INESSS
LE SAVOIR PREND FORME

HTA OF NEW TECHNOLOGIES AND LATE-BREAKING TRIALS: A CASE STUDY OF TRANSCATHETER MITRAL VALVE REPAIR

2019 CADTH Symposium

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DISCLOSURE

INESSS is publicly funded.

I have no actual or potential conflict of interest in relation to this topic or presentation.

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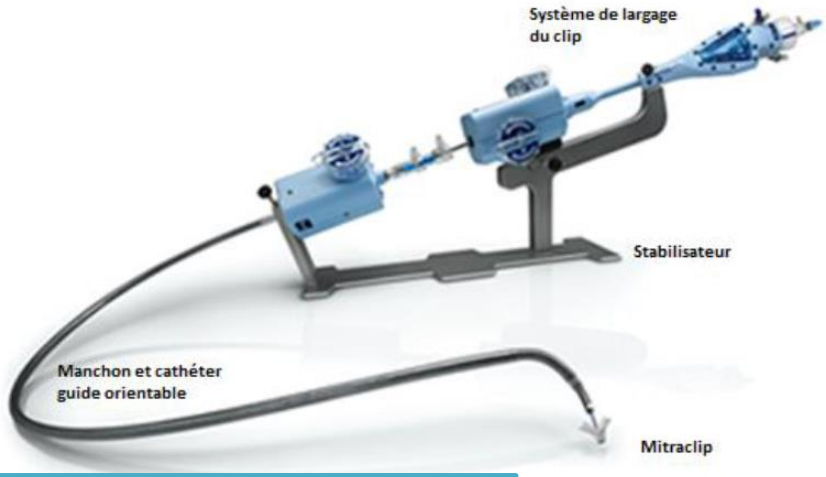
INTRODUCTION

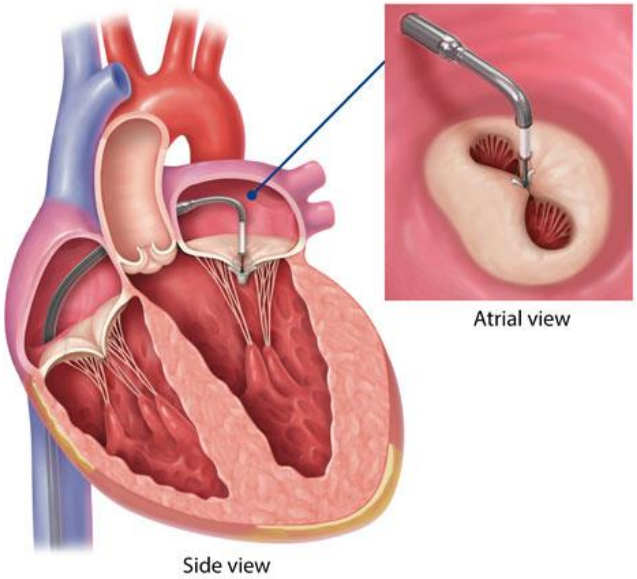
- Mitral regurgitation (MR) occurs when the mitral valve allows a clinically significant volume of blood to flow back from the left ventricle into the left atrium during systole.
- Primary MR results from a structural abnormality in one or more of the valve's components.
- Secondary MR occurs in patients whose valve was structurally normal but has been distorted as a result of left ventricular dilation and dysfunction.

MITRACLIP® DEVICE

TRANSCATHETER MITRAL VALVE REPAIR WITH A CLIP (TMVRc)



Since 2003, over 50,000 patients have been treated for MR with a percutaneous device



3 programs already exist in Québec

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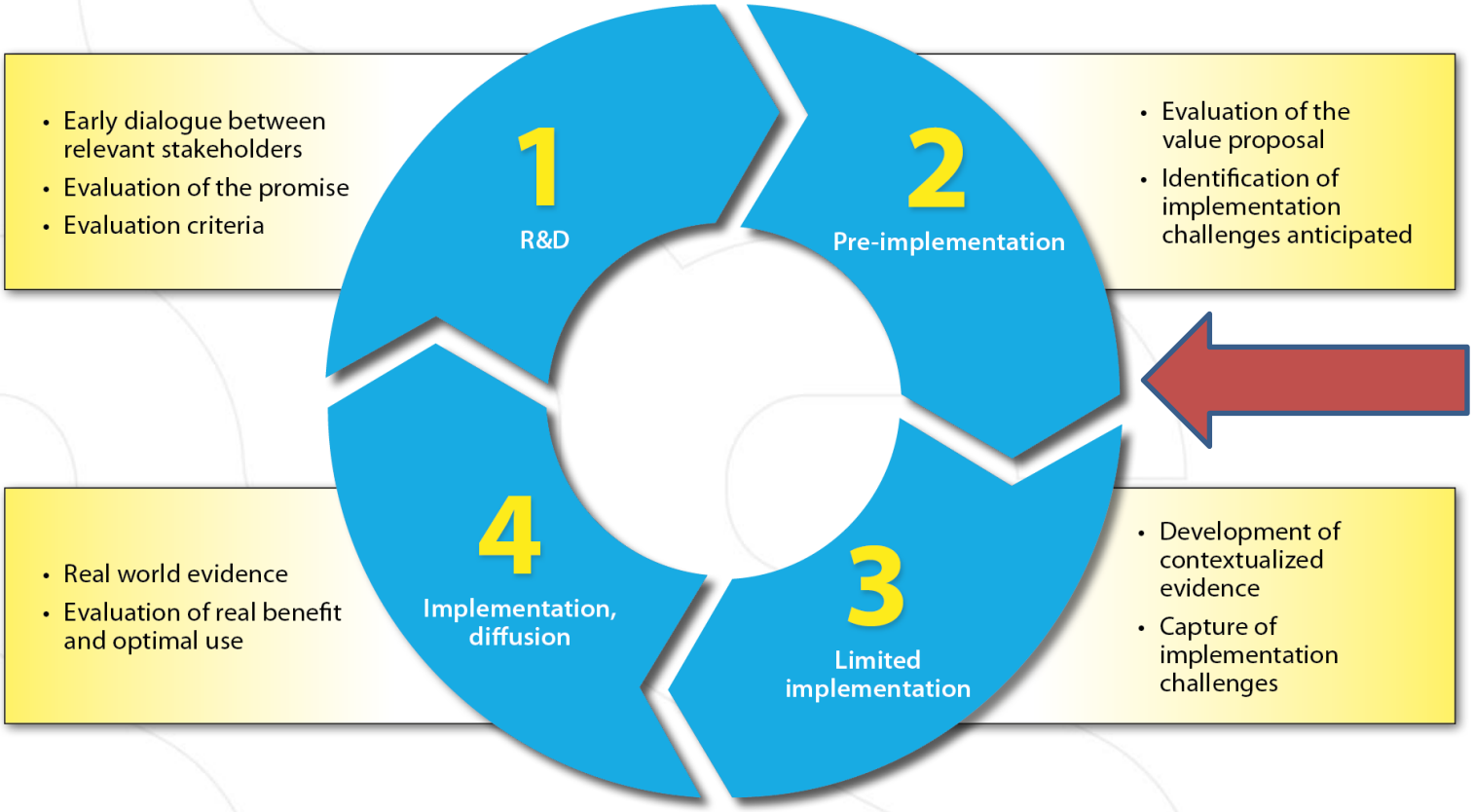
MANDATE

The Quebec Health Ministry asked INESSS to determine the relevance of reimbursing transcatheter mitral valve repair with a clip (TMVRc) for the treatment of mitral regurgitation.

A MODEL OF ITERATIVE EVALUATION THROUGHOUT THE LIFECYCLE OF TECHNOLOGIES



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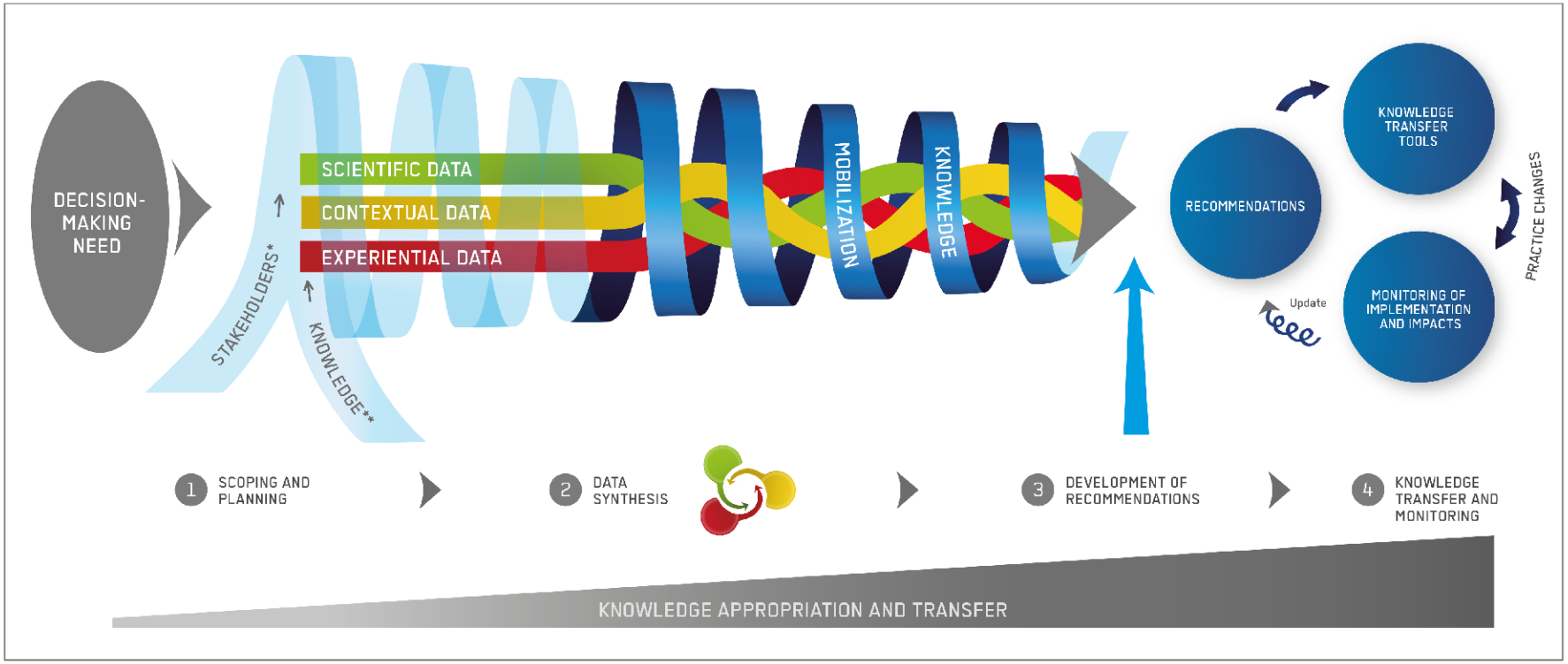
METHODS USED IN THE DEVELOPMENT OF RECOMMENDATIONS



*Health and social service professionals, administrators/managers, representatives from associations or bodies, experts, patients, service users, caregivers, citizens, etc.
** Knowledge derived from scientific research, the context and experience.

SCIENTIFIC DATA

- Guidelines
- HTA reports or decision summaries
- Meta-analyses
- Systematic reviews

NEW RCT RESULTS
MITRA-FR
COAPT

CONTEXTUAL DATA

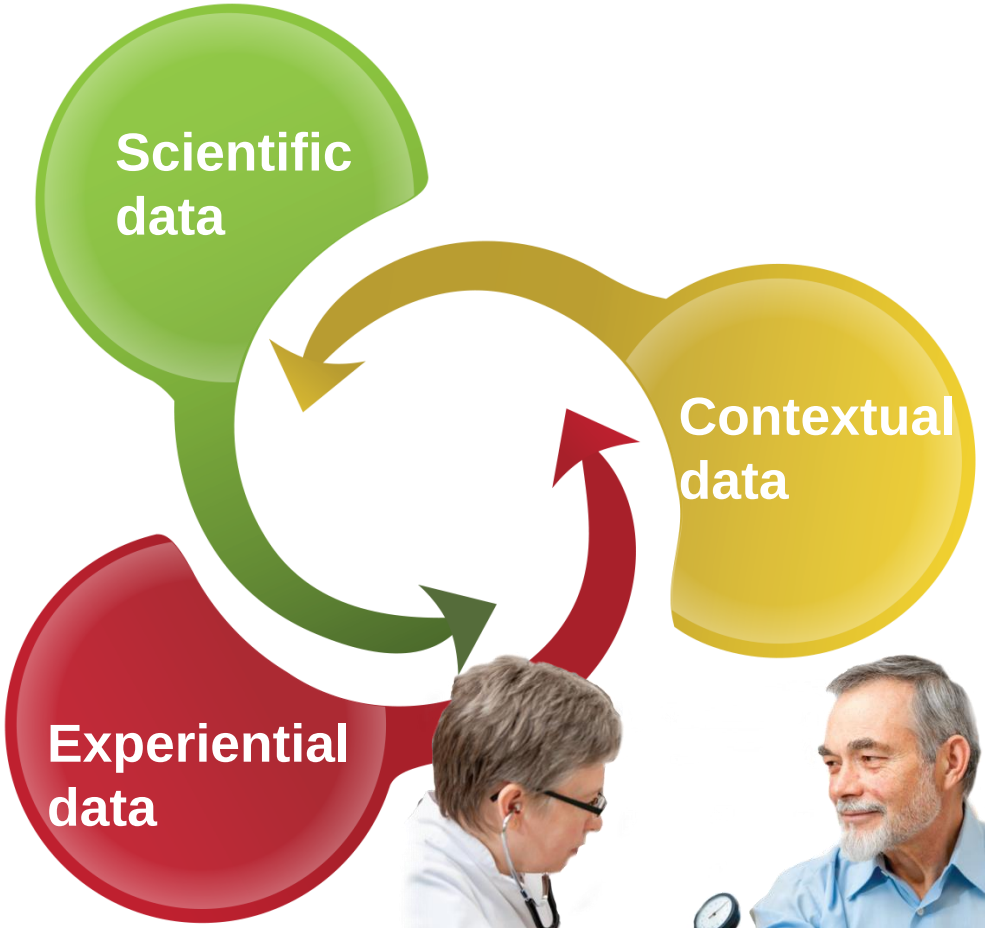
Consultation with:

- Inter-disciplinary clinical expert committee
- Inter-disciplinary scientific committee
- Interview with industry representative
- Permanent scientific committee

EXPERIENTIAL DATA

Consultation with:

- Clinical teams
- Hospital managers
- Patient representatives



REASONS FOR REFUSAL

Organization	Region	Year	Reason for refusal				
			Insufficient evidence				Lack of comparative studies
			Safety	Efficacy	Cost effectiveness	Benefits	
MSAC	Australia	2016		X		X	
EUnetHTA	Europe	2015	X	X			
AGENAS	Italy	2015		X			X
SAPACT	South Australia	2015	X	X		X	
NHC	New-Zealand	2013		X		X	
NHS	UK	2013			X		
LBI	Austria	2012	X	X			X

AGENAS: Agenzia nazionale per i servizi sanitari regionali, **EUnetHTA**: European Network for Health Technology Assessment, **LBI**: Ludwig Boltzmann Institut, **MSAC**: Medical Services Advisory Committee, **NHC**: National Health Committee, **NHS**: National Health Service, **SAPACT**: South Australian Policy Advisory Committee on Technology.

CONDITIONS FOR USE OF TRANSCATHETER MITRAL VALVE REPAIR USING A CLIP

Conditions for use	Organization	Health Canada	HAS	SHTG	OHTAC	FDA	NICE
	Region	Canada	France	Ireland	Ontario Canada	US	UK
	Year	2017* 2014	2017* 2015	2016	2015	2013	2009
Patient selection							
Primary mitral regurgitation		X	X			X	
Severity 3+		X	X	X		X	
Symptomatic		X	X			X	
High/prohibitive surgical risk		X	X	X	X	X	
Satisfies ultrasound eligibility criteria			X				
Life expectancy >1 year			X				
Heart Team decision		X	X			X	X
Registry participation		**X**	**X**	**X**	**X**	**X**	**X**
Use in designated centres only			X		X		

FDA : Food and Drug Administration, **HAS** : Haute Autorité de Santé, **NICE** : National Institute for Health and Clinical Excellence, **OHTAC** : Ontario Health Technology Advisory Committee, **SHTG**: Scottish Health Technologies Group.

2015

Ontario
Health Quality Ontario

Mitral Valve Clip for Treatment of Mitral Regurgitation: An Evidence-Based Analysis

MT ANSARI, N AHMADZAI, K COYLE, D COYLE, D MOHER

Limitations

Because of serious concerns of risk of bias, indirectness, and imprecision, evidence is of very low quality.

Conclusions

No meaningful conclusions can be drawn about the comparative effectiveness, harms, and cost-effectiveness of mitral valve clips in the population with chronic mitral regurgitation who are at prohibitive risk for surgery.

RESULTS

- Our literature review began after the date of the HQO systematic review, which concluded that there were serious limitations in the existing body of evidence and that no conclusions could be drawn about safety or effectiveness.
- In the period from 2015 to 2018, we found more observational evidence with serious limitations.
- However, 50 000 procedures have been performed around the world and the procedure appears to be relatively safe.

EXPERIENTIAL DATA: KEY MESSAGES

- Clinical experts want to use new technologies to meet an unmet patient need, and they believe the intervention improves quality of life despite the lack of scientific evidence. *"Leap of faith"*

- MR is associated with a heavy symptom burden and patients are willing to accept some uncertainty in the hope of a successful treatment.

- Majority of patients being treated have secondary MR.

CONTEXTUAL DATA: KEY MESSAGES

- Clinician believe patient selection is the cornerstone of program results, but it remains a challenge since the patient factors to be considered and their relative importance remain unclear.
- Clinicians estimate that 60% of the patients they treat have secondary MR despite the lack of official approval for this indication.
- Industry representatives are closely involved in the current Mitraclip programs.

LATE-BREAKING RESULTS

MITRA-FR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonnet, N. Piriou, T. Lefèvre, C. Piot, F. Rouleau, D. Carrié, M. Nejjari, P. Ohlmann, F. Leclercq, C. Saint Etienne, E. Teiger, L. Leroux, N. Karam, N. Michel, M. Gilard, E. Donal, J.-N. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D. Maucort-Boulch, C. Barnel, G. Samson, P. Guerin, A. Vahanian, and N. Mewton, for the MITRA-FR Investigators*

CONCLUSIONS

Among patients with severe secondary mitral regurgitation, the rate of death or unplanned hospitalization for heart failure at 1 year did not differ significantly between patients who underwent percutaneous mitral-valve repair in addition to receiving medical therapy and those who received medical therapy alone. (Funded by the French Ministry of Health and Research National Program and Abbott Vascular; MITRA-FR ClinicalTrials.gov number, NCT01920698.)

COAPT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

G.W. Stone, J.A. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, B. Whisenant, P.A. Grayburn, M. Rinaldi, S.R. Kapadia, V. Rajagopal, I.J. Sarembock, A. Brieke, S.O. Marx, D.J. Cohen, N.J. Weissman, and M.J. Mack, for the COAPT Investigators*

CONCLUSIONS

Among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The rate of freedom from device-related complications exceeded a prespecified safety threshold. (Funded by Abbott; COAPT ClinicalTrials.gov number, NCT01626079.)

LATE-BREAKING RESULTS

- A number of methodological differences between the two RCTs were identified, but most importantly, selection of patients was much more rigorous in the COAPT trial (than in the MITRA-FR trial).

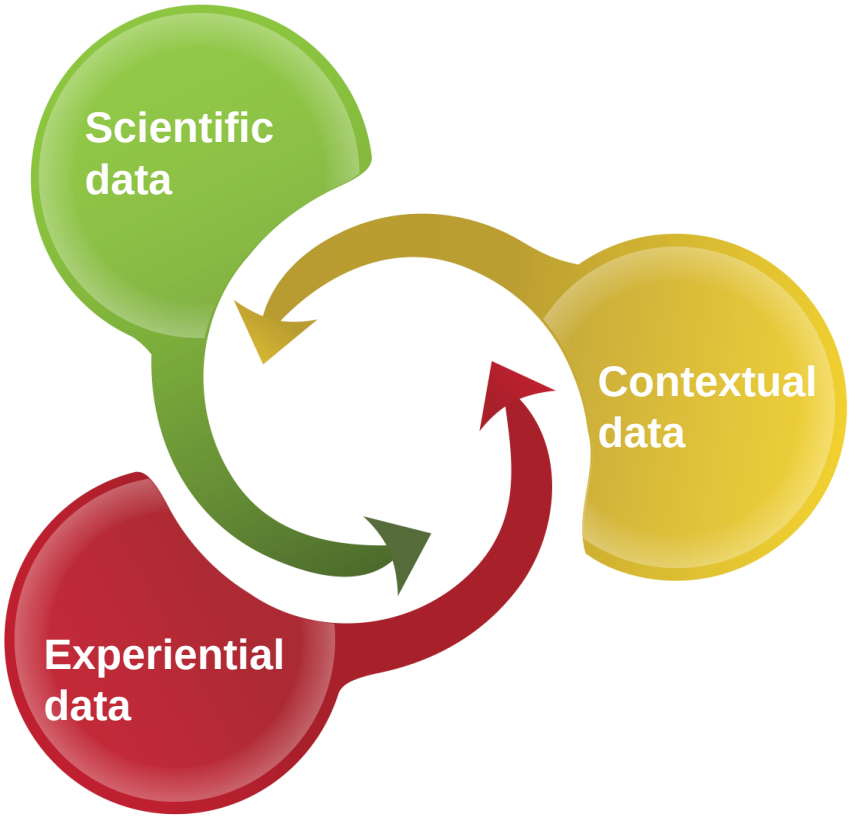
- In COAPT, over 1,500 patients were screened in order to identify the 652 participants.

IMPORTANT METHODOLOGICAL DIFFERENCES WERE IDENTIFIED

		MITRA-FR	COAPT
Key inclusion/ exclusion criteria	Primary endpoint	All-cause death and hospitalization for CHF at 1 year	Hospitalization for CHF at 2 years
	Hospitalization for CHF Biomarkers	At least one within 1 year	At least one within 1 year and/or corrected BNP ≥300 pg/ml or corrected NT-proBNP ≥1500 pg/ml
	Heart failure severity	No inclusion criteria	ACC/AHA stage D heart failure
	Left ventricular dimensions	No exclusion criteria	LVESD ≤70mm
	Coronary artery disease	No exclusion criteria	Untreated coronary artery disease requiring revascularisation
	Right ventricle	No exclusion criteria	Right-sided congestive heart failure with moderate or severe right ventricular dysfunction
	Pulmonary disease	No exclusion criteria	COPD with home oxygen therapy or chronic oral steroid use Estimated or measured PAP >70mmHg
	Number of patients screened	450	1576
	Number of patients enrolled (ITT)	304	614

Mitral regurgitation in heart failure – Time for a rethink
F. Praz et al. in press

DATA SYNTHESIS



RECOMMENDATIONS

Given the significant uncertainty regarding the value of TMVRc in the real-world setting, INESSS recommends that:

- The use of TMVRc be limited to a small number of facilities designated by the Health Ministry.

(*according to recommended criteria*)

RECOMMENDATIONS

- The designated facilities should participate in a provincial registry that will be used to assess the value of this technology in the real-world care setting.

  The data to be compiled should include at least the following measures:

  - The level of regurgitation severity (pre- and post-procedure);
  - Quality of life (pre- and at 1 year post-procedure);
  - Functional capacity (pre- and at 1 year post-procedure);
  - Hospital readmissions at 1 and 2 years;
  - Vital status at 1 and 2 years.

CONCLUSION FROM SUBMITTED ABSTRACT

- Health technology assessment of new medical devices is particularly important to guide their appropriate introduction into our public healthcare system.
- However, it is particularly challenging due to the often smaller body of evidence and corresponding higher level of uncertainty, as well as the risk of rapid evolution of evidence.

CONCLUSION

This experience highlights all the challenges we face when evaluating new health technologies.

Thank you for your attention…

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RECOMMENDATIONS

- TMVRc should be available to patients with primary MR:
  - who have symptoms attributable to chronic, severe mitral regurgitation, despite optimal medical treatment according to the current guidelines and;
  - in whom surgical replacement or repair of the mitral valve is contraindicated or considered overly risky and;
  - who have favourable anatomical conditions and;
  - who are likely to see their quality of life improve and whose existing comorbidities would not interfere with the benefit that correcting the mitral regurgitation is expected to provide.

RECOMMENDATIONS

- TMVRc should be available to patients with secondary MR:
  - who have persistent symptoms, despite optimal medical treatment (as defined in the protocol for the COAPT trial [Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation] [Stone *et al.,* 2018]) and;
  - who meet the selection criteria for the COAPT trial, particularly with regard to the regurgitant orifice area (> 30 mm^2) and left ventricular dilation (end-diastolic dimension ≤ 70 mm).

RECOMMENDATIONS

- The following conditions should be met by facilities offering TMVRc:
  - Patients should be selected by a multidisciplinary Heart Team that includes an expert in interventional cardiology, a cardiac surgeon, an echocardiologist and a cardiologist who is an expert in managing advanced heart failure;
  - An informed decision-making process should be implemented to support patients in their therapeutic choice, in line with their care goals and life plan.

RECOMMENDATIONS

- The Health Ministry should ensure a standardized method to identify patients who have undergone TMVRc in medico-administrative databases, in order to facilitate the monitoring of longer-term clinical outcomes.

NEW INDICATION

March 14th 2019:

FDA approves new indication for valve repair device to treat certain heart failure patients with mitral regurgitation

The new indication, approved today, is for treatment of patients with normal mitral valves who develop heart failure symptoms and moderate-to-severe or severe mitral regurgitation because of diminished left heart function (commonly known as secondary or functional mitral regurgitation), despite being treated with optimal medical therapy. Optimal medical therapy includes combinations of different heart failure medications along with, in certain patients, cardiac resynchronization therapy and implantation of cardioverter defibrillators.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633479.htm