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Lessons learned from NOACs and CV drugs launched in EU5 and the US – a HTA review and evidence generation standpoint

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Introduction

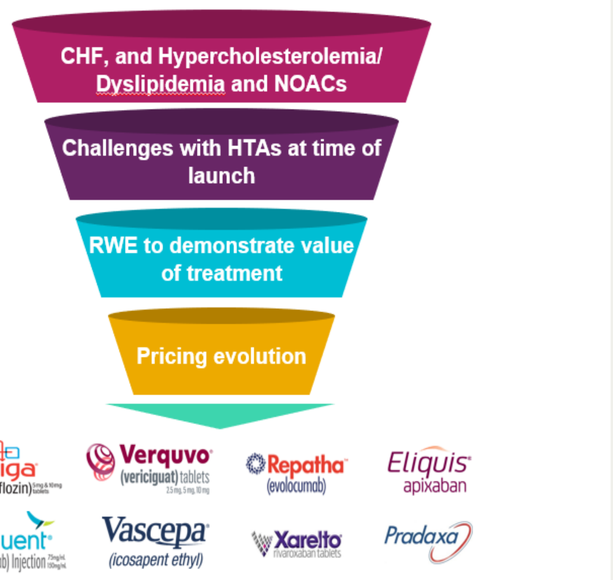
Novel Oral Anticoagulants, first approved in 2011, despite entering into a seemingly uncompetitive TA dominated by 50 year old warfarin, suffered from underwhelming uptake. This trend was seen with other drugs in the cardiovascular therapeutic area. In order to understand the unique barriers to uptake and strategies employed to overcome barriers, 8 analogues were selected across 3 indications: Anticoagulants for stroke prevention in NVAF, dapagliflozin and vericiguat in HFrEF, and PCSK-9 inhibitors with icosapent ethyl hypercholesterolemia/dyslipidemia.

We looked at evidence package and payer dynamics pre and post launch, guideline and pricing evolution, and contracting. Recurring concerns cited poor trial design and lack of robust clinical data. RWE did not address these concerns. Price was a key factor, as SoC competitors were reliable and cheap generics. It was found that across drugs and indications, guideline evolution was the biggest driver of uptake, mitigating poor HTA review over time. However, ensuring that data meets payer expectations is critical to obtaining positive HTA review, the key driver of rapid, timely uptake.

Objectives

Analogue research was undertaken to understand how payers react to a developing evidence package at launch and the impact of longer-term outcomes data post-launch in EU5 and the US. This research also served to determine the optimum evidence package, guideline evolution and payer dynamics at launch & post-launch. One of the focus areas was to understand price evolution over time and potential use of managed entry agreements (MEAs) while also assessing the use of improved adherence to support reimbursement and pricing.

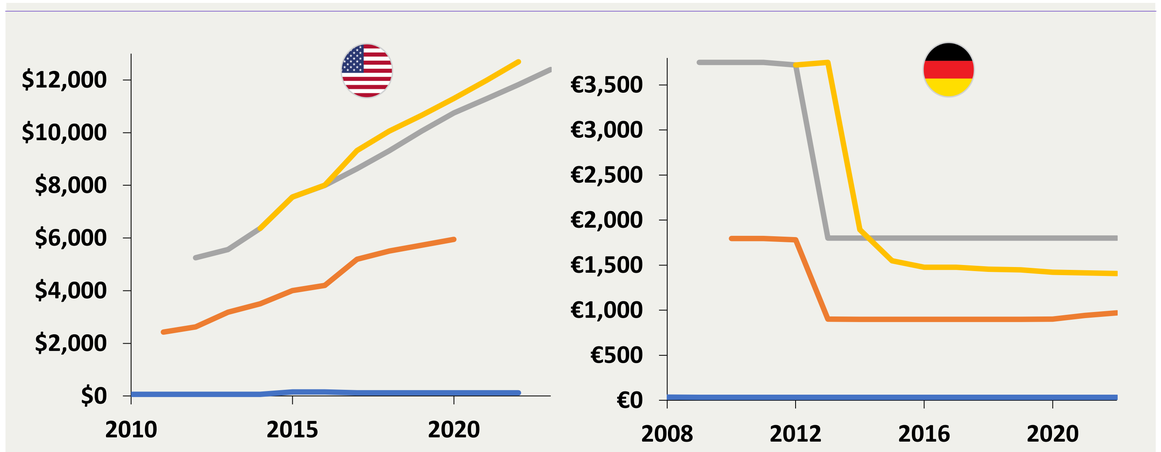
Figure 1: Analogue Selection: NOACS and CV Drugs



Methods

Analogue research was performed on dapagliflozin, icosapent ethyl and vericiguat indicated in chronic heart failure to identify the evidence package at launch & post-launch (i.e., with & without long-term outcomes data), payer dynamics at launch & after (i.e., after outcomes data), guideline evolution (based on data readouts), pricing evolution and use of any MEAs to support these launches. The research was supplemented with two additional drugs, evolocumab and alirocumab, indicated in dyslipidaemia. Three new oral anticoagulants (NOACs) were selected as analogues: rivaroxaban, dabigatran etexilate and apixaban. NOACs have revolutionised the anticoagulant market overtaking and largely replacing warfarin as the drug of choice. However, the path to widespread uptake took time and needed to address clinicians' and payers' initial concerns.

Figure 2: Pricing Evolution of NOACS in Germany and US



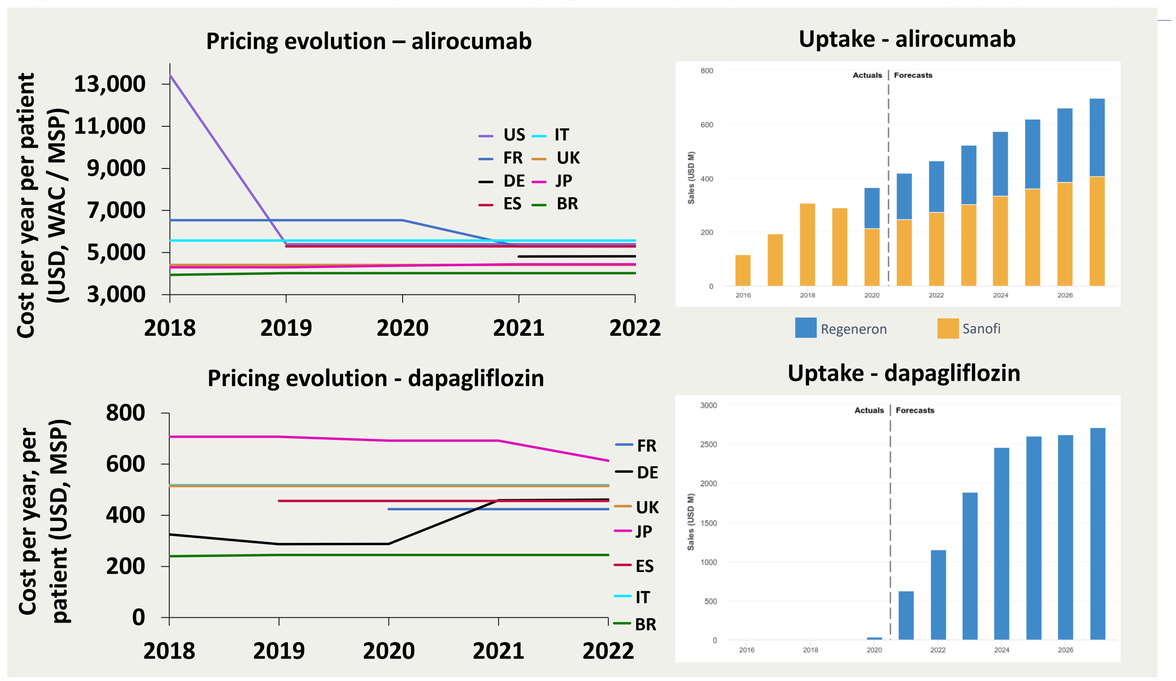
→ **Price of NOACs in US steadily increase by over 120% over 10 years**

→ **Price of NOACs in Germany suddenly decrease by 50% after 4 years**

Results

All analogues studied here faced certain common barriers that impaired uptake including criticism of trial data relating to the trial design (non-inferiority vs head-to-head), use of SoC (vs placebo), trial duration (3-month trial insufficient for a chronic condition) and choice of appropriate endpoint (surrogate vs patient relevant endpoint). RWE rarely moves the needle, whereas guideline inclusion is the biggest driver of uptake.

Figure 3: Price evolution and uptake of dapagliflozin (CHF) and alirocumab (dyslipidemia)



- **NOACs**

The quality of the trial data was a concern in all geographies due to the use of non-inferiority trials; RWE submission did not impact re-evaluation. Clinicians were reluctant to switch from warfarin due to the lack of reversing agent for NOACs and the proven reliability of with the treatment. Pricing was a concern mainly outside of the US, with the US having the strongest uptake despite increasing prices (Fig. 2). In Europe, however, price drops for NOACs as seen in Germany (Fig. 2) were a driver of uptake, to compete with extremely low prices of generic warfarin. Financial incentives for prescribing warfarin also limited uptake in countries such as the UK, where GPs were paid for providing INR monitoring services. Nonetheless, the biggest driver of uptake was guideline evolution, which was updated from recommending NOACs only for patients intolerant/ineligible for warfarin to being first line in all patients.

- **CHF drugs**

Vericiguat's failure to meet its primary endpoint led to poor uptake in the US despite equivalent price to dapagliflozin. Negative evaluation by leading HTA bodies (G-BA and HAS) increased the likelihood of further negative evaluations. As a result, Bayer did not apply for reimbursement in Italy, Spain and the UK. Dapagliflozin uptake and evaluation was favorable despite criticism of the placebo-controlled trial (most HTA bodies considered sacubitril/ valsartan as SoC), as a result of superior mortality data. Some HTA bodies restricted dapagliflozin to specific subpopulations (NYHA II-III in Spain, or as an add on to SoC in the UK), factoring in the possibility of no added benefit due to lack of direct comparator. Despite the price of dapagliflozin remaining stable in the EU, uptake is projected to increase sharply as a result of early favorable guideline inclusion resulting from accelerated trial data submission.

- **Hypercholestrolemia/Dyslipidemia drugs**

Alirocumab and evolocumab, both PCSK-9 inhibitors designed to treat hypercholesterolemia and dyslipidemia, suffered from lower than predicted uptake vs existing therapies. A highly critical ICER report published in 2018 provided a potential explanation for low uptake, leading to a dramatic (60%) price cut in the US - a rare occurrence. The intended effect of increasing uptake was achieved. Prices in Europe have remained stable, with uptake also remaining low due to concerns about efficacy (only a modest reduction in LDL-C, with LDL-C seen as a surrogate endpoint) and long-term safety. RWE did not address these concerns so did not move the needle. As a result of insufficient data, and the relatively low price of competitors such as statins which have proven efficacy, most HTAs recommended the use of PCSK-9 inhibitors with restrictions, limiting uptake and this is compounded by guidelines, which recommend them as third line. In class competition involving patent litigation may also have played a part in slow uptake. Icosapent ethyl has suffered from low uptake as guidelines state that a Cochrane meta-analysis found no effect on mortality and a slight effect on CHD.

Conclusion

Payers expect active comparators for standard of care and appropriate endpoints. Failure to meet payers' requirements (e.g., placebo-controlled studies) will drastically reduce the likelihood of obtaining positive HTA outcomes. In order to address payer concerns, a critical evidence review, and further evidence generation will be required. Price reductions are rare in the US, but in the case of PCSK-9 inhibitors, stimulated uptake. It is crucial for products to obtain positive HTAs in order to achieve premium launch price and inclusion into global treatment guidelines is important for faster uptake.

References

1. Access.cortellis.com. Clarivate ; 2. Ahajournals.org. *Home | AHA/ASA Journals*; 3. Aifa.gov.it; 4. Clarivate/DRG. *Biopharma Insights*; 5. Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde - CONITEC. *Recomendações da Conitec*; 6. Context Matters. *Dashboard*; 7. Escardio.org. *European Society of Cardiology*; 8. Gemeinsamer Bundesausschuss. *The Federal Joint Committee*; 9. Haute Autorité de Santé.*Professionnels*; 10. NICE. 2022; 11. Pmda.go.jp. *Pharmaceuticals and Medical Devices Agency*; 12. Sanitarios, A., .:: *CIMA* ::. *Centro de información de medicamentos*.Cima.aemps.es.