Original Research

IMPACT OF NON–VITAMIN K ORAL ANTI–COAGULANTS ON WARFARIN UTILISATION AND NHS BUDGET IN UK

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ABSTRACT

Introduction: Vitamin K anticoagulants were the mainstay prophylaxis of stroke in patients with atrial fibrillation and thromboembolic diseases. Non-vitamin K oral anticoagulants were approved for use in UK. To evaluate the impact of the introduction and change in guidelines on the utilisation of newer agents on the prescribing oral anticoagulants in UK. **Methods:** A segmented regression of interrupted time series analysis of the primary care data of oral anticoagulants from England, Scotland, Northern Ireland, and Wales between 2001 and 2021. **Results:** The overall utilisation of oral anticoagulants increased from 85.8, 9, 2.8, and 7.3 million defined daily doses in 2001 to 430, 36, 14.1, and 26.5 million defined daily doses in 2021 in England, Scotland, Northern Ireland, and Wales respectively. In 2021, the market domination changed from warfarin to apixaban. Segmented regression analysis showed that with the change in the National Institute for Health and Care Excellence clinical guidance in 2014, the utilisation of vitamin K anticoagulants decreased significantly by 2.39e+07, 1675341, 604863 and 2065009 defined daily doses annually in England, Scotland, Northern Ireland, and Wales, respectively. The overall expenditure on oral anticoagulants increased from £16, £1.6, £0.5, and £1.3 million in 2001 to £751, £60, £25, and £44.5 million in 2021 in England, Scotland, Northern Ireland, and Wales respectively. **Conclusion:** Prescribing oral anticoagulants changed in response to the change in clinical guidance. This suggests that the UK physicians followed evidence-based practice and changed to non-vitamin K oral anticoagulants primarily when recommended by the National Institute for Health and Care Excellence.

Keywords: Apixaban, Dabigatran, Edoxaban, Rivaroxaban, Warfarin

Introduction

Stroke is the fourth common cause of death in England and Wales, the third in Scotland and Northern Ireland, and the second worldwide. In 2020, two-thirds of stroke survivors were discharged with a disability (Stroke Association, 2018; Brain Research UK, 2021). Atrial fibrillation (AF) is a contributing factor in up to 1 in 5 cardioembolic strokes in the UK (Bray et al., 2017). Despite the National Institute for Health and Care Excellence (NICE) and international guidance from the European Society of Cardiology recommendations to prescribe anticoagulants for AF patients for secondary prevention of stroke, studies and reports showed that between 2009 and 2015, anticoagulants continue to be under-prescribed and about 25% of eligible patients with AF do not receive anticoagulant medicines (Holt et al., 2012; NICE, 2014a; Barra & Fynn, 2015; Rose et al., 2019; Ajabnoor et al., 2022).

For decades, vitamin K antagonists (VKAs), warfarin, phenindione, and acenocoumarol were the only available oral anticoagulants in use in UK (Le Heuzey et al., 2014). VKAs were the mainstay prophylaxis of stroke in patients with atrial fibrillation (AF) and thromboembolic diseases, including the treatment of venous thromboembolism (VTE) (Clayville et al., 2011).

Warfarin has been the most commonly used VKA in the world due to its proven efficacy and low cost. The disadvantages of its use are that warfarin (and other VKAs) requires close monitoring of the International Normalised Ratio (INR) measurements, have a narrow therapeutic index, food and drug interactions, and serious side effects such as bleeding (Zirlik, & Bode, 2017; Morgan et al., 2018). Non-vitamin K oral anticoagulants (apixaban, dabigatran, edoxaban, and rivaroxaban) (NOACs) are non-inferior if not superior alternatives to VKAs as prophylaxis of stroke in patients with non-valvular AF and have a better safety profile (Connollyet al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013).

Figure 1 shows the timeline of the market entry and approvals of direct oral anticoagulants. Previous research has shown that the uptake of NOACs is variable between different countries (Le Heuzey et al., 2014; Loo et al., 2017; Morgan et al., 2018). In the UK, new medicines' marketing authorisation process is regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). Then these licensed medicines are subjected to a further review by NICE to ensure their safe and effective use through producing evidence-based guidance (The King's Fund, 2020). For a single medicine, the assessment process by NICE would take a year on average. Limited number of studies explored whether the market entry of NOACs or NICE guidance has an impact on the utilisation of these medicines and increases patients' access to these life-saving medicines. This would provide an insight for initiatives and policymakers about period between medicines' marketing authorisation and approval in which many strokes can be averted with NOACs. The aim of this study is to explore the trends of the utilisation of NOACs and the impact of the change in guidelines on the uptake of NOACs in England, Scotland, Northern Ireland, and Wales.

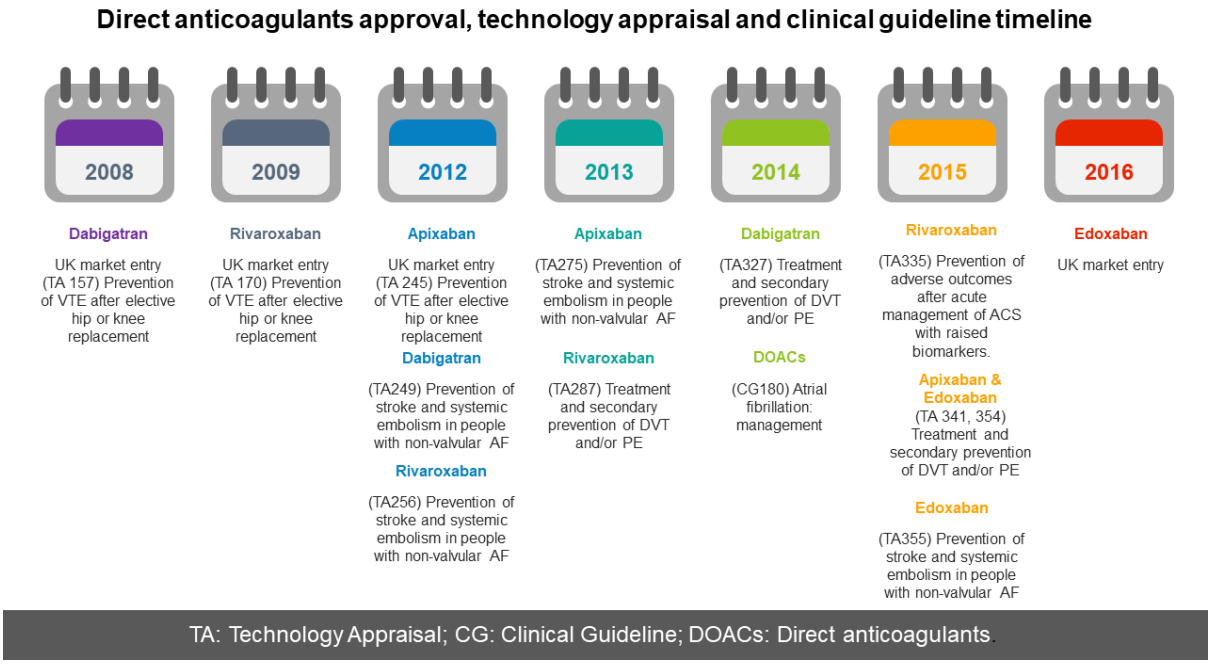

Figure 1: Direct oral anticoagulants approval, change in guidelines and market entry in UK (NICE, 2012a; 2012b; 2012c; 2013a; 2013b; 2014a; 2014b; 2015a; 2015b; 2015c; 2015d)

Methods

Data source

The study was a retrospective analysis of primary care use of VKAs and NOACs (acenocoumarol, apixaban, dabigatran, edoxaban, phenindione, rivaroxaban, and warfarin) in England, Scotland, Northern Ireland, and Wales. Primary care data on the annual volume and net ingredient cost of medicines for the period between 2001 and 2021 were derived from the National Health Service (NHS) Digital (NHS Digital, 2022), Public Health Scotland (Public Health Scotland, 2022), Health and Social Care Business Services Organisation (HSC Business Services Organisation, 2022), NHS Wales Primary Care Services (NHS Wales Primary Care Services, 2022), for England, Scotland, Northern Ireland, and Wales, respectively.

These databases provide annual information about medicines prescribed in primary care and dispensed by community pharmacies in these countries. To compare and contrast the volume of utilisation of different medications, the volume of utilisation was converted to defined daily dose (DDD) according to the World Health Organization (WHO) index for each medicine. The DDD index was for acenocoumarol 5mg, apixaban 10mg, dabigatran 300mg, edoxaban 60mg, phenindione 100mg, rivaroxaban 20mg and warfarin 7.5mg (WHO Collaborating Centre for Drug Statistics Methodology, 2022). The expenditure on these medications was calculated from drug tariff prices, (set out by the Department of Health and Social Care).

Statistical analysis

To explore the impact of the market entry of the NOACs and the change in NICE guidance that included NOACs on the utilisation of VKAs in England, Scotland, Northern Ireland and Wales, a segmented regression of an interrupted time series analysis was performed using Linden method (Linden, 2015). The analysis involved two interventions; the first was the market entry of dabigatran and rivaroxaban first in 2009 and apixaban in 2012 on the utilisation of VKAs. The second intervention, was the change in NICE clinical guidance (CG 180) of AF to include dabigatran, rivaroxaban, and apixaban in June 2014 (NICE, 2014a) and technology appraisals (TA 327, 335, 341, 354, and 355) in 2015 on the utilisation of VKAs and overall utilisation of all oral anticoagulants (OACs) (NICE, 2015a; 2015b; 2015c; 2015d). All analyses were performed using Stata 13MP software. Holt-Winters seasonal smoothing approach and Prais-Winsten ordinary least-squares regression approach were used to adjust for the present seasonality and autocorrelation.

Results

Volume of utilisation of oral anticoagulants

Between 2001 and 2008, the volume of utilisation of VKAs (warfarin, phenindione, and acenocoumarol) increased gradually in UK from 85.8, 9, 2.8, and 7.3 million DDD to 126, 12.1, 3.9, and 10.2 million DDD in England, Scotland, Northern Ireland, and Wales respectively. Warfarin was the most commonly utilised and dominant VKA in these countries, and achieved about 99.5 % of the utilised oral anticoagulants during this period. Following the market entry of non-vitamin K oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban (Figure 1)) and the change in NICE guidance to include the utilisation of newly approved oral anticoagulants (NOACs) and approval of dabigatran, rivaroxaban, apixaban and edoxaban for stroke prevention in AF patient and other indications (in 2014 and 2015), the overall volume of utilisation of OACs increased substantially. The volume of utilisation between 2009 and 2021 tripled to achieve 430, 36, 14.1, and 26.5 million DDD in 2021 in England, Scotland, Northern Ireland, and Wales respectively. During this period (2009 -2021) the market share of the OACs changed and warfarin lost market dominance to apixaban in all studied countries; apixaban achieved 40%, 37%, 58%, and 40% in England, Scotland, Northern Ireland, and Wales respectively in 2021 (Figure 2).

Changes in OACs utilisation

The interrupted time series analysis showed that the trend of utilisation of VKAs, between 2001 and 2008, increased significantly by 5884176 DDDs (CI 95% 4932809 - 6835543), 487343 DDDs (CI 95% 381368 - 593319), 160100 DDDs (CI 95% 131320 - 188880) and 444630 DDDs (CI 95% 303145 - 586115) annually in England, Scotland, Northern Ireland and Wales, respectively. Following the market entry of dabigatran and rivaroxaban in 2009, the level of utilisation of VKAs did not change significantly whereas the trend of VKAs utilisation did increase (Figure 3).

Following the change in NICE clinical guidance for AF to include apixaban, dabigatran, edoxaban and rivaroxaban in June 2014, the trend of utilisation of VKAs decreased significantly by 2.39e+07 DDDs (CI 95% -2.55e+07 - -2.23e+07), 1675341 DDDs (CI 95% -1851742 - -1498941), 604863 DDDs (CI 95% -650792 - -558933) and 2065009 DDDs (CI 95% -2291243 - -1838776) annually in England, Scotland, Northern Ireland and Wales, respectively. In contrast, the trend of overall utilisation of oral

anticoagulants (VKAs plus NOACs) increased significantly by 2.17e+07 DDDs (CI 95% 1.82e+07 - 2.52e+07), 2235584 DDDs (CI 95% 1990559 – 2480610), 580622 DDDs (CI 95% 324270 – 836973) and 789,107 DDDs (CI 95% 466,585 – 1,111,629) in England, Scotland, Northern Ireland and Wales, respectively (Figure 3).

Expenditure on oral anticoagulants

Between 2001 and 2008, the expenditure on OACs decreased by 10% - 20% in UK from £16, £1.6, £0.5, and £1.3 million Sterling pounds to £12.5, £1.45, £0.4, and £1.15 million Sterling pounds in England, Scotland, Northern Ireland, and Wales respectively, despite the increase in utilisation. In contrast, following the market entry of non-vitamin K oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban (Figure 1)) and the change in NICE guidance to include the newly approved oral anticoagulants (NOACs) and approval of rivaroxaban, apixaban and edoxaban for stroke prevention in AF and other indications (in 2014 and 2015), the expenditure on oral anticoagulants increased substantially. The expenditure in 2021 was £751, £60, £25, and £44.5 million Sterling pounds in England, Scotland, Northern Ireland, and Wales respectively.

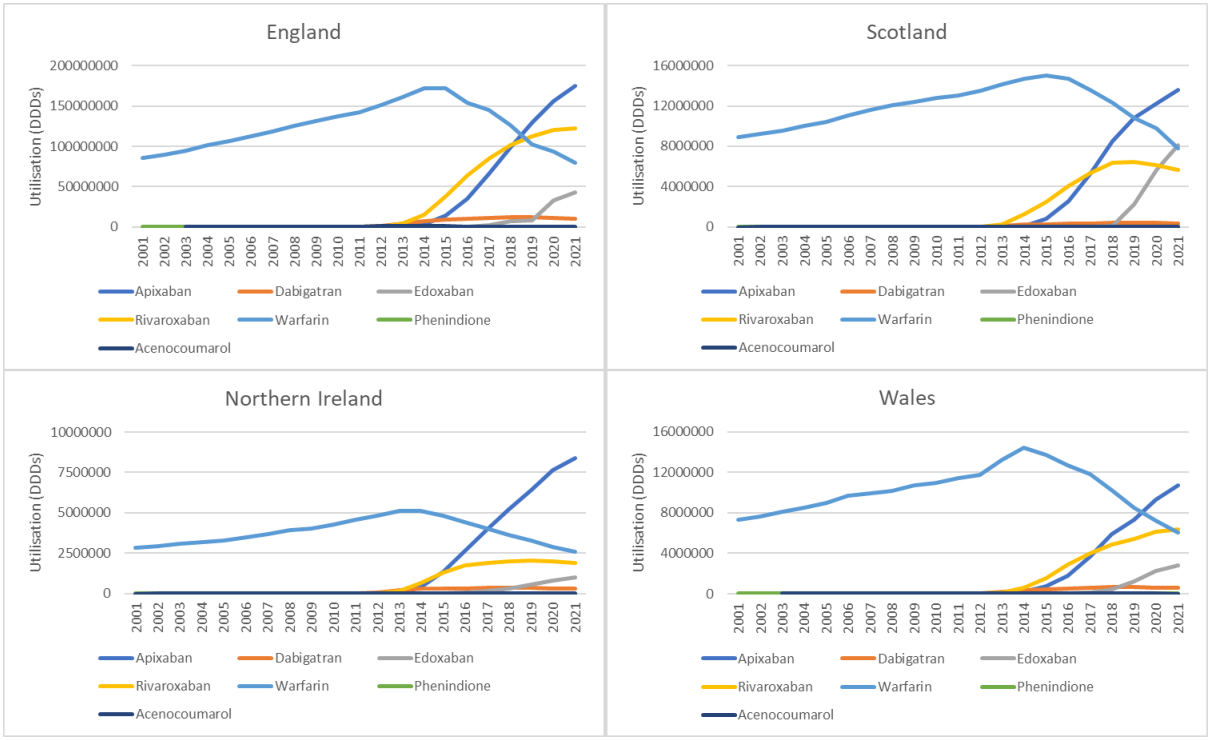

Figure 2: Oral anticoagulants utilisation in England, Scotland, Northern Ireland, and Wales

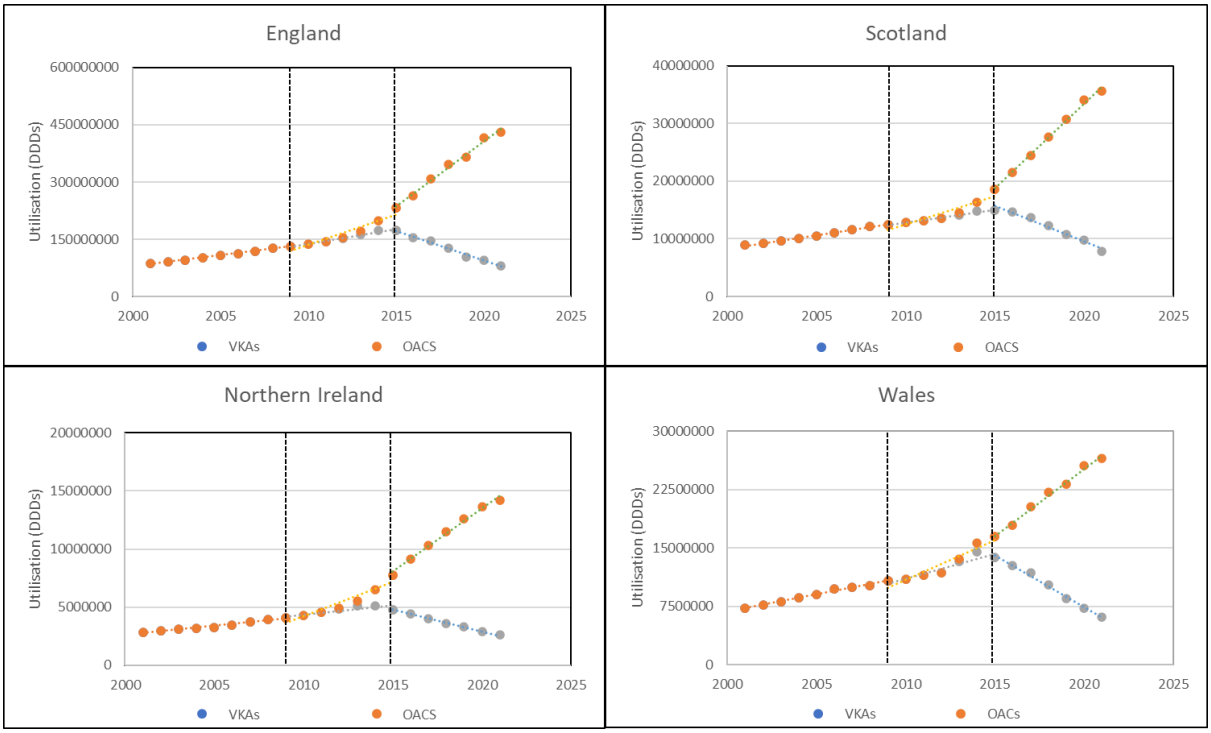

Figure 3: Utilisation of Vitamin K anticoagulants versus overall oral anticoagulants in England, Scotland, Northern Ireland, and Wales

Discussion

This study showed that the change in NICE guidance, rather than the market entry of newer agents (NOACs) changed the market of OACs. Before the market entry of NOACs, three VKAs were in the market, however, warfarin was the market dominant. This result was in line with the study by Morgan et al., (2018) conducted in Australia in which warfarin was the only prescribed anticoagulant before the entry of NOACs. McIlmoyle and Tran (2018) also found that warfarin dominated the American OACs market. Despite the fact that acenocoumarol, phenindione, and warfarin have similar effects on prothrombin time (McCormick et al., 2014), warfarin was the most commonly prescribed VKA due to its low price and longer duration of action compared with acenocoumarol and phenindione, therefore, warfarin associated with higher stability of anticoagulation and avoiding factor seven fluctuations (Barcellona et al., 1998). Clinical Commissioning Groups within the British National Health Services (NHS) issued guidelines to reserve acenocoumarol and phenindione for patients who were unable to tolerate warfarin (NHS, 2018).

With the market entry of NOACs, the uptake of the newer agents was slow and small and warfarin remained the market dominant until 2014-2015 in the studied countries. The uptake of NOACs was more evident beyond 2014. This result was in line with a previous English study by Loo et al., (2017) and the results of the EORP-AF study conducted in nine European countries between 2012 and 2013 which showed that NOACs were only prescribed in 8.4% of AF patients (Van Brabandt et al., 2016). The first approved NOACs was dabigatran in the mid of 2008 and started to be prescribed in 2009. However, dabigatran appeared to be a less attractive choice for prescribers possibly due to the perceived safety concerns about bleeding. These concerns were further augmented with reports that

indicated the lack of long-term safety, unavailability of antidote, short duration of action that requires twice-daily administration and other side effects like dyspepsia (Riva & Ageno, 2015). In contrast, rivaroxaban and apixaban gained more traction following the ROCKET-AF and ARISTOTLE clinical trials. The longer duration of action of rivaroxaban permits its use in once-daily regimen (Bielecki et al., 2018) and apixaban was associated with the least bleeding complications (Bonde et al., 2020). This slow uptake of NOACs might have been a result of NICE guidance and technology appraisals recommended NOACs for less common indications like the prevention of venous thromboembolism after total hip or total knee replacement in adults in comparison with the main indication of NOACs, atrial fibrillation (AF) management, that was licensed in UK in June 2014.

Subsequent the publication of the clinical guidance (CG 180) in June 2014, which recommended the use of either a NOAC or a VKA for patients with nonvalvular AF and an anticoagulant with aspirin (or other antiplatelet) for the prevention of non-valvular AF-related stroke, increased the uptake of NOACs (NICE, 2014a). This was evident with the increased uptake of NOACs and decreased utilisation of VKAs in all UK nations. Among NOACs, apixaban and rivaroxaban were the most commonly utilised agents beyond the change in guidance. This result could be attributed to the clinical trials that suggested that apixaban had the most favourable efficacy and safety profile compared to other NOACs and VKAs (Hernandez et al., 2017; Vinogradova et al., 2018).

These results were further augmented by the results of the segmented regression analysis that indicated that the market entry of NOACs did not affect the prescribing pattern of OACs in the UK and suggested that the new agents (NOACs) were reserved for selected indications for newly diagnosed patients. The change in NICE guidance shifted warfarin from market domination and the use of apixaban and rivaroxaban sharply increased. This increase together with the gradual decrease in the utilisation of warfarin suggested patients switching from older agents to the newer agents. During the COVID-19 pandemic, the NHS in UK published clinical guidance recommended switching patients on warfarin to NOACs to avoid regular monitoring of the INR and reducing visits to the primary care units during lockdown (England NHS & Improvement NHS, 2021; Patel et al., 2021). The results of the segmented regression were in line with the study by Morgan et al., (2018) which aimed to determine the change in the utilisation of OACs in a sample of the Pharmaceutical Benefits Scheme in Australia. They found that the change in the utilisation of OACs was evident following the expansion of the indications of the newer agents to include stroke prevention in AF patients.

Regarding the expenditure on OACs in the UK, before the market entry of NOACs, despite the gradual increase in the utilisation of VKAs, expenditure decreased by 10-20%. This reduction in the expenditure was attributed to the shifting from prescribing branded agents like (Marevan)® to the generic version of warfarin. Between 2009 and 2014 the expenditure increased massively due to the increased prescribing of VKAs and the also prescribing of the new branded agents which were expensive agents compared with generic warfarin.

This study has several limitations. The utilised data were at a gross national level and limited to the primary care setting, therefore, we cannot determine the rate of switching from VKAs to NOACs and vice versa. The expenditure of OACs was based on the British National Formulary (BNF) tariff prices and are not the real paid cost since these prices are subjected to discounts and these data are

considered confidential. On the other hand, the strength of this study includes the time frame of 20 years for four nations and the use of segmented regression of an interrupted time series analysis which is considered a robust quasi-experimental design for a study.

Conclusion

The trend of prescribing OCAs was not affected by the introduction of NOACs. Rather, the trend changed in response to the change in NICE clinical guidance. This suggests that the UK physicians followed evidence-based practice and changed to NOACs only when strong evidence on the safety and efficacy became available and recommended by NICE. With the availability of guidance and evidence about NOACs efficacy, the safety profile influenced the prescribing pattern and apixaban become the market dominant in UK.

Conflicts of Interest

The author declares no conflicts of interest.

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