- ESO (2014): No recommendation

PCC:

- Animal and healthy volunteer data suggests partial reversal
- British Committee for Standards in Haematology (2013)

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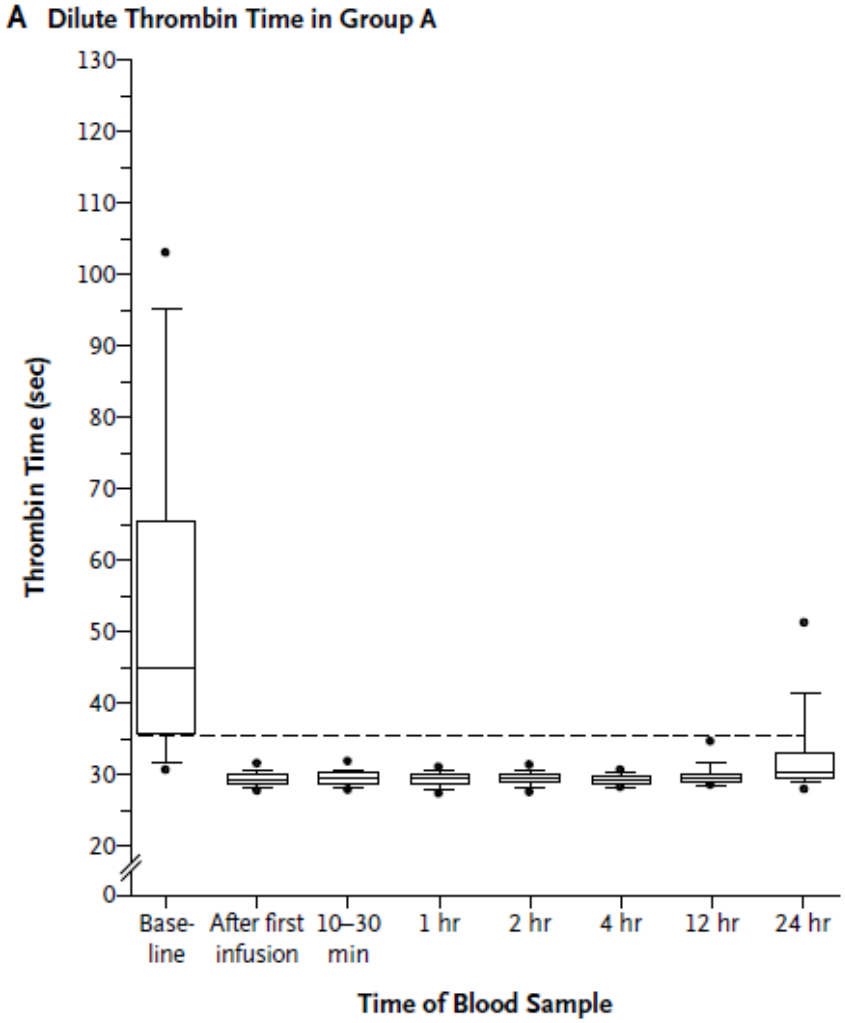
DOAC-ICH: Idarucizumab

- Dabigatran antidote, humanised Fab
- Dabigatran - 350x higher affinity for idarucizumab than thrombin
- Rapid & complete reversal
- No prothrombotic effects in volunteers; 1 in 90 pts (RE-VERSE AD)
- RE-VERSE AD included 18 ICHs
- £2400 per dose (5 g)



Pollack *et al. N Engl J Med*, 2015:373,511–20.

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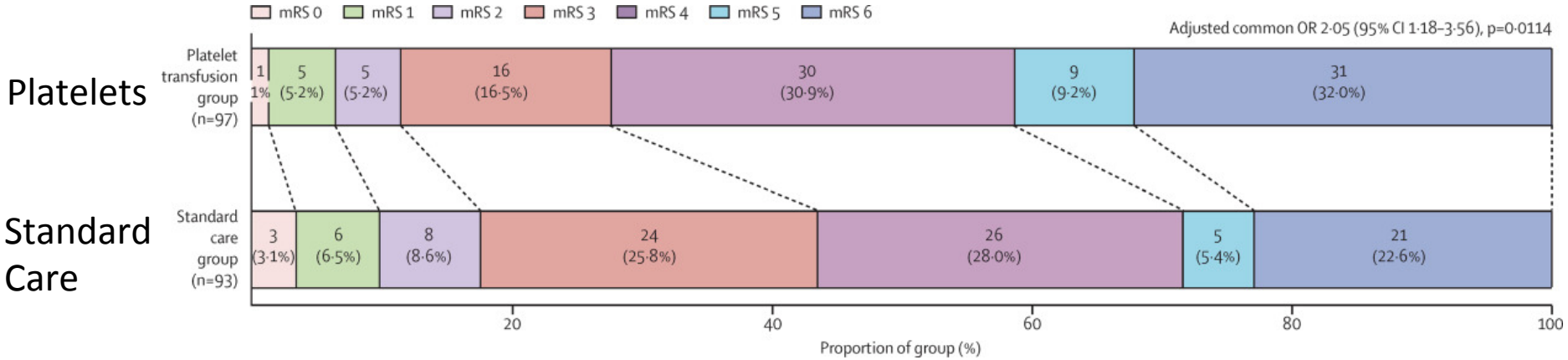
Platelet transfusion – for ICH on antiplatelets

- Sometimes used in practice – makes sense?
- PATCH trial: platelet transfusion vs. standard care
  - 190 pts, < 6 h post onset, on antiplatelet drugs



Baharoglu *et al*, *Lancet*, 2016

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	INTERACT2	ATACH-II
Target SBP – intensive group	< 140 mmHg by 1 h stop if < 130 mmHg	110-139 by 2 h
Target SBP – standard group	< 180 mmHg target 160/90 (AHA 2010)	140-179 by 2 h
Agents used	α-blocker (urapadil) – 32.5% Ca^{2+} channel blocker – 16.2% Nitroglycerin – 14.9% α/β blocker (labetalol) – 14.4% Diuretics – 12.4% Nitroprusside 12.1% Others – 12%	**First line**: nicardipine **Second line**: Labetolol Urapadil Diltiazem

Anderson et al.(2013) *N Engl J Med.*368:2355-65; Qureshi et al.(2016) *N Engl J Med.*375:1033-43.

	INTERACT2	ATACH-II
SBP achieved with treatment	*Mean at 1 h:* 150 mmHg (intensive) 164 mmHg (standard)	*Mean minimum 0-2 h:* 129 mmHg (intensive) 141 mmHg (standard)
Primary outcome	mRS 4-6 52.0% (I) vs 55.6% (S) (p=0.06)	mRS 4-6 38.7% (I) vs. 37.7% (S) (p=0.72)
Secondary outcomes	**Ordinal shift: 0.87 (0.77–1.00) p=0.04** EQ5D: 0.60 (I) vs 0.55 (S);p=0.002 SAEs: 23.3% (I) vs 23.6% (S)	Ordinal shift: 1.07 (p=0.56) EQ5D: 0.7 (I) vs 0.7 (S); p=0.47 **Renal AEs: 9%(I) vs.4%(S) p=0.002**

Anderson et al.(2013) *N Engl J Med.*368:2355-65; Qureshi et al.(2016) *N Engl J Med.*375:1033-43.

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Current UK practice

2016 RCP guideline: recommends INTERACT intervention

Survey of BASP members Feb 2017 (243 respondents):

Question	Response
Is there a hyperacute ICH BP protocol in place at centre?	Yes - 69%
Do you routinely deliver the INTERACT intervention?	Yes - 57%
If not, why not?	No locally agreed protocol – 25% Not convinced by evidence – 13% Not confident can safely deliver – 8% Lack resources – 6%
Preferred first line parenteral drug for BP lowering in ICH?	Labetalol – 56% GTN: IV – 23%, transdermal – 15%

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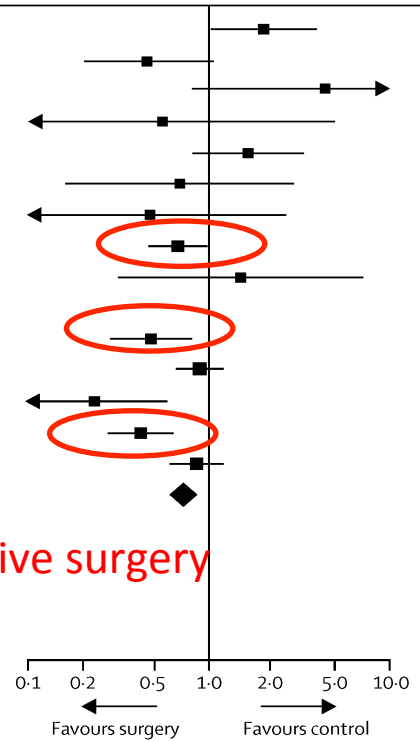
Neurosurgery for ICH

- **Infratentorial ICH**
  - Risk of brainstem compression, herniation syndromes, hydrocephalus
  - Procedures – EVD / posterior fossa decompression / haematoma evacuation
- **Supratentorial ICH – procedures**
  - Early haematoma evacuation in the stable patient
  - Haematoma evacuation in the deteriorating patient
  - External ventricular drainage for hydrocephalus
  - External ventricular drainage and clot lysis?

Early haematoma evacuation in the stable patient

A

	Surgery	Control	Peto odds ratio (95% CI)
McKissock, et al[15] (1961)	71/89	60/91	2·00 (1·04–3·86)
Auer, et al[11] (1989)	28/50	37/50	0·46 (0·20–1·04)
Juvela, et al[14] (1989)	25/26	21/26	4·39 (0·81–23·65)
Batjer, et al[12] (1990)	6/8	11/13	0·55 (0·06–4·93)
Chen, et al[19] (1992)	40/64	31/62	1·66 (0·82–3·34)
Morgenstern, et al[16] (1998)	9/15	11/16	0·69 (0·16–2·94)
Zuccarello, et al[17] (1999)	4/9	7/11	0·48 (0·09–2·69)
Chen, et al[13] (2001)	86/263	97/230	0·67 (0·46–0·96)
Teernstra, et al[18] (2001)	33/36	29/33	1·51 (0·32–7·12)
Hosseini, et al[32] (2003)	0/1	0/1	Not estimable
Hattori, et al[33] (2004)	60/121	82/121	0·47 (0·28–0·79)
Mendelow, et al[20] (2005)	346/468	378/496	0·89 (0·66–1·19)
Pantazis, et al[34] (2006)	36/54	49/54	0·24 (0·10–0·60)
Wang, et al[35] (2009)	87/194	120/181	0·42 (0·28–0·63)
Mendelow, et al (2013)	174/297	178/286	0·86 (0·62–1·20)
Total (95% CI)	**1695**	**1671**	**0·74 (0·64–0·86)**



Total events: 1005 (surgery), 1111 (control)

Test for heterogeneity: χ^2=39·29, df=13 (p=0·0002), I^2=66·9%

Test for overall effect: Z=4·00 (p<0·0001)

Minimally invasive surgery

Mendelow et al. (2013) *Lancet* 382:397–408

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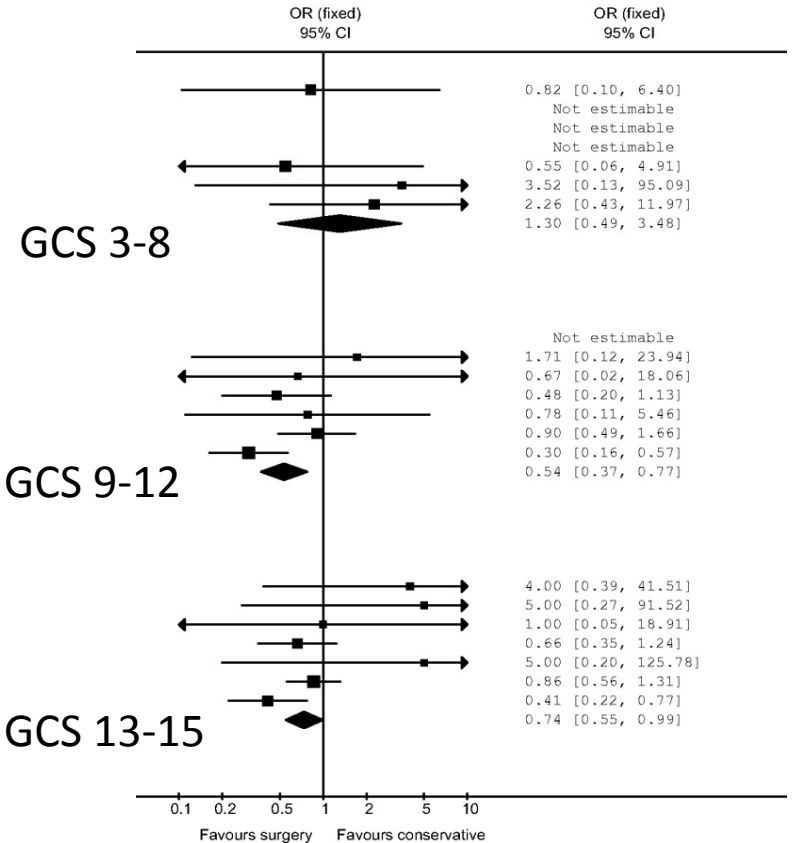
Early haematoma evacuation

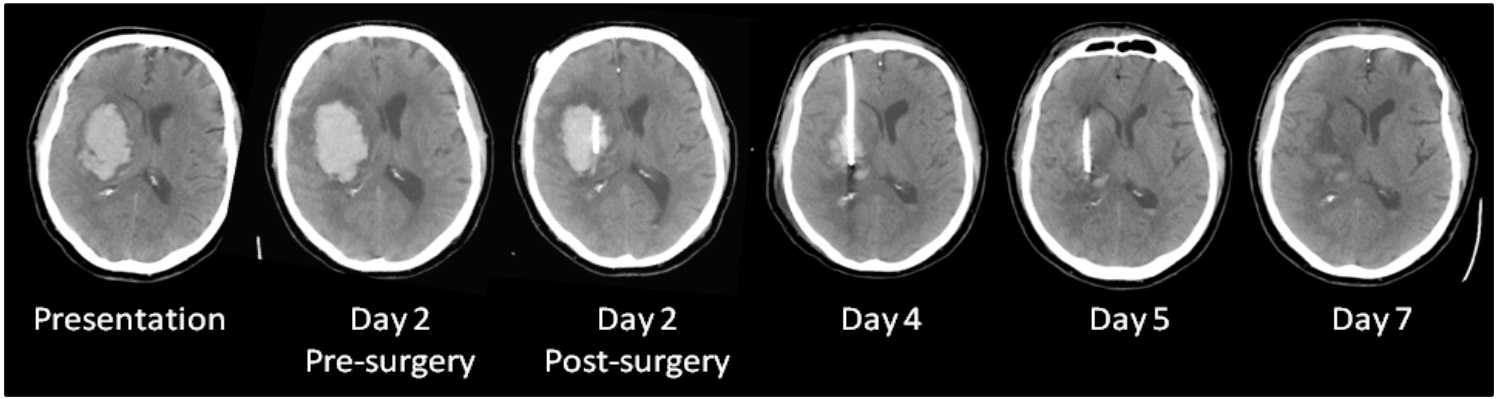
- IPD meta-analysis – 2186 cases
- Overall benefit in cases:
  - Onset to randomisation < 8h
  - Age 50-70
  - GCS 9-12
  - ICH volume 20-50 ml



Gregson et al. (2012) *Stroke* 43: 1496-1504

MISTIE III: MIS and tPA for ICH

- Catheter *in situ* from 1-2 days post onset, for 3-6 days
- tPA administered in to haematoma via catheter every 8 h
- **Phase II trial**:
  - 96 patients (54 surgery, 42 conservative)
  - 180d mRS ≤ 3: 21% cons vs. 33% MIS (adjusted for p=0.049)



Hanley et al. (2016) *Lancet Neurol; 15: 1228-37*

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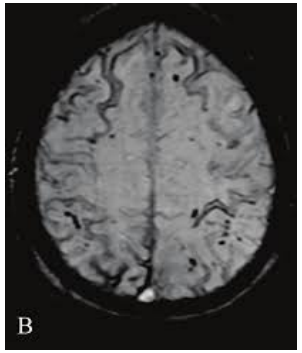
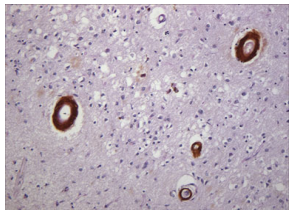
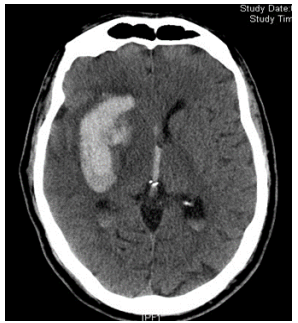
Aetiology of ICH

STRUCTURAL

- **Hypertensive microangiopathy**
- **Cerebral amyloid angiopathy**
- **Neoplasm (primary/ metastasis)**
- **Haemorrhagic transformation of cerebral infarction**
- Intracranial vascular malformation
- Intracranial arterial aneurysm
- Intracranial venous thrombosis
- Dural arteriovenous fistula
- Septic arteritis / vasculitis







HAEMOSTATIC/ HAEMODYNAMIC

- **Hypertension**
- **Anticoagulation**
- **Thrombolytic treatment**
- Antiplatelets
- Clotting factor deficiency
- Thrombocytopaenia

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Further investigation

- **Aim:** Identify causes needing specific treatment
  1. Vascular malformations – surgery / endovascular / radiosurgery
  2. Tumours – surgery / radiotherapy / chemotherapy
  3. CVST – anticoagulation
  4. Endocarditis - antibiotics
- **Options:**
  - CT angiography – readily available at most centres
  - MRI/MRA – detailed assessment of brain parenchyma, evidence for CAA (microbleeds, siderosis, enlarged PVS)
  - Catheter angiography - high sensitivity for vascular malformations, but risk of complications

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The acute management of intracerebral haemorrhage part 2

Hyperacute management: how to do it?

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Acute Bundle of Care for ICH (ABC-ICH) project

Design: Single centre quality improvement project and evaluation

Site: Salford Royal Hospital, Greater Manchester, UK

Aim: 10 percentage point reduction in 30-day case fatality after admission with acute ICH by the end of 2016.

Methods:

- Model for Improvement used to conduct QI project
- Improvement phase: June 2015 – June 2016
- Data entered in QI registry from Jun 2013 – Jan 2017
- All spontaneous ICH included (excluded traumatic ICH, haemorrhagic transformation)

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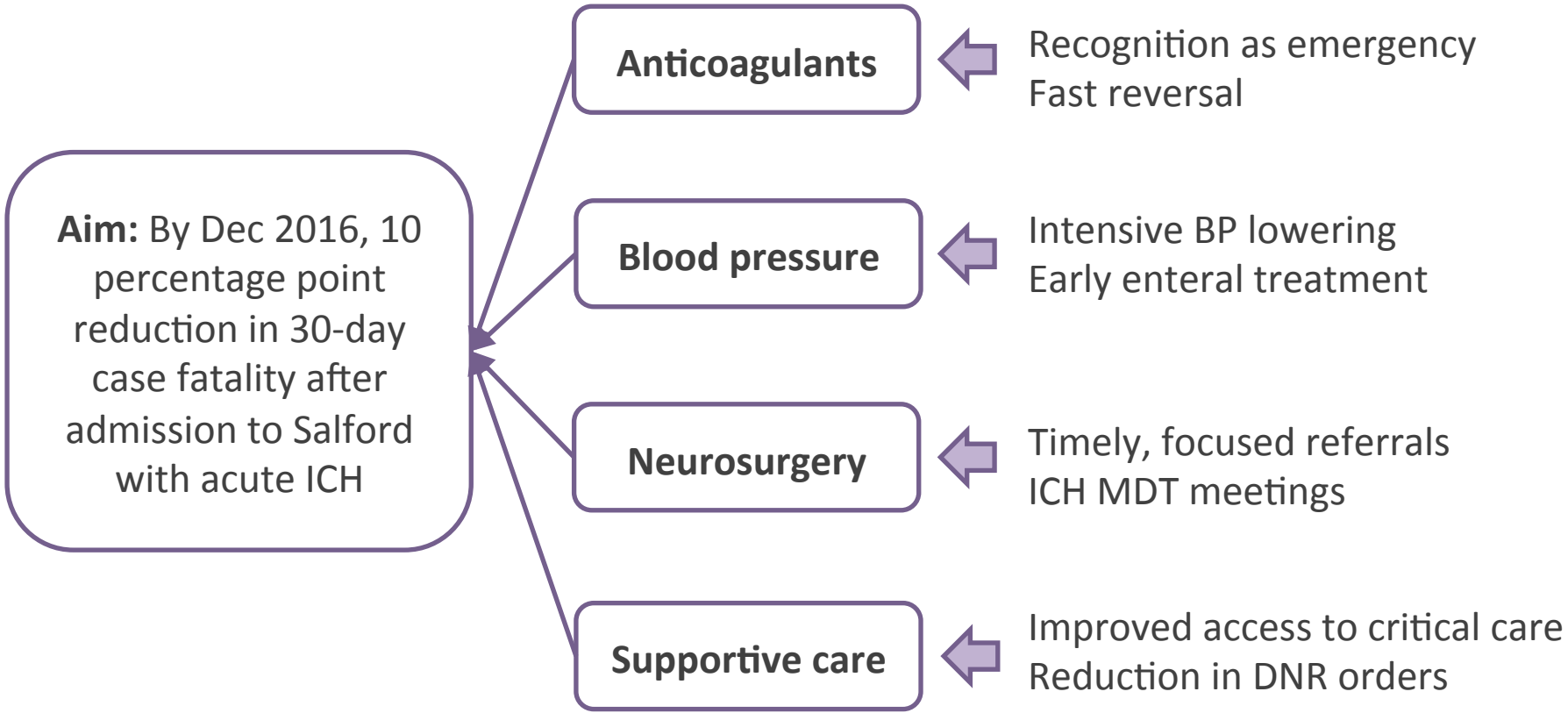
Driver diagram



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The ABC hyperacute care bundle

A. **Anticoagulant reversal:** Deliver reversal agent < 90 min from arrival
B. **Blood pressure lowering:** Deliver intensive blood pressure lowering with needle-to-target time < 60 min
C. **Care pathway:** Refer patients with good pre-morbid function (mRS ≤ 2) and any of the following to Neurosurgery:
    - GCS < 9
    - Posterior fossa ICH
    - Obstructed 3rd/4th ventricle
    - Haematoma volume > 30 ml

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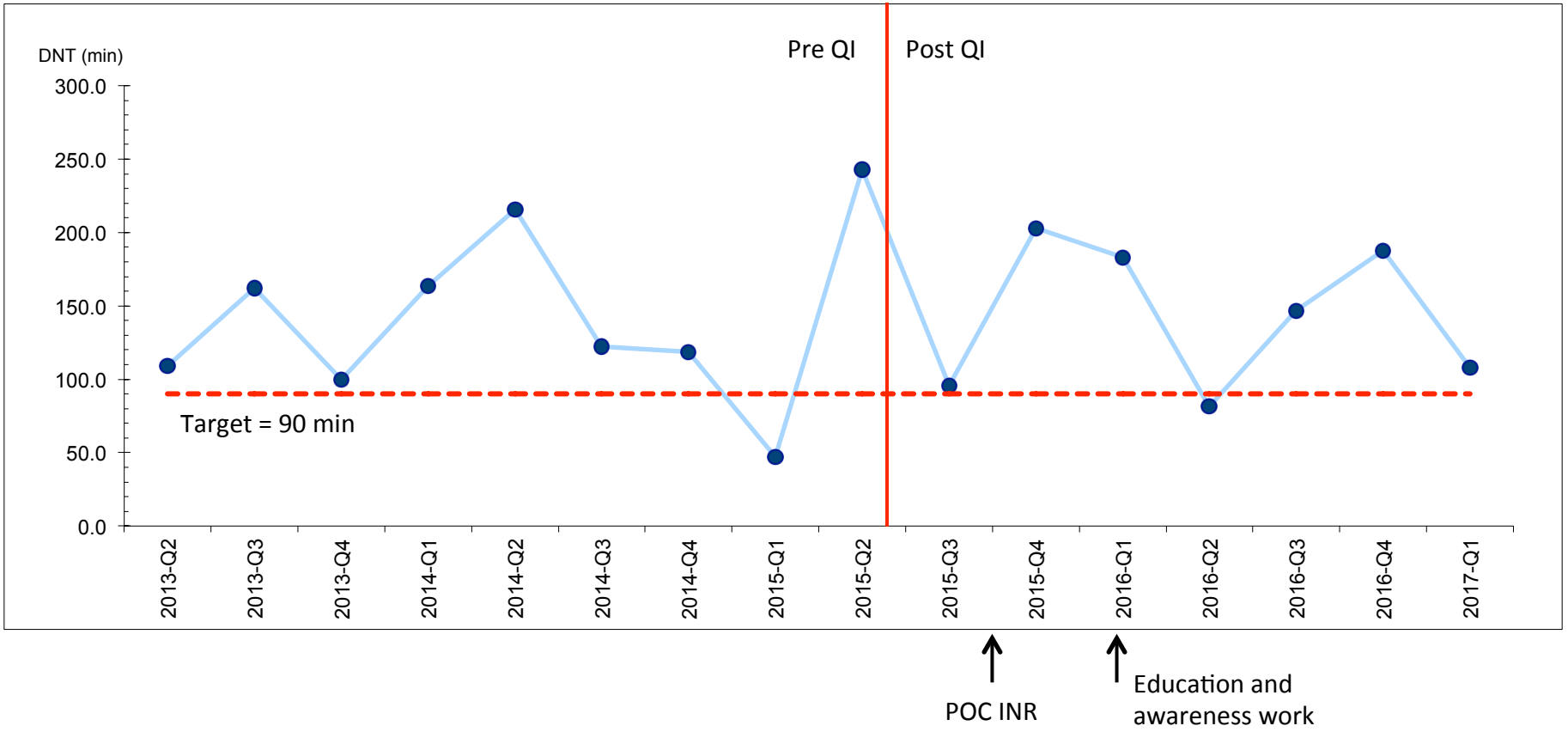
Anticoagulant reversal – DNT by quarter



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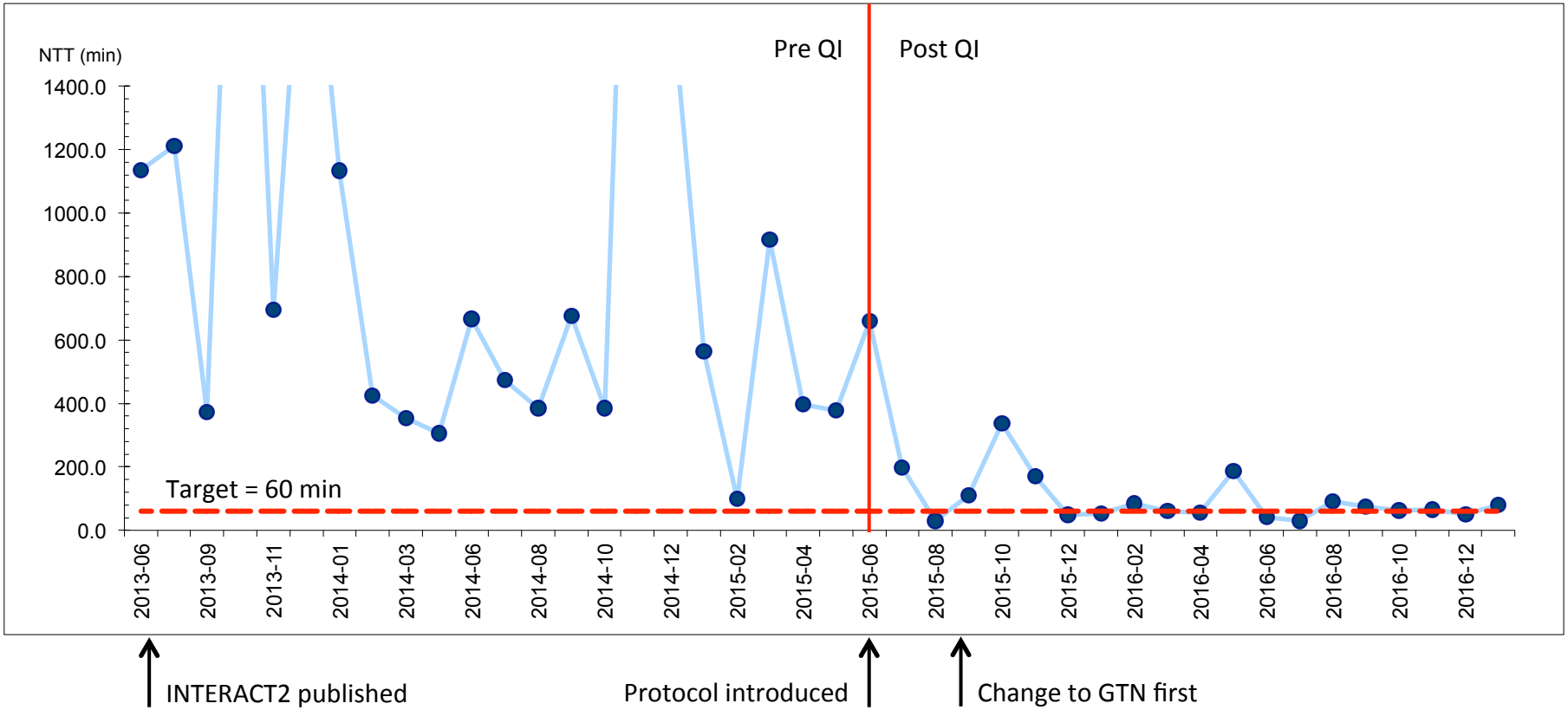
Intensive BP lowering – NTT by month



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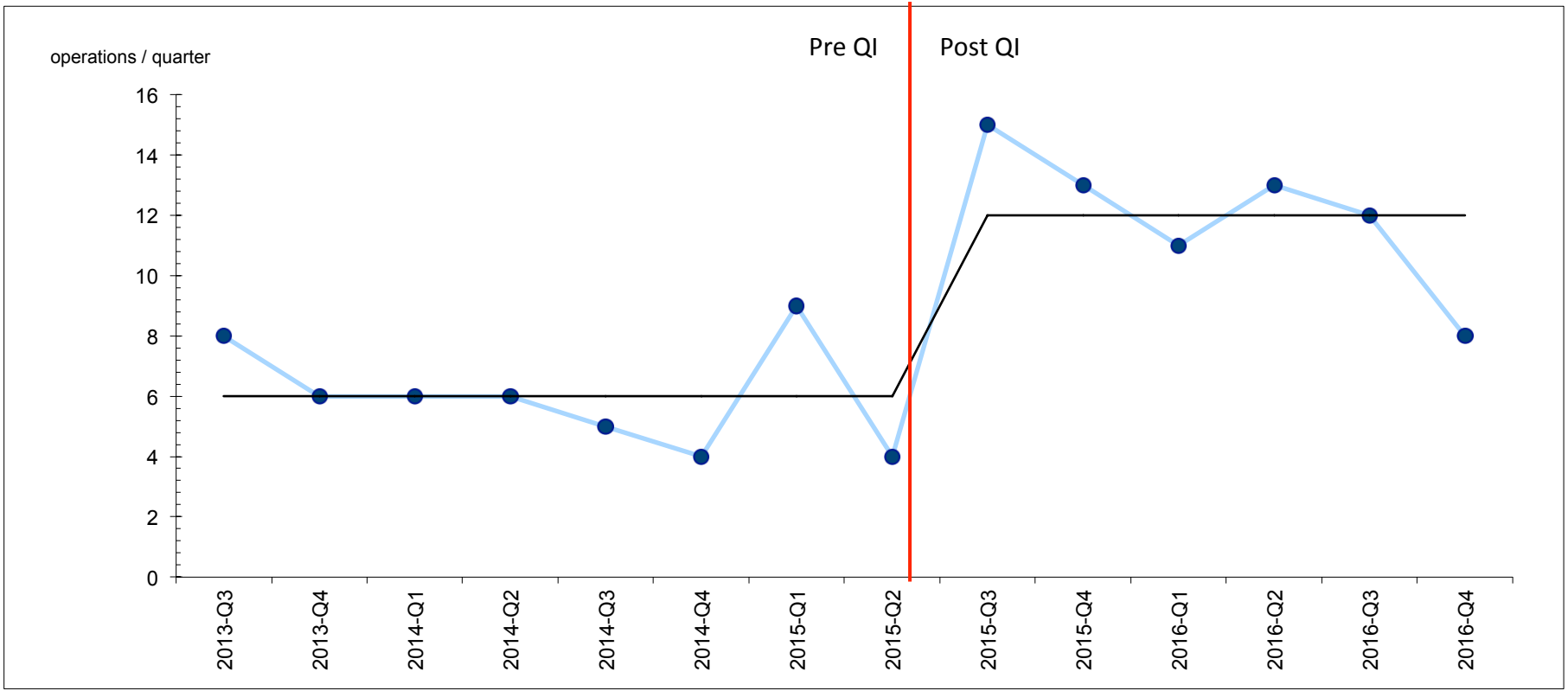
Neurosurgery - operations per quarter



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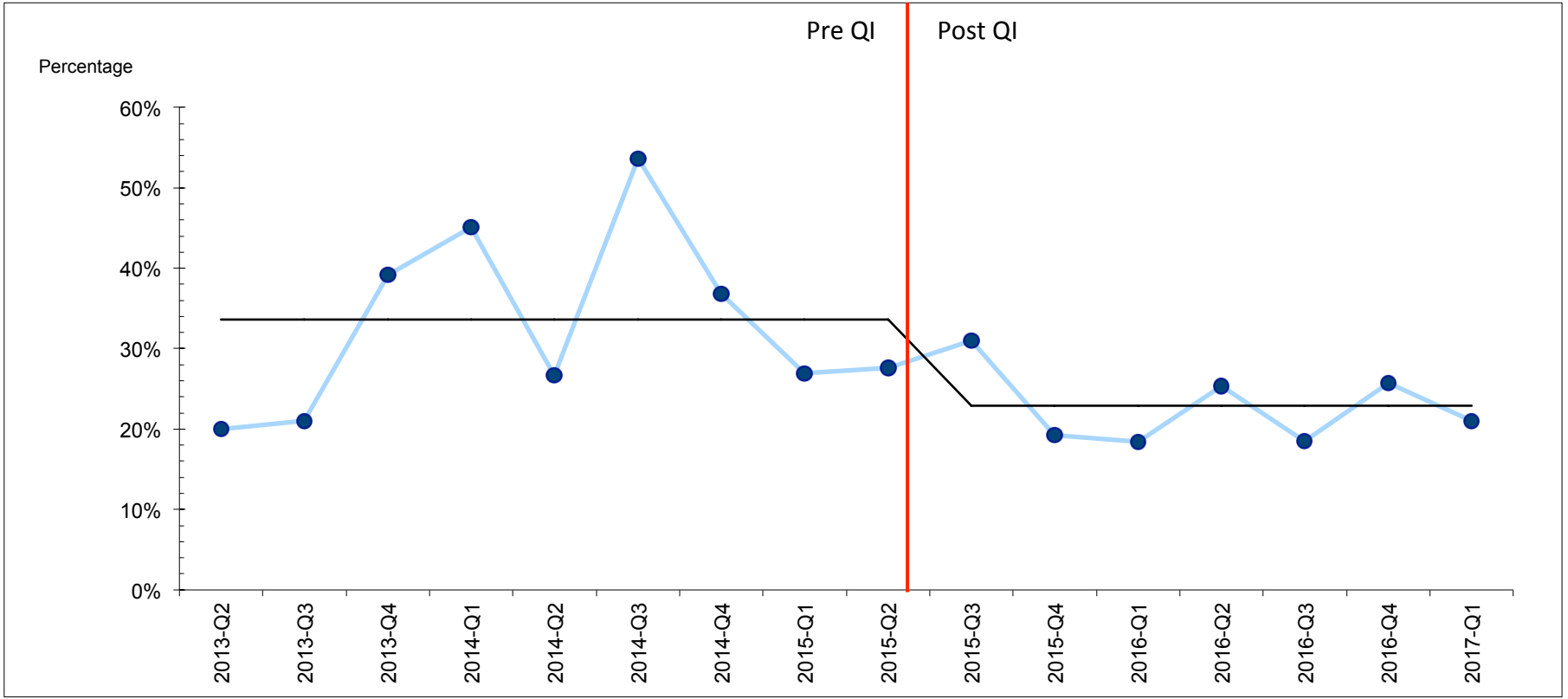
DNR order by < 24 h - % by quarter



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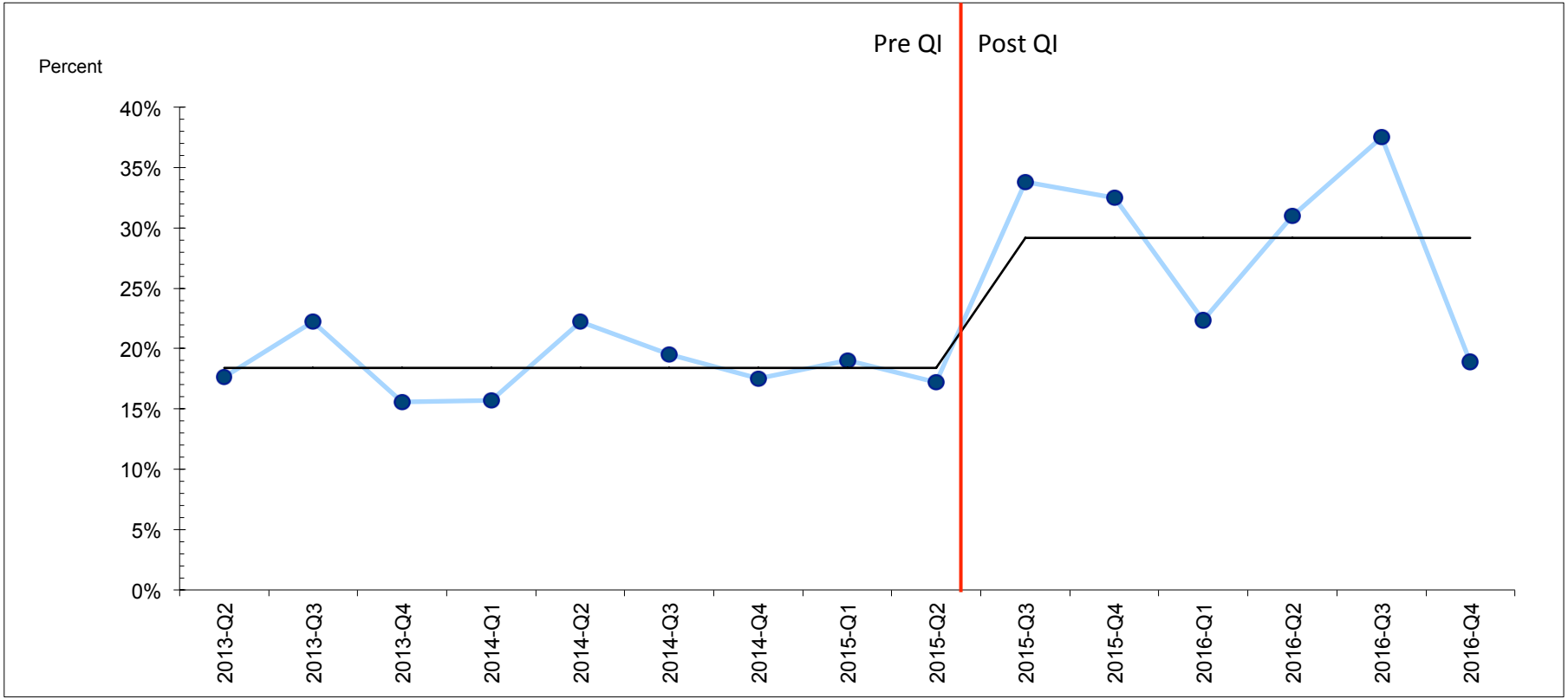
Critical care admissions - % by quarter



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Baseline characteristics

Factor	Pre QI (n=381)	Post QI (n=449)	p
Age	71.8 (57.0 – 81.2)	70.6 (56.8 – 80.3)	0.96
Premorbid mRS (0-2)	305 (80.1%)	370 (82.4%)	0.42
Anticoagulant	55 (14.4%)	57 (12.7%)	0.48
Sex (female)	199 (52.2%)	232 (51.7%)	0.89
GCS	14 (10-15)	14 (11-15)	0.94
Infratentorial	45 (11.8%)	55 (12.2%)	0.92
IVH	147 (38.7%)	168 (37.4%)	0.72
ICH volume (ml)	19.0 (6.4 – 51.7)	17.1 (5.1 – 44.8)	0.18

Pre QI: Jun 2013 – May 2015; post QI: Jun 2015 – Jan 2017. Excluded 39 cases not under stroke or neurosurgery (14 pre, 25 post)

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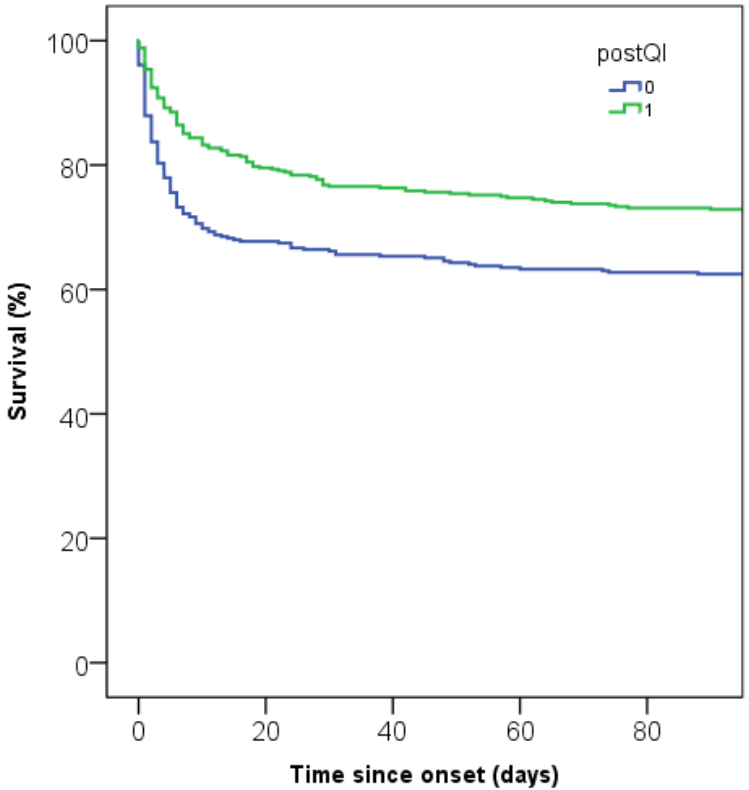
Kaplan-Meier analysis



Pre-QI project commencement:

- Jul 2013 – May 2015
- 381 cases admitted
- 30-day case fatality = 33.9%

Post-QI project commencement:

- Jun 2015 – Jul 2016
- 449 cases admitted
- 30-day case fatality = 23.4%

Logrank test: **p=0.001**

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Cox regression analysis

Factor	HR	95% CI	Sig.
GCS	0.87	0.84 to 0.89	<0.0001
Anticoagulant	1.38	1.06 to 1.81	0.018
Infratentorial	1.78	1.32 to 2.39	<0.0001
IVH	1.38	1.11 to 1.73	0.05
ICH vol	1.007	1.005 to 1.009	<0.0001
Age	1.053	1.043 to 1.063	<0.0001
Post QI	**0.67**	**0.54 to 0.84**	**<0.0001**
Post QI (unadj)	0.69	0.55 to 0.86	0.001

ABC-ICH: GM scale-up

Aim: A 10% reduction in death and severe disability (mRS 4-6) after acute ICH by April 2018 in Greater Manchester

Implementation:

- Launch bundle at Stepping Hill and Fairfield from Apr 2017
- Greater Manchester care pathway introduced April 2017

Measurement:

- App/EPR tools for acute team linked to dashboard of key measures
- Collection of mRS (disability scale) at 6 monthd

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Greater Manchester ICH care pathway

GCS ≤ 8

1. Stabilise
2. Reverse anticoagulation
3. Refer to neurosurgery if mRS < 3
4. Discuss with HASU (if not accepted by NS)

GCS ≥ 9

1. Reverse anticoagulation
2. Blood pressure lowering (at HASU only)
3. Refer to neurosurgery if mRS < 3 and:
   - Post fossa, *or*
   - Obstructed 3rd/4th ventricle, *or*
   - Haematoma volume > 30 ml, *or*
   - GCS 9-12
4. Transfer to HASU if < 48 h post-onset

http://gmsodn.org.uk – Intracerebral Haemorrhage Pathway section

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CONNECTED HEALTH CITIES
A nhsa project

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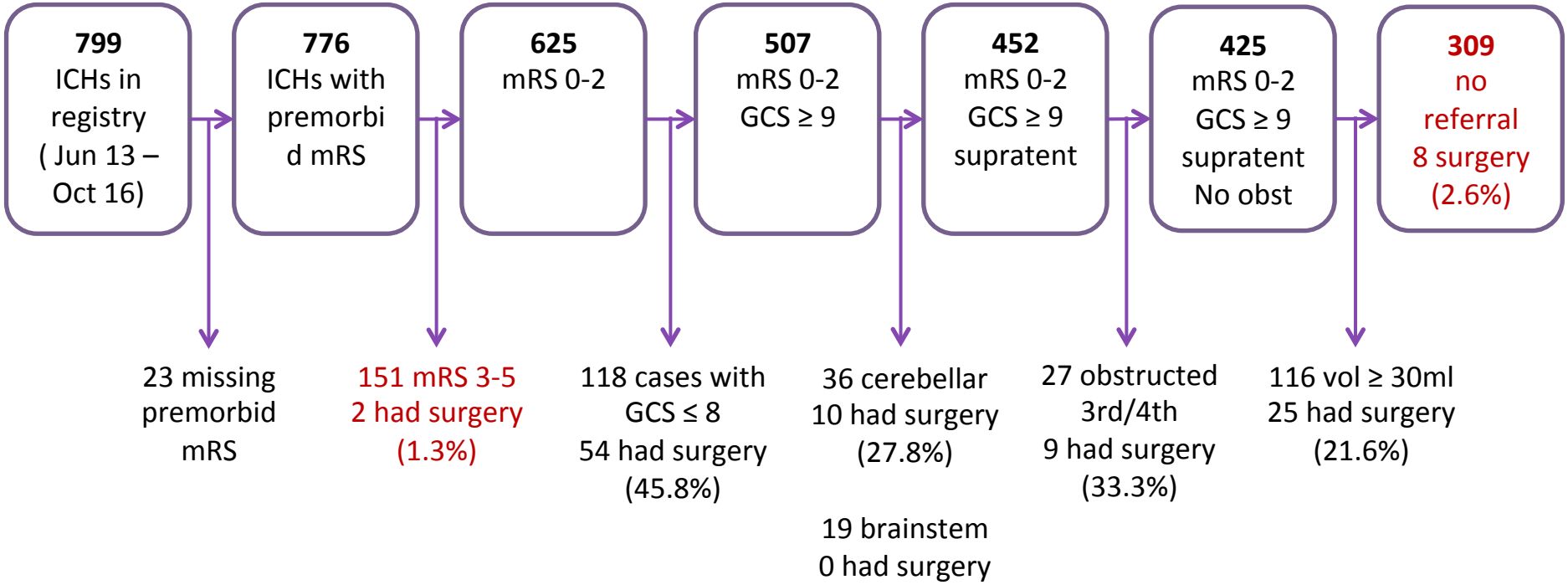
Neurosurgical criteria – retrospective analysis



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Operations not meeting criteria

mRS ≥ 3 (2 cases, 0.3% of all cases)

- mRS 3, 78, obstructive hydrocephalus, R cerebellar, EVD at day 2, died day 6
- mRS 4, 51, learning difficulties, obstructive hydrocephalus, EVD, died day 10

mRS 0-2, no indication (0.6% of all cases)

- 1 case with surgery in first 7 days due to HE
- 2 surgery > 1 week later for delayed hydrocephalus
- 2 for biopsy of lesion semi-electively
- 3 in MISTIE