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Guest Editorial

Health Technology Assessment of Entresto and Coaguchek XS System

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Entresto

Chronic heart failure affects poorly the quality of life, it results in recurrent hospital admissions, persistent annoying symptoms and a high rate of mortality within 5 years. The standard care in patients with chronic heart failure is angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), along with beta blockers and diuretics. ACEI or ARBs are known for decades as the first line in treatment of chronic heart failure, reducing both morbidity and mortality. Recently a large randomized controlled trial (RCT) called paradigm-HF concluded that the new drug sacubitril valsartan is superior to ACEI in the treatment of certain population with chronic heart failure.

Health technology assessment (HTA) regarding the new drug was held in multiple countries, table 1 shows the comparison between the HTA done in Canada [1] and the other done in United Kingdom (UK) by NICE [2].

Variables	CADTH Canada [1]	NICE [2]
Briefly outline the decision context	CDEC recommended entresto for the treatment of chronic heart failure patients with ejection fraction <40%, dyspnea NYHA class II-III and high levels of plasma BNP.	NICE recommended entresto as an option for treatment of HF patients with EF less than or equal 35%, taking a stable dose of ACEI and in NYHA class II-IV.
Type of recommendation	CDEC recommended entresto to be in the list of treatments for heart failure.	NICE recommended entresto as an option for the treatment of heart failure patients.
Rationale for recommendation	One double blinded RCT (PARADIGM-HF) concluded that entresto decreased overall CV mortality and hospitalizations by 20% over enalapril.	According to Paradigm-HF trial entresto was more effective than enalapril in reducing hospitalizations and overall mortality in heart failure patients. Network meta-analysis showing entresto to be more effective than ARBS in the treatment of HF patients was considered by NICE. TITRATION trial phase II showing the safety and tolerability of entresto in high doses.
Was budget impact mentioned explicitly? What comments were made on this?	No	Yes Estimated budget for the new drug and its cost saving were clearly mentioned according to current number of patients and assumed increase among the coming years. The committee has concluded that the cost effective analysis regarding entresto versus ACEI or ARBs is at the highest level that could be accepted as cost effective by the NHS which is from £20.000 to £30.000 per QALY.

ICER and variation by sub-group	The manufacturer estimated ICUR by $29,999 per QALY for entrseto in comparison with ACEI for overall patients.	ICER determined by the company according to paradigm-HF trial is £17,939 per QALY for entresto in comparison to ACEI. Subgroup analysis shows that western Europe subgroup has statistically non-significant superiority for entresto with ICER £20,550 per QALY.
Key items of clinical evidence considered	The paradigm-HF double blinded active randomized trial that compared the efficacy and safety of entresto in comparison to ACEI plus b-blockers for the treatment of heart failure.	Primary endpoints in paradigm-HF trial; mortality and first hospitalization favors entresto over ACEI. Network meta-analysis demonstrates that entresto was superior to ARBs in mortality and equivalent in hospitalization outcomes.
Key endpoints considered	Effectiveness: CV mortality HF-related hospitalization Safety: Adverse effects, serious adverse effects and withdrawal due to adverse effects.	Effectiveness: Mortality. First hospitalization. Safety: Adverse effects. Discontinuation due to adverse effects.
Performance of key endpoints	Efficacy: Entresto significantly improved overall mortality, mortality related to CV events and time to first HF hospitalization. Safety: Overall adverse events were comparable between the two groups.	Entresto decrease overall mortality and decrease hospitilization in comparison with ACEI. Adverse effects and discontinuation due to adverse effects were comparable between entresto group and ACEI group.
Surrogate endpoints considered and performance	The paradigm-HF trial did not demonstrate an improvement in important clinical endpoints as: Major adverse events like myocardial infarction, stroke, atrial fibrillation. No statistically significant improvement of dyspnea NYHA classification.	NICE did not consider analysis and performance of surrogate endpoints.
Economic model used and whether it was deemed adequate	Cost utility analysis based on a Markov model was done missing a detailed sensitivity analysis.	2-state markov economic model with one way sensitivity analysis.
Were stakeholders consulted? How?	The manufacturer reviewed the CDEC report and did not request the removal of confidential information.	Novartis: the manufacturer, has the right to appeal on the final appraisal and representatives can attend the meetings of the committee without interrupting the committee work. Multiple cardiology societies were invited to participate in this appraisal. Other consultancy organizations: Department of Health, NHS Doncaster CCG, NHS England, NHS Surrey Heath CCG and Welsh Government. Other organizations with commentator right only. Selected clinical experts and patient expert nominations were invited to give their comments.

Similarities and differences in the way the clinical and economic evidence was perceived across agencies	Clinical evidence: Regardless of some clinical concerns, the clinical evidence let the CDEC recommend listing the new drug. Economic evidence: The manufacturer ICUR value was revised and changed by the CDEC.	Clinical evidence: Results of paradigm-HF in reducing overall mortality and hospital admission favoured entresto. Lack of statistically significant effect on western Europe subgroup did not affect the decision-making. Network meta-analysis results supports superiority of entresto over ARBs was considered by the committee. Economic evidence: NICE ended up that ICER for entresto versus ACEI or ARBs is from 26,000 to 30,000 per QALY which is the upper limit for NHS to be cost effective.
Concerns re: CLINICAL EVIDENCE	Paradigm-HF trial did not show an improvement in CV events, nor an improvement in NYHA class.	Population characteristics included in paradigm-HF is not similar to that in real life. No head to head trials comparing entresto to ARBs. Lack of data about long term adverse effects. Weak effectiveness in patients with EF 35-40%. Limited number of patients with NYHA class IV in paradigm-HF trial.
Concerns re: ECONOMIC EVIDENCE	CADTH has re-evaluated the ICUR from 29.999$ to 42.787$ because they mentioned that entresto should be compared economically to the more economic ACEI Ramipril not enalapril and 20 years assumptions for the economic model done by the manufacturer is not real as the mean age for Canadian heart failure patients is 75.	Concerns about economic evidence supposed by the company: Changing the drug doses to be consistent with the UK practise and calculate the drug cost accordingly. Make Ramipril 5mg the comparator. Using the corrected model for western Europe subgroup.
Concerns re: UNCERTAINTIES	Paradigm-HF external validity. Long term effectiveness of the new drug. Assumptions of NYHA distribution after the third year. Assumptions used to estimate QALYs loss during hospital admissions.	Entresto may be less effective in patients with low plasma levels of BNP. Value of using entresto as first line of treatment. Long term effect on cognitive function and angioedema in African origin families. In economic model assumptions: High doses of the drug used in paradigm. Less effect in western Europe population.
Impact of concerns/ uncertainties on appraisal outcome	Re-evaluation of the ICUR value per QALY.	Consider entresto in patients with certain criteria excluding patient characteristics that shows no evidence of benefit from the new drug. Re-evaluation of ICER according to economic concerns.
Other considerations mentioned	Paradigm-HF patients were highly selected. Difference between Canadian population characteristics and trial patients' characteristics. Evidence of improvement in patients with NYHA class II rather than in NYHA class III-IV. Uncertainty about other confounders related to hospital admissions. Early stopped trial. Efficacy of entresto as first line of treatment is still unclear and its long term safety need further evaluation.	The committee received comments regarding increase incidence of angioedema with ACEI in African origin families. The committee concluded to recommend entresto without any signs of unfairness or unlawful discrimination and there is no need to alter its recommendations.
Possibility for risk share (Y/N)	No	No

Summary of key criteria based on which the recommendation was based	Safety and efficacy of entresto versus regular ACEI in the treatment of patients with chronic heart failure according to paradigm-HF trial.	Entersto has superior effect regarding decrease overall mortality in comparison to ACEI or ARBs and it is cost effective according to NHS limits.
Did HTA recommendation constitute funding/coverage decision as well?	Not mentioned	Yes, recommended coverage by NHS.

Table 1: *HTA of Sacubitril valsartan (Entresto) in adults for the treatment of chronic heart failure.*

HTA reports differ from country to another according to the key factors used by each system, different population characteristics in each country and different economic impacts. Regarding the recommendations, NICE was more restricted in patient characteristics than CADTH. Although both HTA bodies rely on the same paradigm-HF trial but NICE has chosen the proven patient characteristics who will benefit most from the new drug. NICE included the budget in their report as they recommend coverage by NHS while CADTH did not. Both CADTH and NICE were concerned by the clinical and cost effectiveness of the new drug and this was the drive for listing the new drug, while NICE had more involvement of stakeholders than CARDTH.

The manufacturer was in need to express more clinical evidence regarding comparison of its new medication to ARBs.

CoaguChek XS system

Long term anticoagulation by vitamin K antagonist is used in many conditions like atrial fibrillation, deep venous thrombosis and artificial heart valves implantation. Vitamin K antagonist target is to reach double the normal international normalized ratio (INR), it has a wide patient variability. All patients on vitamin k antagonists need regular monitoring of INR as both over and under anticoagulation have are serious adverse events. Coaguchek XS system is a used for immediate INR test like the device used in diabetics. The device could limit venipunctures and multiple clinic visits provided that it is accurate and affordable. We compared HTA analysis of coaguchek XS system in UK [3] and France [4] in table 2. Both countries assessed the new technology but in different patient characteristics. NICE recommended the device in patients with AF or artificial heart valves, while HAS recommended it in children on long term vitamin K antagonist. NICE assessed the device usage relying on the proven clinical benefits and cost effectiveness analysis which favours the new device. While HAS was concerned only by the accuracy of the test results and recommended the device according to expected benefits without supporting clinical trials. HAS recommended the device usage in children without delay and asked for supporting clinical data thereafter, we can understand this idea to decrease known suffering of children with the traditional laboratory testing.

Variables	NICE [3]	HAS [4]
Briefly outline the decision context	CoaguChek XS system is a good alternative to regular testing for INR in patients taking vitamin K antagonists as long as the patient has the ability to use it and willing to do.	The committee recommended the device to be included in the reimbursement list for children of age less than 18 and on long term vitamin k antagonists.
Type of recommendation	Recommended for use in specific patients' characteristics.	Inclusion in the reimbursement list (restricted).

Rationale for recommendation	Patients on long term Vitamin K antagonists need regular follow up of INR values to ensure proper anticoagulation and avoid complications. A systemic review including 26 RCTs favors coaguchek over regular laboratory tests.	Seven prospective studies were carried for assessment of self testing of INR in children. These studies were evaluating the accuracy of results in comparison to standard venipuncture test. Accuracy was comparable between the two groups.
Was budget impact mentioned explicitly? What comments were made on this?	Yes Usage of this device is cost saving as it reduces the complications caused by improper coagulation and reduce tests done in clinics.	No
ICER and variation by sub-group	The ICER was £319 per QALY gained in coaguchek group compared with standard care. Variation in subgroups were related to indication for anticoagulation and age, coaguchek system usage in patients with artificial heart valves is more effective and less cost than standard care where in patients with atrial fibrillation ICER is £4160 per QALY for coaguchek system in comparison to standard care.	No
Key items of clinical evidence considered	Studies addressing these clinical outcomes were included: Incidence of bleeding or thrombosis. Morbidity and mortality. Adverse events (wrong INR results).	Results of INR tests using coagulometer is comparable to standard laboratory results. Patient satisfaction.
Key endpoints considered	Bleeding. Thromboembolic events. Mortality. Performance and test results accuracy.	Not clearly defined rather than assumptions about benefits of using the device in children.
Performance of key endpoints	No difference in bleeding between intervention group and standard group. Thromboembolic events were halved in coaguchek system group. Mortality was less in coaguchek group only in subgroup of patients with artificial valves.	NA
Surrogate endpoints considered and performance	Time to test results were significantly shorter in coaguchek group. Patient adherence was comparable between the two groups. Anxiety during waiting test results: no difference. Acceptability of the new test: acceptable. Quality of life: improved with the new test through patients' survey results.	Accuracy of the device results. Patient satisfaction. Device results is comparable to traditional laboratory results. Patients are highly satisfied.
Economic model used and whether it was deemed adequate	Cost effective analysis based on a Markov model was done and sensitivity analysis. The External Assessment Group designed a new economic model for assessment of self-testing and self-management using the new device.	Not done.
Were stakeholders consulted? How?	Yes. Registered stakeholders were invited to attend the workshops and comment on this HTA report including manufacturer, sponsors, medical experts and organizations, patient group representatives and governmental bodies.	Yes The committee listened to the: Manufacturer, patients and their families, and expert doctors before finalizing the appraisal.

Similarities and differences in the way the clinical and economic evidence was perceived across agencies	Clinical evidence: The committee accepted the clinical evidence supporting the use of coagulocheck system in both atrial fibrillation and artificial valves patients. Economic evidence: The committee considered the economic evaluation done by the external assessment group.	The committee perceived the intermediate clinical evidence with acceptance and was confident with the expected benefits.
Concerns re: Clinical evidence	The committee observed the better clinical outcomes in self-management than self-testing, may be self-management patients are more qualified for self-care, so self-testing may be a step towards self-management. The committee also noticed that atrial fibrillation patients should have effective outcome as artificial valve patients.	The committee noticed that there is no clinical trials studied directly the clinical benefit of coagulometer usage in children.
Concerns re: Economic evidence	The committee noticed that self-management dominates standard care but self-testing is not cost effective. The committee assumed that if self-testing was related to increase in time in therapeutic range rather than adverse events, it could be cost effective.	NA
Concerns re: Uncertainties	The control arm in the trial evaluating adverse events related to self-testing, has tight control of INR which is not the real case in UK population. This could decrease apparently the effectiveness to be noticed in the intervention group.	The clinical effect of using the device in children upon the adverse effects of the disease is still unknown.
Impact of concerns/uncertainties on appraisal outcome	Re-evaluation of cost effectiveness by the committee let them concluded that both self-management and self-testing are cost effective.	The above concern did not affect the appraisal outcome that was mainly dependent on expected benefits from the device usage in children.
Other considerations mentioned	The committee was concerned by the additional cost of traveling to reach the clinic for follow up and low productivity of the patient in the standard care arm. The committee considered initiation of software to help patients in dose adjustment after testing in order to let most of the patients be self-management. Moreover, the committee concluded that even after adding the cost of the software, still it will be more cost effective than standard care.	The usage of this device should be restricted to close training for usage and evaluation for this training and overall quality control for test results, patient education about self-management.
Possibility for risk share (Y/N)	No	No
Summary of key criteria based on which the recommendation was based	Effectiveness of coagucheck system in reducing the risk of thromboembolic events in patients on long term vitamin K antagonists. Decreasing mortality in subgroup. Cost saving by usage of the new device.	The device is non inferior to the traditional test and it is assumed to improve the patients' quality of life through decrease number of venipuncture, need to go to the clinic, days out of school and overcome needle phobia. Thus the committee included the device in the reimbursement list according to these expected benefits.
Did HTA recommendation constitute funding/coverage decision as well?	The patient has to pay for the device and the NHS cover training , consumables and follow up expenses.	Yes

Table 2: *HTA of CoaguChek XS system.*

Entresto versus Coaguchek system

Along different HTA reports included in this study, NICE seems to be more restricted and need strong evidence to recommend a new technology. Moreover, across different countries medications listing seem to have more restrictions than diagnostic devices.

Across the four cases presented in this paper, all of them used strong clinical evidence and cost effectiveness analysis to reach their decision except the HAS where these data were not available. HAS insured safety usage of the diagnostic device and was convinced by the expected benefits and asked for future clinical data, where these criteria cannot be used in new medication assessment.

The manufacturer need to involve the device in more clinical trials, especially in certain populations like children, decrease the initial price of the device to attract more patients and continuous improvement of the device accuracy.

Regarding the HTA agencies involved in this paper, both CADTH and HAS need more involvement of stakeholders in their appraisals, give more attention to the budget and costs of the new technology and more adherence to strong clinical evidence like NICE.

Conclusion

The outline of HTA reports across different countries and different technologies seems to have a similar backbone with difference in details according to technology complexity, data available and country regulations.

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