Analysis of Clinical and Economic Evidence focused on RWE in Medicare Drug Price Negotiations: Sacubitril/Valsartan, Rivaroxaban, and Apixaban

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BACKGROUND

- Inflation Reduction Act (IRA) grants the Centers for Medicare & Medicaid Services (CMS) the authority to negotiate prices for high-expenditure Medicare drugs.[1]
- Manufacturers must submit comprehensive evidence packages to inform CMS's determination of a drug's Maximum Fair Price (MFP).
- Of 10 selected drugs for negotiations, Rivaroxaban, Apixaban and Sacubitril/Valsartan contribute to ~50% of total Part D gross prescription drug costs, and all 3 are used in management of cardiovascular disease patients.[2,3]
- Analyzing these submissions offers valuable insights into CMS's negotiation strategies and MFP determination.

OBJECTIVE(S)

- To compare clinical and economic evidence, with a focus on real-world evidence (RWE), considered by the CMS in determining MFPs for sacubitril/valsartan, rivaroxaban, and apixaban under the IRA's Medicare Drug Price Negotiation Program.

METHODS

- Evidence packages submitted by manufacturers for the 3 drugs and CMS's guidance documents were reviewed.
- Evidence documents included details about MFP explanation, redacted summaries of the negotiation meetings, redacted summaries of data submitted by the manufacturer and other stakeholders.
- A qualitative comparative analysis was conducted focusing on RWE for clinical, safety and economic outcomes.

RESULTS

All three drugs:

- Manufacturers used the second pathway for negotiation with CMS **(*Figure 1*).**
- List prices reduced sharply after negotiations with CMS during negotiations.
- Submissions incorporated RWE throughout MFP determination **(*Figure 2*)**.
- Evidence included data from Medicare FFS and registry data from both U.S. and ex-US sources (e.g., Taiwan National Health Insurance Research Database).
- Stakeholder input included perspectives from physicians, pharmacists, patient advocacy groups, and individual patients and caregivers.[4]

Apixaban & Rivaroxaban: Indicated for nonvalvular atrial fibrillation (NVAF)

- Rivaroxaban ($197) and apixaban ($231) were evaluated for stroke prevention and venous thromboembolism (VTE) treatment.
- Apixaban's higher MFP was supported by a broader body of RWE, including over 10 studies out of 239 total references (~4.2%)

Sacubitril/Valsartan: Indicated for heart failure with reduced ejection fraction (HFrEF)

- Sacubitril/valsartan's MFP ($295) was informed by its clinical benefit, supported by RWE demonstrating reduced hospitalizations and improved patient-reported outcomes.
- 3/94 (~3.2%) real-world based data were utilized by CMS for MFP negotiation.

Overall, CMS consistently prioritized RWE alongside randomized controlled trials to assess comparative effectiveness, safety in diverse populations, and treatment adherence in real-world settings.

Figure 1. Price Negotiation Pathway taken by the three drugs

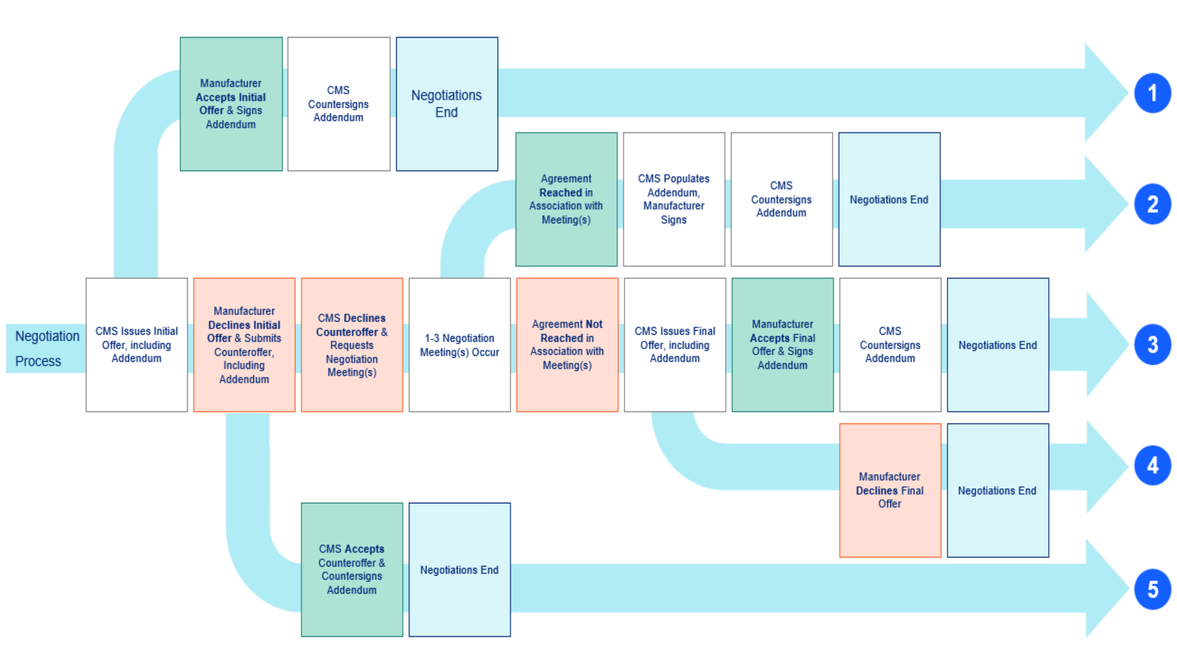
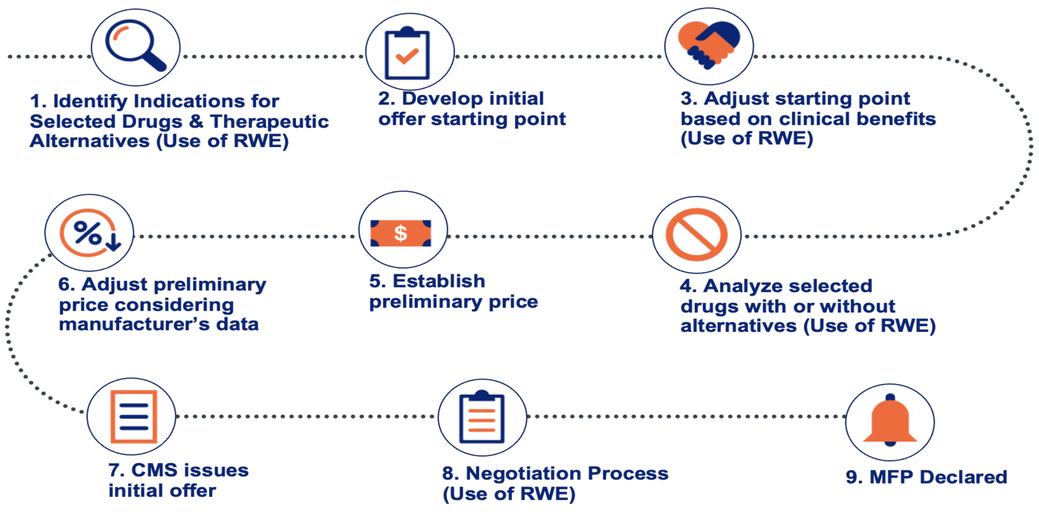


Figure 2. Use of RWE at each level during negotiation life cycle



CONCLUSION

- RWE played a pivotal role in CMS's holistic evaluation of clinical and economic value, particularly in differentiating between therapeutically similar agents.
- Integration of RWE into negotiation framework underscores its growing importance in value-based pricing and policy decisions.

1. Evidence Submission Framework

Feature	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Entresto Sacubitril/Valsartan)
Icer Report	Yes – Joint report with Rivaroxaban, CMS used its internal assessment	Yes – Joint report with Apixaban, CMS used its internal assessment	No ICER report; CMS only used internal and public data
Primary Indication	NVAF	NVAF	HFrEF
Comparators	Warfarin, Dabigatran (primarily)	Warfarin, Dabigatran (primarily)	Enalapril (from PARADIGM-HF trial), Valsartan (PARAGON-HF), Enalapril (PIONEER-HF)
Need Assessment	Quantitative (health shortfalls) + qualitative (patient interviews)	Same as Eliquis	Patient-focused listening session (HRQoL)[3]

2. Clinical and Economic Evaluation

Criteria	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Entresto Sacubitril/Valsartan)
Net Benefit vs Warfarin	High certainty of small net benefit	High certainty of small net benefit	Significant reduction in CV death and HF hospitalization
Net Benefit vs Dabigatran	Moderate certainty of small benefit	High certainty of comparable benefit	No direct comparison
Cost-Effectiveness	ICER used QALY and budget impact models, may not have been used by CMS	ICER used QALY and budget impact models, may not have been used by CMS	CMS likely used internal modeling; no ICER QALY data available. Data included cost-of-care in terms of per patient per month (PPPM)
Safety Profile	Major bleeding was lower than warfarin[6]	Major bleeding was lower than warfarin[6]	
Patient Centered Outcomes			Kansas City Cardiomyopathy Questionnaire
Real-World Evidence*	Real-world studies (e.g., ARISTOPHANES, ORBIT-AF) were used to assess comparative effectiveness and safety	Registries (e.g., XANTUS and GARFIELD-AF)	Registries (CHAMP-HF & others)

3. Negotiation Process with CMS

Step	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Entresto Sacubitril/Valsartan)
Initial CMS Offer	Likely based on ICER value-based price range	Likely based ICER value-based price range	Based on CMS internal analysis
Effectiveness measures	Equal Value of Life Years (evLY)	evLY	-
Stakeholders' voice	Patient Advocacy groups, cardiologists, pharmacists (Total 17 different entities)	Patient Advocacy groups, cardiologists, pharmacists (Total 10 different entities)	Chronic Care Policy Alliance, AARP, American Society for Preventive Cardiology (Total 13 different entities)

4. Unique Considerations

Eliquis & Xarelto:

- Shared ICER report due to similar indications and mechanisms of action.
- ICER provided multiple pricing scenarios and emphasized stroke prevention, bleeding risk, and adherence.
- CMS used ICER's ratings to inform price ceilings and floors.

Entresto:

- No ICER report; CMS relied on trial data (e.g., PARADIGM-HF) and patient input
- Emphasis was on reducing hospitalizations and mortality in heart failure.
- Manufacturer accepted CMS's final offer without further negotiation.

****List of Registries/Databases** – Taiwan National Health Insurance Research Database (NHIRD), US – Medicare Claims Database, Healthcare Cost and Utilization Project (HCUP) Database, GARFIELD-AF Registry, PINNACLE Registry*

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