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Research Paper

Synthetic certainization in medical controversy: Evidence synthesis, NICE recommendations and the drug-device complex in stroke prevention

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The National Institute for Health and Care Excellence (NICE) recommends rivaroxaban for stroke prevention in patients with non-valvular atrial fibrillation in England. While not a directive to practitioners, that advice is widely regarded as authoritative and intended to guide practice. Yet a medical device, INRatio2-PT for monitoring coagulation/blood-clotting and producing crucial data on rivaroxaban in its key clinical trial, was defective. Following discovery of the defective device, a medical controversy about the therapeutic value of rivaroxaban ensued. Drawing on social science theories of medical controversies, such as 'chronic contestation', 'closure', 'corporate bias', and 'countervailing powers', this article describes the unfolding of the INRatio2-PT/rivaroxaban controversy and seeks to explain it. We explore the role of key protagonists based on documentary and interview data. Our findings about the media partly support 'countervailing powers' theory, while those regarding industry and regulators support 'corporate bias' theory. We found little evidence of chronic contestation of medical knowledge-claims. Rather, we contend that a sociological process of closure through synthetic certainization of knowledge-claims that rivaroxaban is efficacious and cost-effective evolved via the combined political power and interests of the medical-industrial complex, capitalist industry, and the regulatory state. Synthetic certainization, together with a regulatory ideological commitment to innovation, curtailed contestation and discouraged the medical profession from facing troubling uncertainties.

Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia, affecting 60 million people worldwide, 1.5 million patients in the UK and 10.5 million in the USA (Mahase 2023, Mbroh et al. 2025, McNulty 2024). It is associated with a five-fold increased risk of blood clots within the heart and stroke, if clots formed in the heart become detached and obstruct blood-flow to the brain - thromboembolism (Stroke Association 2024). AF and stroke-risk reduction treatment, are, therefore, significant public health phenomena. Some patients with AF have heart-valve disease, but over 70% have non-valvular AF (Molteni et al. 2014).

Anti-coagulants reduce stroke risk in AF patients by inhibiting blood-clotting. This is a delicate balance because excessive anticoagulation could cause fatal bleeding. Warfarin, the first oral anticoagulant (in clinical use since 1954), has a narrow therapeutic window (safest, most-effective dose range); hence doctors need to establish correct dosage by monitoring patients' clotting characteristics (Hogarth & Martin 2021). Monitoring devices (coagulometers) were developed for use in clinics and GP surgeries, or by patients themselves, for more precise dosage monitoring/adjustment (Harris et al. 2013). From the 2000s, new oral anti-coagulants (NOACs) entered the market as alternatives to warfarin which, according to their manufacturers, were more convenient, cost-saving innovations that could be administered as fixed oral doses without monitoring or dose adjustments (AstraZeneca 2003, Boehringer Ingelheim 2009). The global market for NOACs is now worth over US$12 billion (Boehringer Ingelheim 2025, Daiichi-Sankyo 2024, Johnson & Johnson 2025, Pfizer 2024).

One NOAC, rivaroxaban, was jointly developed by pharmaceutical companies Bayer and Janssen, the latter a subsidiary of Johnson & Johnson (J&J), and approved into the UK market as safe and efficacious for stroke-risk reduction treatment of non-valvular AF by the EU drug regulatory authority, the European Medicines Agency (EMA) in September 2011, and into the US market by the American drug regulatory agency, the Food and Drug Administration (FDA) in November 2011 (Davis 2012). The EMA evaluation was endorsed by the British drug-product regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA). In May 2012, England's cost-effectiveness regulator, the National Instititute for Health and Care Excellence (NICE)[1] recommended that rivaroxaban should be prescribed on the NHS for stroke-risk reduction in non-valvular AF, despite being over 20 times more expensive than warfarin (NICE 2012). Huge commercial interests were at stake. By 2018, global sales of rivaroxaban reached US$6 billion: US$3.6 billion for Bayer and US$2.47 billion for J&J (Sandberg 2019).

Crucial evidence for the safety, efficacy, and cost-effectiveness of rivaroxaban came from a large, randomized controlled trial known as ROCKET-AF (14,000 non-valvular AF patients across 45 countries), sponsored by J&J/Bayer. During the trial, which compared warfarin with rivaroxaban between December 2006 and June 2009, patients taking warfarin were monitored with a coagulometer known as INRatio2-PT. However, in December 2014, Alere, the manufacturer of INRatio2-PT declared that the coagulometer was defective. In July 2016, INRatio2-PT was withdrawn worldwide for generating inaccurate results (Stovall 2015, Sutter 2016). Use of the defective coagulometer in ROCKET-AF raised the possibility that falsely-low results caused over-anticoagulation with warfarin, potentially increasing stroke rate through haemorrhage compared with rivaroxaban, which could have made rivaroxaban appear more effective (and safer) than it really was. A major medical controversy ensued, involving the medical device and pharmaceutical industries, the medical profession, investigative journalists, government regulatory agencies, organized patients and the courts, about whether rivaroxaban was efficacious, cost-effective or even safe.

This article subjects that controversy to social scientific analysis, revealing the politics underlying currently prevailing 'technical certainties' advanced by NICE about stroke-risk reduction treatment of non-valvular AF. While NICE is frequently subjected to political pressures from external stakeholders, our case-study of medical controversy and evidence production seeks to deepen understanding of how such processes play out, thereby facilitating improvements to regulatory policy that will serve public health. The authority of NICE means its endorsements are often interpreted by doctors, patients and the mass media as certified knowledge accomplished by techno-scientific calculations. Our case-study of the

[1] In 1999, NICE was ostensibly established to advance NHS and public health interests by ensuring that new health technologies recommended in the NHS were good value for money (Abraham & Balendran 2025).

INRatio2-PT/rivaroxaban controversy shows how socio-economic and political interests underpin NICE's guidance development and recommendations in ways not routinely appreciated.[2]

Bertotti and Miner (2019) have shown how gynaecology textbooks reinforce certainty around 'pharma-contraceptive safety' (intrauterine and hormonal methods) by transforming benefits and lack of risks into 'non-contentious facts'. Relatedly, we show how the INRatio2-PT/rivaroxaban controversy was closed down, enabling the manufacturers and NICE to continue asserting the cost-effectiveness of rivaroxaban for NHS prescription. We refer to this as 'synthetic certainization' – a sociological process in which knowledge-claims are produced giving the impression of greater medico-scientific certainty than really exists. Furthermore, we demonstrate that such synthetic certainization was not technically inevitable, and involved political trajectories favouring some interests and ideologies over alternative pathways to medical knowledge more consistent with public health.

Theoretical Context

Debate in critical public health about the complexity of drug trials has focused on how trial evidence may be derived from interactional contexts of the trial participants, such as adequacy of consent, colonialism of recruitment, and social inequalities undermining trust (Kingori 2015, McLaren et al. 2025, Shoveller et al. 2016). Our case-study adds a new dimension by directing attention to the complex interaction between trial technologies, namely, the 'drug-device complex'.[3] Social scientists typically research medical devices and pharmaceuticals separately because these industries are distinct, with discrete regulatory systems (Abraham 1995, Faulkner 2009). Neglect of the drug-device complex is illustrated by the fact that coagulometers used in pharmaceutical clinical trials are typically not even named in publications of trial results (Cohen 2016). There have been case-studies of pharmaceuticals and/or medical devices in isolation or parallel (Hogarth et al. 2022, Maggetti et al. 2017, Ross et al. 2015, Wall & Brown 2010). Here we present the first social science analysis of a controversy derived from *embedded interaction* between a pharmaceutical and medical device.

Like Brante and Elzinga (1990) in their theory of scientific controversies, our methodology details the emergence, envelopment and closure of controversy, together with analysis of the social interests/determinants behind controversy and its political consequences (particularly for public health). Early social science models of *medical* controversies focused on the medical profession, neglecting other political forces and 'black-boxed' processes of knowledge-production within medical innovation (Freidson 1970, Larson 1977, McKinlay 1981). Case-studies of pharmaceutical controversies expanded that narrative. To explain regulatory outcomes as well as processes, Abraham's 'corporate bias' theory emphasized how the interests of the pharmaceutical industry and government regulatory agencies relate to the medical-industrial complex, and to bias in who gets 'the benefit of the scientific doubt' in medical knowledge-production (Abraham 1994). Gabe and Bury (1996) conceptualized drug controversies as indicative of a wider cultural dynamic involving a fragmentation of medical dominance, so that expert knowledge becomes 'chronically contestable'. This may be contrasted with the emphasis of Brante and Elzinga (1990) on how controversies reach closure**.**

Gabe et al. (2012) applied a 'countervailing powers' framework to argue that the media and elements of the regulatory state, such as New Zealand's pharmaceutical regulatory agency (PHARMAC),

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[2] NICE produces recommendations subject to revision, rather than generating new knowledge directly from original research. However, sociologically, we regard the recommendations produced from their evidence synthesis of research findings as a form of knowledge/knowledge-claims.

[3] This sociological concept differs from the technical category of 'combination products' like nicotine patches, syringes ready-primed with drug contents, or contraceptive implants.

challenge promotional claims of the pharmaceutical industry and its experts. At an elementary level, the countervailing powers framework, which 'instructs researchers through the process of identifying the domain, the major actors, and the relations between them', has been used to explain expansion of medicines use, though other approaches pre-date/share that research process (Abraham 1995, Abraham 2010, Busfield 2010, Light 2010, p. 271). The *distinctive* features of the countervailing powers framework become evident when the medical profession is conceptualized as a countervailing power *against* markets/bureaucracy (Light 1991, 2010) or when 'the media' and parts of the regulatory state are conceptualized as countervailing powers *against* the interests of the pharmaceutical industry (Gabe et al. 2012) – the latter implying a departure from Abraham's corporate bias theory, which emphasizes the extent to which the regulatory state prioritizes the interests of the pharmaceutical industry over other interests. The countervailing powers framework says little about knowledge controversies or certainization, though Gabe et al.'s (2012) application of it to Herceptin in New Zealand addresses knowledge controversy in terms of the alignments of the social forces involved.

Discussion of clinical trial evidence in critical public health has often challenged its external validity - how well the knowledge produced can be generalized beyond the trial context (McLaren et al. 2025, Rosengarten & Savransky 2019, Woolcock 2013). This leaves unattended matters of *internal* validity – the coherence/reliability of the knowledge-claims pertaining to the trial context itself – which can proliferate into wider contextual issues such as informed prescribing/consent-to-use. Here we shed additional light on the public health implications of pharmaceutical trials' internal validity by exploring how the INRatio2-PT/rivaroxaban controversy supports or challenges key theoretical concepts, particularly closure versus chronic contestation, and corporate bias versus countervailing powers. Furthermore, we suggest a new social science concept in understanding medical controversies, namely, *synthetic certainization*, together with an *ideology of innovation*, in order to capture the empirical reality involved.

Methods

Our research was conducted between 2017 and 2023, and updated during 2024-2025. We analysed data from exhaustive documentary/archival literature, semi-structured interviews and observations at meetings relating to NICE assessment of pharmaceuticals and medical devices. Analysis is based primarily on publicly available documents; eighteen interviews were conducted for elaboration when necessary.

Systematic review of relevant social science, medical, legal and pharmaceutical literature was undertaken, including legal files from large, patient 'class-action' court cases in the US, pharmaceutical trade-press periodicals, including annual reports of relevant pharmaceutical/medical-device firms, *Scrip:World-Pharmaceutical-News* and *Pink Sheet*. Key search terms were 'Alere', 'cost-effectiveness', 'efficacy', 'EMA', 'FDA', 'INRatio', 'NICE', and 'rivaroxaban'. This was combined with comprehensive analyses of websites of NICE, EMA and FDA; appropriate NICE Evidence Review Group reports; and EMA and FDA regulatory reviews about rivaroxaban and INRatio2-PT.

Interviewees were 'informants' selected for expert knowledge about NOACs, and/or involvement in pharmaceutical regulation/cost-effectiveness regulation (Abraham & Lewis 2000). Some interviewees requested anonymity when subjected to secrecy laws/gagging clauses claiming to protect commercial interests; others are named with consent. All interviews were completed with informed consent and approval from the Research Ethics Office, King's College London (Research Ethics Number MR/15/16-14), audio-recorded and transcribed; then analysed in line with research objectives. Relevant multi-stakeholder meetings were also observed, including NICE fora, annual conferences and workshops, with field-notes thematically coded and analysed.

Emergence: Coagulometry, Alere, and NICE approval of INRatio2-PT

At least 7 million people take anticoagulants worldwide, including 2.5 million on oral anticoagulants in the UK (Faulkner 2009, Orlowski at al. 2021). Coagulometers can help doctors prescribe the appropriate dosage for patients on warfarin. An internationally standardized measurement of coagulation, the International Normalized Ratio (INR), is the ratio of the patient's blood-clotting time to that of a normal sample. In AF patients, INR<2 is generally associated with increased risk of clotting and thromboembolism due to clotting, while INR>4 increases risk of major bleeding (Faulkner 2009). Coagulometry was initially based in laboratories; industrial innovation produced mobile/hand-held devices, known as 'point-of-care' devices, transportable to primary-care settings, including clinical trial sites. Promissory reports of coagulometer innovation led to adoption and routinization of such devices in the global market, estimated at US$1.98 billion in 2024 (Verified Market Research 2026).

To be reliable, 'point-of-care' coagulometers must produce accurate readings aligned with established laboratory measures. INRatio2-PT was initially developed by the biotechnology firm, HemoSense, and cleared for the US market by FDA in 2002 (FDA 2002, Meier 2011, Zuckerman et al. 2011). FDA issued two warning letters regarding INRatio2-PT in 2005-2006 because investigators found evidence that INR readings from INRatio2-PT were significantly different from hospital laboratory readings (FDA 2005, FDA 2006). In 2007, HemoSense was acquired by Inverness, which changed its name to Alere in 2010 (FDA 2016).

In September 2014, NICE developed diagnostic guidance DG14 recommending INRatio2-PT as a clinically effective and cost-effective device for self-monitoring coagulation status (INR) by patients taking warfarin. INRatio2-PT was cheaper than alternative coagulometers. Specifically, NICE concluded that 'the evidence indicates that the precision and accuracy of [the INRatio2-PT] monitors are comparable to laboratory-based INR testing' (NICE 2014a). NICE guidance CG180 also promoted INRatio2-PT for self-monitoring by patients taking warfarin for stroke prevention (NICE 2014b, NICE 2014c). However, deeper analysis of NICE's guidance reveals the precarious nature of its knowledge-base:

> ….no direct evidence of clinical effectiveness was identified exclusively for the INRatio2-PT monitor from the systematic review (NICE 2014a, p.24, NICE 2018, p. 25)

Envelopment: The Medical-Industrial Complex and the Drug-Device Controversy

Less than three months after NICE published DG14 recommending INRatio2-PT to the NHS, in December 2014, Alere declared a 'Class I recall' of INRatio2-PT, which implied 'a reasonable probability' that its use could 'cause serious adverse health consequences or death' (FDA 2014a, p.1). This recall was based on post-marketing information that, in patients with particular medical conditions such as anaemia or elevated levels of fibrinogen, INR results reported by INRatio2-PT were lower than contemporaneous results from a laboratory device (FDA 2016). Alere received 18,924 reports of malfunctions during 2013-2014, including three associated deaths (FDA 2014b). Initially, the device remained on the market with a labelling change, but in July 2016, Alere withdrew INRatio2-PT from the market and discontinued manufacturing it, after becoming aware of 'the potential, in certain cases, of the Alere INRatio system to provide an INR result that was significantly lower than a result obtained using a laboratory INR system' (Alere 2016).

In September 2015, nine months after Alere's recall, Janssen informed FDA that the defective INRatio2-PT device had been used to monitor INR and adjust warfarin doses at all study sites in the

ROCKET-AF comparative trial of rivaroxaban and warfarin. By this time, rivaroxaban had already been marketed/used routinely for about three years. While the trial was sponsored by J&J/Janssen and Bayer, data management was co-ordinated by Duke University Clinical Research Institute (DCRI) (Patel et al. 2011). In ROCKET-AF, INR measurements were to be made at least every four weeks and sites were instructed to use only INRatio2-PT to adjust warfarin doses. Blood samples were also taken from most patients at weeks 12 and 24 for testing with a standardised laboratory-based device at Duke University (FDA 2016).

In October 2015, Janssen informed the Executive Committee for ROCKET-AF about the recall. The Executive Committee was not independent of the commercial interests of the trial-sponsors because its 11-person membership included one member from J&J and one from Bayer, as well as three from Duke University (see Patel et al. 2011, Supplementary Appendix). In response to the recall notification, DCRI researchers performed post-hoc subgroup analyses of data from ROCKET-AF to investigate the alleged malfunctioning of INRatio2-PT on behalf of the Executive Committee (Patel et al. 2016a). Industry influence on this re-analysis is not clear. According to *The New York Times*, J&J stated that their employee on the Executive Committee 'recused himself from the conduct of the re-analysis, the drafting of the research letter, and provided no feedback before it was submitted', but 'Bayer declined to comment' (Thomas 2016, p.3). Moreover, Patel, main author of the re-analysis published in *The New England Journal of Medicine* (*NEJM*), was reported as stating that 'the *entire* [emphasis added] executive committee and team on the letter helped revise and work on the response' (Cohen 2016, pp. 3-4). Logically, that included the Bayer and J&J representatives.

Whatever influence the drug manufacturers might have had, the DCRI re-analysis was certainly *consistent* with their commercial interests. It assumed that inaccurate INRatio2-PT measurements in ROCKET-AF were limited to patients with recall-related medical conditions (anaemia and elevated fibrinogen levels) and focused on identifying trial patients with and without those conditions in order to compare efficacy and safety outcomes between rivaroxaban and warfarin within those subgroups. In February 2016, DCRI researchers published their conclusions in *NEJM*:

> These results are consistent with the overall trial findings and indicate that possible malfunction of the point-of-care device used for INR measurement in the ROCKET-AF trial that potentially led to lower INR values than would be obtained by laboratory testing did not have any significant clinical effect on the primary efficacy and safety outcomes in the trial (Patel et al. 2016a, p.787).

However, this analysis was soon challenged by Robert Powell, former Director of Pharmacometrics at the FDA Office of Clinical Pharmacology. Drawing on an assessment report by the EMA (2016a), in July 2016 Powell published a letter in *NEJM* refuting the assumption that discrepant readings by INRatio2-PT in ROCKET-AF were confined to recall-related medical conditions (Powell 2016).[4] The Executive Committee for ROCKET-AF and its researchers from Duke University also faced criticism for being insufficiently forthcoming in using laboratory INR measurements for comparison with INRatio2-PT readings - a better way to evaluate the malfunctioning of INRatio2-PT, than assuming that lower point-of-care INR values were limited to recall-related conditions (Gardner 2016). In an interview with us, Powell concluded: '[T]he reality is that with the error from this device, you can't completely identify the impact'.

In response to Powell, DRCI researchers then acknowledged that discrepancies between INRatio2-PT and laboratory INR readings were not limited to recall-related conditions. They accepted that in ROCKET-AF, INRatio2-PT was found, in most cases, to have falsely reported lower INRs than

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[4] An EMA (2016a) investigation in January 2016 found no evidence that lower INR measurements by INRatio2-PT in ROCKET-AF, compared with laboratory INR values, were influenced by anaemia/elevated fibrinogen, directly contradicting the assumption of Duke University researchers' initial analysis.

the true value, thereby inducing patients to unnecessarily increase their warfarin dose and risk of bleeding. If this led to adverse clinical events in the warfarin arm of the trial, the defective coagulometer would have biased the trial in favour of rivaroxaban. Clearly, the Duke-J&J-Bayer collaboration could have acknowledged this earlier to establish the relevant medical knowledge. Their approach in this controversy supports Abraham's (1994) theory of interest-based bias in industry-sponsored trials.

Nonetheless, DRCI researchers insisted that the results of the original trial remained robust because the defective INRatio2-PT device did not significantly affect clinical events:

> Event-rates among warfarin-treated patients with discrepant values were higher for both bleeding and [ischaemic] stroke than among those with non-discrepant values….If INR values that were potentially underestimated by the point-of-care device had led to clinical events, then higher rates of bleeding but not of [ischaemic] stroke would have been expected in the patients receiving warfarin.…These results are consistent with the originally reported overall trial results (Patel et al. 2016b, p.391).

In an interview with the *British Medical Journal (BMJ)*, Powell further disagreed with the DRCI researchers' reasoning that the defective coagulometer could not have significantly affected the clinical trial results because it was associated with both higher rates of bleeding and ischaemic strokes among warfarin patients. He claimed 'the incidence of both ischaemic stroke and bleeding increase with warfarin treatment as the INR goes above 4' (reported in Cohen 2016, p.3).

While (unnecessarily) larger doses of warfarin being prescribed in ROCKET-AF clearly increased the risk of bleeding and haemorrhagic strokes, it is not so obvious why it would lead to increased ischaemic strokes which are typically associated with excessive blood-clotting. However, some medical experts support Powell's position, arguing that extra-cranial haemorrhage (e.g. gastrointestinal bleeding) could also result in ischaemic stroke due to massive blood-loss and hypotension that deprives the brain of an adequate supply of oxygen. In interviews with us, Consultant Gastroenterologist Dr Walter Melia confirmed that profuse gastrointestinal bleeding could lead to ischaemic strokes and Consultant Cardiologist Dr Ranjadayalan explained that patients who have coronary heart disease are very sensitive to sudden drop in blood pressure that can result in ischaemic strokes. On this view, the association of *both* increased bleeding *and* increased ischaemic strokes among warfarin patients using INRatio2-PT in ROCKET-AF would be consistent with the trial being biased in favour of rivaroxaban.

Despite obvious scientific uncertainty generated by a crucial medical device of diagnostic measurement being defective throughout an entire clinical trial, there is no evidence of the medical scientists within the Duke-J&J-Bayer collaboration ever offering to conduct a second (perhaps smaller) clinical trial with a reliable coagulometer to try to confirm rivaroxaban's efficacy, even while allowing the drug to stay on the market. Confirmation of 'experimentation' is a canon of scientific method, especially if defective experimental equipment is suspected. Yet this confirmatory pathway to medical knowledge was apparently not considered by this segment of the medical-industrial complex.

Countervailing Media: *BMJ* Investigative Journalism

In 2015, the *BMJ* launched an investigation of ROCKET-AF led by medical journalist Deborah Cohen. She reported that several clinical investigators in ROCKET-AF had become concerned about the reliability of INRatio2-PT in 2007, and some Executive Committee members emailed those concerns to Janssen. The company then established a safety programme in early 2008 called COVANCE, which provided on-demand checks of point-of-care INR values with same-day laboratory INR measurements to reassure concerned trial investigators (Bayer 2016).[5] In total, trial investigators submitted 149 samples

[5] Janssen acknowledged the existence of COVANCE in court in 2016 (Cohen 2016).

to COVANCE (71 for warfarin and 78 for rivaroxaban) out of more than 366,000 point-of-care INR measurements taken in ROCKET-AF - less than 0.05% (Bayer 2016).

Cohen (2016) claimed that neither data/information about the existence of COVANCE, nor trial investigators' concerns about the accuracy of INRatio2-PT, were shared with the Data and Safety Monitoring Board during the trial or with regulatory authorities when rivaroxaban was approved for marketing but the drug manufacturer denied this (Bayer 2016). In Gabe et al. (2012)'s terms, the *BMJ* investigation acted as a countervailing power against the arguments of the manufacturers and regulators.

Internal Validity and Industry-Dependent Regulatory Closure of Uncertainty

Following the Class I recall of INRatio2-PT, the EMA, FDA and Janssen independently attempted to analyse the impact of using INRatio2-PT in ROCKET-AF. Paired measurements of same-day INR results (one point-of-care INRatio2-PT reading and one laboratory-based reading), were available at weeks 12 and 24 of the trial for about 87% of warfarin trial participants (FDA 2016). Upon EMA's request, the manufacturers submitted comparative data analysis of these paired measurements and claimed that 'the effect of potentially discrepant INR readings does not alter the conclusions of the ROCKET AF trial' (EMA 2016a, p.21).

These analyses revealed discrepancies in 38% of INRatio2-PT readings: 34% were lower than laboratory-based INR measurements and 4% were higher (EMA 2016a, p.39). The EMA then requested further analyses from the drug manufacturers on stroke and bleeding outcomes 'to provide reassurance that the results and conclusions from the ROCKET-AF trial are still valid' (EMA 2016a, p.21). After assessing those data, EMA's expert advisory Committee for Medicinal Products for Human Use (CHMP) acknowledged that INRatio2-PT was faulty, but concluded:

> ….the benefit/risk balance remains unchanged and favourable for treatment with rivaroxaban in the prevention of thromboembolism in non-valvular atrial fibrillation….the information provided in the SmPC [Summary of Product Characteristics][6] is currently appropriate and does not warrant any amendment. The modified calculated INR values discussed in this report should be viewed as informative for the assessment of the INR values provided by the faulty device…it is considered that an update in the SmPC is not relevant and would provide more confusion to the prescriber (EMA 2016a, p.41).

Martin Rose from FDA's Division of Cardiovascular and Renal Products led a similar analysis in 2016. The FDA Commissioner was Robert Califf, a senior cardiologist, who had been co-principal investigator of ROCKET-AF while at Duke University. According to the *Pink Sheet*, 'Califf played a prominent role in securing a positive [FDA] advisory committee recommendation for the anticoagulant', but regarding the 2016 re-analysis, FDA stated that 'Dr Califf was recused of the matter' and 'was not involved in the agency's re-analysis of the ROCKET-AF data' (Sutter 2016).

In October 2016, Rose acknowledged that it was likely that patients in ROCKET-AF received higher doses of warfarin than they would have if INRatio2-PT had not been defective. However, he surmised that 'the effects of this increased intensity of anticoagulation on clinical outcomes were likely to have been quite modest', and that 'it seems very unlikely that if the device had performed similarly to the [laboratory] INR assessment device at Duke, the benefit/risk profile of rivaroxaban compared to warfarin would have been notably different from the profile based on the observed results of ROCKET-AF (Sutter 2016, p.3). Accordingly, in October 2016, FDA announced that rivaroxaban's benefits

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[6] 'Summary of Product Characteristics' is an EU legal document about drug characteristics for doctors.

continued to outweigh its risks, and that the drug's label for prescribing doctors should not be changed to reflect the impact of using INRatio2-PT in ROCKET-AF.

Unconvinced, Powell noted that 'discrepancies in the INRatio2-PT readings did not occur in the same patients at weeks 12 and 24, and this variation would have occurred throughout the study' which compounded the uncertainty regarding the reliability of the trial (Cohen 2016, p.3). Indeed, Powell's view of the trial's endemic uncertainty was shared by the DCRI researchers themselves, who stated:

> [W]e acknowledge the limitations of these analyses. To be fully informative, we would need to provide paired central-laboratory and point-of-care INR values *throughout the trial* [emphasis added] and these values are not available (Patel et al. 2016b, p.391).

Moreover, the EMA investigation had found that of the 767 blood samples with high laboratory-based INR>4 at 12 weeks, 219 samples (29%) had reported falsely low INRatio2-PT values of INR<3 thereby exposing a large proportion of patients taking warfarin to potentially dangerous effects of dose adjustments (EMA 2016a, p.19). Powell was concerned that EMA did not investigate relevant consequential factors that could have had a bearing on the comparative risk-benefit assessment of rivaroxaban and warfarin, such as how many patients on warfarin had major bleeding as a result of falsely low INRatio2-PT readings, and whether errors in such readings changed the proportion of time that warfarin patients were in the therapeutic range in ROCKET-AF (Powell 2016, EMA 2016a p.19).

Powell was not alone in his concerns. A former FDA regulator, Dr Thomas Marciniak described the EMA assessment as a 'whitewash' that ignored the 'serious device inaccuracies that those analyses reveal' (reported in Cohen 2016, p.3). Meanwhile, Dr Steve Nisson, a member of the FDA Scientific Advisory Committee that reviewed rivaroxaban for approval into the US market in 2011, was reported as commenting:

> Given the fact that the device was inaccurate, there is no way anybody can tell you what would have happened in the trial (Thomas 2016, p.3).

In January 2016, the EMA's CHMP further concluded that Janssen and Bayer were 'not aware of any potential impact of the identified deficiencies of INR device system on the ROCKET studies until Sept 9, 2015' (EMA 2016a, p.7). That assertion converged with the commercial and reputational interests of the industry, but was inconsistent with the existence of the COVANCE programme subsequently verified by court proceedings and made public by the *BMJ* investigation. In July 2016, the EMA analysed the COVANCE data and re-asserted that 'the additional information submitted in relation to the COVANCE re-check programme do not alter the January 2016 conclusion…' (EMA 2016b, p.34).

The evaluations of rivaroxaban's regulators (EMA and FDA) were significantly dependent on (re-analysed) data and information provided by manufacturers. Such dependence had led the EMA astray at least in relation to the existence of COVANCE reminiscent of Abraham's (1994) characterization of regulatory bias as giving manufacturers the benefit of the doubt. More poignantly, the manufacturers had presided over a trial using a defective device fundamental to the production of accurate data. Yet the EMA and FDA never insisted or even proposed that a fresh (perhaps shorter/smaller) trial should be conducted independently of the manufacturers to ascertain the efficacy (and safety) of rivaroxaban, under conditions of non-defective experimental equipment, even while leaving the drug on the market, let alone withdrawing the drug until a fresh trial had been completed. This alternative pathway to the production of medical knowledge about rivaroxaban was, it seems, never entertained by the regulators. Rather, the regulators chose to represent ROCKET-AF as providing 'certainty' to prescribers and underlined this trajectory of knowledge affirmation by rejecting the idea that the product label for doctors should be modified to even inform them that pivotal trial results had involved use of a defective coagulometer. A controversy about internal trial validity had expanded to wider public health concerns about informed prescription and consumption.

Industry Closure, Organised Patients, and the Courts

Studies of patients' experiences of medication often focus on users' adherence/compliance or patients' campaigns for greater access to pharmaceuticals, perhaps as 'assimilated allies' of drug companies within a 'patient-industrial complex' (Abraham 2009, Moore et al. 2024, Ozieranski et al. 2022). However, sometimes patients believe that they have been harmed by pharmaceuticals and organize as 'injury-oriented adversarial consumers' (Abraham 2010, p.610). In 2015, patients and relatives of deceased patients filed US lawsuits against Bayer and Janssen alleging that they or their relatives had suffered injuries, including internal bleeding, strokes and death, from taking rivaroxaban. They claimed that the companies downplayed rivaroxaban's risks and aggressively marketed the drug as an alternative to warfarin, while doctors and patients were not fully informed of the risks. One legal case involved 5,000 rivaroxaban patients, including families of 500 patients who died after taking the drug. US litigation grew to 25,000 plaintiffs' lawsuits against the manufacturers – one of the world's largest pharmaceutical litigations in recent history[7] (Coppock 2019, Sandberg 2019).

Six cases went to court in the US, not involving the UK courts. All were won by Bayer/Janssen, who argued successfully that rivaroxaban's label describing the drug's risks and benefits was approved by FDA (Sandberg 2018, 2019). Nonetheless, in March 2019, Bayer and Janssen agreed to pay the plaintiffs US$775 million to settle all cases, but admitted no liability, so allegations against the companies regarding rivaroxaban remain unproven. Indeed, Bayer re-asserted its view that 'the safety profile of Xarelto [rivaroxaban] remains positive and unchanged as confirmed time and again by regulatory agencies worldwide' (Coppock 2019).

The total settlement cost was just 12.7% of the drug's total US$6 billion sales in 2018 (Sandberg 2019). Bayer commented that 'this favourable settlement allows the company to avoid the distraction and significant cost of continued litigation' (Sandberg 2019, p.1). Janssen elaborated:

> With a settlement, it is our hope that plaintiff lawyer ads about Xarelto [rivaroxaban] will significantly diminish, and that this will give doctors the confidence to continue making the appropriate care decisions for their patients (cited in Dyer 2019).

This drug-device controversy had not gone unnoticed by US government lawyers. In 2017, the US Attorney's Office for New Jersey, FBI and Department of Health and Human Services' Office of Inspector General co-ordinated a legal case against Alere. They alleged that the company had 'violated the [US] False Claims Act' because Alere had 'from 2008 to 2016 knowingly sold defective INRatio2-PT blood coagulation monitors used by Medicare[8] beneficiaries taking anticoagulant drugs, such as warfarin' (Office of Public Affairs 2021). In July 2021, Alere agreed to pay the US Government $38.75 million to resolve allegations without admitting liability, so the allegations remain unproven (Office of Public Affairs 2021).

Growing claims by patients and lawyers that this drug-device complex had harmed some patients and the interests of public health, particularly in relation to the litigation discovery of COVANCE, presaged further contestation, in Gabe and Bury (1996)'s terms, about the therapeutic value of rivaroxaban and Alere's coagulometers. Such uncertainty threatened the manufacturers' commercial interests so they used their enormous financial resources to close it down - a further pillar in the process of synthetic certainization upon which doctors' confidence in prescribing rivaroxaban was built.

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[7] At that time, only litigation against Merck's rofecoxib and Eli Lilly's olanzapine were larger (Sandberg 2019).

[8] Medicare is a US Government programme which disburses funds to help eligible American pensioners and/or elderly patients afford medicines.

NICE: From Closure to Authoritative Guidance

The EMA and FDA were responsible for evaluating rivaroxaban's safety and efficacy, but not whether it was superior to warfarin. NICE, on the other hand, as a cost-effectiveness regulator, must make comparative judgements. Given that NICE's primary remit is cost-effectiveness, it merely accepted the validity of ROCKET-AF with its defective monitoring device, as the EMA and FDA did. NICE's assessments are confined 'within the terms of their marketing authorization as described in manufacturers summary of product characteristics' (NICE 2025). Nonetheless, the non-inferiority trial demonstrated that rivaroxaban was equivalent to warfarin, at best. In England, rivaroxaban was over 20 times more expensive than warfarin between 2016 and 2020 (Table 1).

Based on its evidence synthesis, NICE continues to recommend rivaroxaban as being cost-effective for the NHS under technology assessment TA256. After the revelations regarding INRatio2-PT, NICE might have advised the NHS to stop prescribing rivaroxaban until a new trial based on less uncertain data had been completed, or calculated a lower price for the drug due to the uncertainty surrounding its efficacy and safety. Uncertainties about the therapeutic value of rivaroxaban compared with warfarin were compounded by larger numbers of fatal adverse events associated with rivaroxaban (Table 1) by the UK's MHRA.[9]

Yet NICE did not pursue either of these routes in producing its authoritative recommendations for doctors and the NHS arguably because it is restricted by its remit to produce recommendations without contradicting the drug regulatory agencies. A former member of NICE's Evidence-Review-Group (for a NOAC) confirmed in an interview with us that 'NICE doesn't have power to overrule the EMA'. Both routes would have meant acknowledging uncertainties involved in ROCKET-AF and contradicting the regulatory agencies. On the contrary, NICE guidance TA256 and CG180 recommend rivaroxaban for stroke prevention, without mentioning the controversy or the inaccuracies with INRatio2-PT, although TA256 and CG180 (currently NG196) were both reviewed in 2021. *Synthetic certainization* by omission resulted.

Anticoagulant	Number of Prescriptions (2018)	Prescription Costs (2018)	Number of Deaths (2008-2011)	Number of Deaths (2011-2019)
Rivaroxaban	3,921,741	£194,482,896	12	408
Warfarin	8,243,486	£8,854,504	46	277

Table 1: Rivaroxaban compared to warfarin. Sources: Drug Safety Profile (MHRA 2026a, MHRA 2026b) and Prescription Cost Analysis (NHS England 2019)

Discussion

In this controversy, the 'knowledge' re-affirmation, at least by manufacturers, regulators and elements of the medical-industrial complex, supports Abraham's thesis that industry and government regulatory authorities dominate regulatory policy decisions (Abraham 1994, Abraham & Sheppard 1998). Our case-

[9] Suspected adverse reactions to drugs on the market are reported voluntarily to the MHRA by doctors and patients. Such observational data are considered less reliable than controlled trials; doctors might report suspected adverse reactions to newer drugs more than older ones.

study supports Gabe et al.'s (2012) contention that the media can be a countervailing power against dominant claims-making of industry and regulators. However, as with the Halcion controversy in the US, countervailing media coverage did not alter the regulatory *outcomes* in the UK, EU or US (Abraham & Sheppard 1998). Fragmentation of medical expertise, including organized patients' claims-making in court cases, partly supports Gabe and Bury (1996)'s theory of contestation and pluralism of knowledge-claims. However, we detected little evidence to support their grander theory of '*chronic* contestation' [emphasis added]. Rather, we found that dominant actors used their economic and political power to successfully close down contestations through *synthetic certainization*, belying an apparently pluralistic political landscape.

Main and Ozieranski (2021) and Gabe et al. (2012) found that PHARMAC, which has similarities to NICE, functioned as a countervailing power against commercial interests of the pharmaceutical industry, at least in terms of regulatory *process*.[10] In principle, NICE might be expected to be such a countervailing force within the regulatory state because it is ostensibly dutied to attain good value for money for the NHS - which may conflict with pharmaceutical companies' commercial interests in charging high prices (Abraham 2009). However, there is little evidence of NICE exhibiting such countervailing powers in our case-study. Charlton (2025, p.75) argues that, particularly since 2012, NICE has been 'increasingly happy to offer some new technologies the benefit of the doubt' in order to foster innovation.

While an ideology of innovation fostering faster market access is in the interests of pharmaceutical manufacturers, it is questionable whether this is in the interests of patients and public health because it diminishes the medical knowledge-base about efficacy, safety, and cost-effectiveness of new drugs (Davis & Abraham 2013). Furthermore, as our case-study shows, this ideology may be coupled with *synthetic certainization* which forges professional and public trust/confidence in drugs underpinned by controversial evidence. While not necessarily a conspiracy, this can scarcely be in the interests of public health because doctors and patients are not fully informed about treatments they prescribe/consume, and it conflicts with NICE's publicly declared principles of transparency and informed decision-making (NICE 2012).

Conclusion

Framing medical controversies in terms of 'medical dominance' is inadequate because capitalist industry and government regulatory authorities may be the dominant agents. There is little evidence of NICE, FDA or EMA exhibiting countervailing powers in our case-study. Rather, these regulatory agencies consistently awarded the benefit of the scientific doubt to the interests of industry in a fashion decidedly reflective of corporate bias. While the countervailing power of the media is ever-present, its influence may be precarious when pitted against both industry and government. A multi-pronged process of *synthetic certainization*, quite the opposite of chronic contestation, was accomplished not by medical dominance *per se*, but more precisely by capitalist industry and the regulatory state. We make no attempt to adjudicate the efficacy/safety or cost-effectiveness of rivaroxaban, but we do contend that medical knowledge, which presently passes for authoritative factual advice to prescribing doctors, could have taken a different trajectory of production and potentially turned out differently. If a fresh, techno-scientifically unassailable, trial of rivaroxaban had been completed, then robust medical knowledge could have been produced. Such a course, which would have risked contradicting the reported efficacy/safety outcomes of ROCKET-AF, was decisively undermined by the combined *synthetic certainization* of ROCKET-AF by

[10] Regarding regulatory *outcomes*, even the Herceptin case in New Zealand supports corporate bias theory because the Government over-ruled PHARMAC and funded the drug for use in health-care.

the manufacturers and regulatory agencies. Corporate bias, *synthetic certainization* and a permissive regulatory ideology of innovation determined the trajectory ultimately followed, as well as techno-scientific imperatives. Evidently, such politics of internal validity in trials may spread to wider public health concerns about informed consent and systems of oversight and scrutiny.

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Conflicts of interest

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