

In collaboration with



**Advanced Certificate Course in
Cardiology**

24-25th March 2018, New Delhi
(Saturday – Sunday)

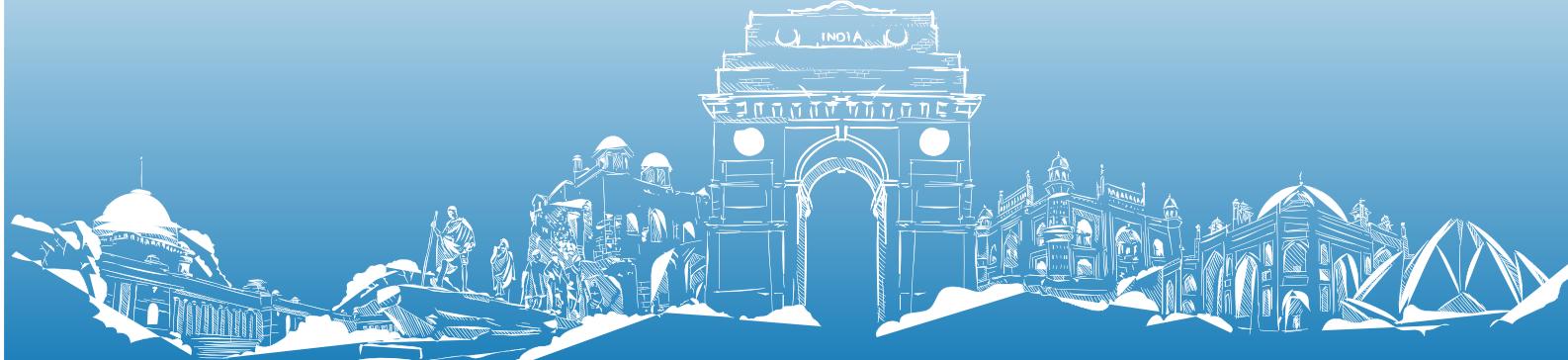
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SUMMARY BOOKLET



CONTENTS

Hypertension: What has changed after recent guidelines?	5
Managing resistant hypertension	9
Tricks for pharmacological management of advanced heart failure	12
CRT optimisation – Can we get with response rates to go higher?	16
Long-term DAPT: For whom and how long?	19
Optimising results of PCI – Is imaging guidance an essential way of doing on what is the evidence?	22
Remote monitoring of cardiac implantable electronic devices – Should this be standard of care?	25
Sudden cardiac death – Is it preventable – drugs or device – A critical appraisal	28
Atrial fibrillation – Drugs or ablation, how to decide and which has a better outcome?	30
Transcatheter aortic valve replacement, Status in 2018	33
Will NOACs replace Vit K antagonists, Status in 2018	36



CONTENTS

Management pearls for heart failure with preserved EF management	39
Percutaneous treatment of functional mitral regurgitation	42
Ethics in coronary revascularisation	46
Rule in/Rule out AMI – Troponin timings are having impact on ER timings	49
Antidiabetic medications and CV outcomes – What have recent trials taught us?	53
Revascularization in stable angina – when and how?	56
Revascularization in LV dysfunction – Is there a benefit – How to select patients for medical management, PCI or surgery?	60
Primary pulmonary hypertension – Beginning of a new era in the management	63
Pulmonary hypertension in heart failure – Implications for management	67
Indications for left atrial appendage occlusion in patients with atrial fibrillation	72
Angiography vs. hemodynamic assessment to predict the natural history of CAD	76



Hypertension: What has changed after recent guidelines?



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HYPERTENSION: WHAT HAS CHANGED AND THE WAY FORWARD

(2017 ACC/ AHA/ AAPA/ ABC/ ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/ PCNA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults)

Normotension is an arbitrary epidemiological derived observational value. The latest Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults published by the American College of Cardiology (ACC) and the American Heart Association (AHA) extends the Seventh Report of the Joint National Committee (JNC7) and the Expert Panel Report and comprises updated data from clinical trials.

KEY STEPS FOR PROPER BP MEASUREMENT

- Step 1: Properly prepare the patient.
- Step 2: Use proper technique for BP measurements.
- Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension.
- Step 4: Properly document accurate BP readings.
- Step 5: Average the readings.
- Step 6: Provide BP readings to the patient.

CATEGORIES OF BP IN ADULTS

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

- Individuals with SBP and DBP in 2 categories should be designated to higher BP category.
- BP indicates blood pressure (based on an average of ≥ 2 careful readings obtained on ≥ 2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure).

COEXISTENCE OF HYPERTENSION AND RELATED CHRONIC CONDITIONS

Recommendation for Coexistence of Hypertension and Related Chronic Conditions

Screening for and management of other modifiable cardiovascular disease risk factors are recommended in adults with hypertension.

BP TREATMENT THRESHOLD AND THE USE OF CVD RISK ESTIMATION TO GUIDE DRUG TREATMENT OF HYPERTENSION

Recommendations for BP treatment threshold and use of risk estimation to guide drug treatment of hypertension

Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher, or an average DBP 80 mm Hg or higher.

Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk $< 10\%$ and an SBP of 140 mm Hg or higher, or a DBP of 90 mm Hg or higher.

BP GOAL FOR PATIENTS WITH HYPERTENSION

Recommendations for BP Goal for Patients With Hypertension

For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended.

For adults with confirmed hypertension, without additional markers of increased CVD risk, a BP target of less than 130/80 mm Hg may be reasonable.

CHOICE OF INITIAL MEDICATION

Recommendation for Choice of Initial Medication

For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

MASKED AND WHITE COAT HYPERTENSION

Recommendations for Masked and White Coat Hypertension

In adults with an untreated SBP greater than 130 mm Hg but less than 160 mm Hg or DBP greater than 80 mm Hg but less than 100 mm Hg, it is reasonable to screen for the presence of white coat hypertension by using either daytime ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) before diagnosis of hypertension.

In adults with white coat hypertension, periodic monitoring with either ABPM or HBPM is reasonable to detect transition to sustained hypertension.

In adults being treated for hypertension with office BP readings not at goal and HBPM readings suggestive of a significant white coat effect, confirmation by ABPM can be useful.

RECOMMENDATIONS FOR TREATMENT OF HYPERTENSION IN VARIOUS CONDITIONS

Disease	Recommendations
Atrial fibrillation (AF)	Treatment of hypertension with an ARB can be useful for prevention of recurrence of AF.
Aortic disease	Beta blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease.
Obstructive sleep apnea	In adults with hypertension and obstructive sleep apnea, the effectiveness of continuous positive airway pressure (CPAP) to reduce BP is not well established
Renal artery stenosis	Medical therapy is recommended for adults with atherosclerotic renal artery stenosis. In adults with renal artery stenosis for whom medical management has failed (refractory hypertension, worsening renal function, and/or intractable heart failure (HF)) and those with nonatherosclerotic disease, including fibromuscular dysplasia, it may be reasonable to refer the patient for consideration of revascularization (percutaneous renal artery angioplasty and/or stent placement).

LESSONS FROM LIPIDOLOGY

LDL Cholesterol: Lower the better

- Optimal LDL-C levels are less than 70 mg/dL, if not lower.
- Such levels are associated with protection from CVD & atherosclerosis regression.
- At present, a threshold has not been found below which patients do not benefit from lowering of LDL-C.
- Therefore, when managing patients' LDL-C levels, the prevailing dogma is - the lower the LDL-C, the better is the outcome.

APPLICATIONS

- 130/80 mm Hg is the new 140/90 mm Hg, but there's more to the new guideline with two stages of hypertension and a new name for prehypertension.
- The guideline replaces JNC7.

BP classification (JNC 7 and ACC/AHA Guidelines)				
SBP		DBP	JNC 7	2017 ACC/AHA
<120	And	<80	Normal BP	Normal BP
120-129	And	<80	Prehypertension	Elevated BP
130-139	Or	80-89	Prehypertension	Stage 1 hypertension
140-159	Or	90-99	Stage 1 hypertension	Stage 2 hypertension
≥160	Or	≥100	Stage 2 hypertension	Stage 2 hypertension

Blood pressure should be based on the average of >2 careful readings on >2 occasions
Adults being treated with antihypertensive medication designated as having hypertension

The pharmacological treatment thresholds are largely similar across comorbidities.

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; non-institutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)

Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

BP TREATMENT THRESHOLD AND THE USE OF CVD RISK ESTIMATION TO GUIDE DRUG TREATMENT OF HYPERTENSION

Recommendations

1. Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10 year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher
2. Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP 140 mm Hg or higher or a DBP of 90 mm Hg or higher.

*ACC/AHA Pooled Cohort Equations (<http://tools.acc.org/ASCVD-Risk-Estimator/>) (13a) to estimate 10-year of atherosclerotic CVD. ASCVD was defined as a first CHD death, non-fatal MI or fatal or non fatal stroke.

SUMMARY

- Newer guidelines wishfully create a bridge between Systolic Blood Pressure Intervention Trial (SPRINT) like BP and SPRINT BP.
- Risk stratification is a wonderful idea but need to create more groups within high risk group.
- Academia need to create standardized method for trials, in terms of technique measuring BP parameters, to be correlated with standard risk score.

DAY 1 - SESSION 1 (10:00 - 11:00 am)

Managing resistant hypertension



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RESISTANT HYPERTENSION

- It can be defined as failure to achieve BP goal in patients who are on optimal doses of ≥ 3 antihypertensive agents from different classes, ideally one of which is a diuretic, or it can be defined as controlled hypertension in patients taking ≥ 4 medication classes.
- It is not synonymous with uncontrolled or difficult to treat hypertension.

PATHOPHYSIOLOGY

The mechanisms involved are:

- Increased vascular reactivity- This occurs as a response to several vasoconstrictor agents like epinephrine, norepinephrine and tyramine.
- Abnormal renal salt/water handling – reduced excretion of sodium in urine, with an increase in extracellular fluid volume is an important cause of resistant hypertension
- High aldosterone \pm plasma renin activity – increased aldosterone secretion causes increased sodium re-absorption and potassium secretion by the collecting ducts.
- Inappropriately high sympathetic outflow – Conditions like inflammation, obesity, obstructive sleep apnea lead to hyperactivity of sympathetic outflow resulting in resistant hypertension.
- Increased brain Renin Angiotensin System (RAS) – increased sodium concentrations activate brain RAS to retain more sodium thus contributing to resistant hypertension.
- Variable patterns of cardiac output

TYPES OF RESISTANT HYPERTENSION

- True resistance
- Pseudo / spurious / apparent resistance – This refers to poorly controlled hypertension that seems to be resistant but is not. The causes could be an improper BP measurement technique, non adherence to treatment regimen, white coat hypertension or Osler's sign (non-compressibility of severely arteriosclerotic brachial / radial arteries)

It is of utmost importance to differentiate between true and pseudo resistant hypertension for a proper management of the disease.

RISK FACTORS FOR RESISTANT HYPERTENSION

The major risk factors for resistant hypertension are chronic kidney disease, black race, diabetes, obesity, coronary artery disease, cardiovascular disease, old age and male gender.

INVESTIGATIONS

Proper investigations are required to diagnose resistant hypertension and to rule out pseudo resistant hypertension. When office BP levels are elevated, a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) must be done to rule out pseudo hypertension. A 12 lead ECG and an echo should be performed to assess the cardiac status. Blood investigations like CBC, blood sugar, KFT, Na/K, Lipids, Urinalysis, TSH, plasma aldosterone/renin should be done to further assess the severity of the condition.

MANAGEMENT OF RESISTANT HYPERTENSION

The first step towards management of resistant hypertension is to identify and modify contributing lifestyle factors such as weight loss, moderate intensity exercise (~30min 5-7 days/week), dietary salt restriction (<100mEq Na⁺/day), restriction of alcohol intake (2/d for men; 1/d for women) and a high fiber, low fat diet. Interfering substances like non-steroidal anti inflammatory agents, decongestants, should be discontinued or minimized. Appropriate screening should be done for secondary causes of hypertension which include obstructive sleep apnea, primary aldosteronism, chronic kidney disease, renal artery stenosis, pheochromocytoma, Cushing's syndrome and aortic coarctation.

The most rational pharmacologic treatment is the triple drug regimen which includes ACE inhibitors/ angiotensin receptor blockers + calcium channel blockers + diuretics (thiazides/loop). According to recent studies, additional BP lowering effects of the mineralocorticoid receptor antagonist spironolactone are modest and are considered next in the line of drugs for resistant hypertension management. The other drugs used for treatment of resistant hypertension include beta-blockers (vasodilating preferred), alpha-blockers (doxazocin, prazocin), central sympatholytics (clonidine, methyldopa) and direct vasodilators (Hydralazine, minoxidil).

The drug combinations not preferred are the beta-blocker + thiazide as this may potentiate the development of diabetes mellitus especially in obese individuals, and ACE inhibitor + angiotensin receptor blocker since this combination demonstrated more adverse effects without increase in benefits (ONTARGET trial).

DEVICES FOR RESISTANT HYPERTENSION

In order to improve patient compliance and prevent non adherence to therapy, certain device-based therapies for management of resistant hypertension have been developed that act on the autonomic nervous system. There are primarily four sites of action of autonomic nervous system modulating devices: renal denervation, baroreceptor stimulation, vagal nerve stimulation and spinal cord stimulation.

Renal denervation therapy

This involves visualizing the renal artery with the diagnostic duplex ultrasound device, and tracking of the kidney, followed by delivery of the focal therapeutic ultrasound in a robotic way (14 spots around the kidney) within a 3-min time frame. This disrupts the renal nerve fibers and hence sympathetic nervous system's activity reduces, leading to lowering of blood pressure.

Carotid baroreceptors

Mechanoreceptors are present in the carotid sinus. Stimulation of these receptors by high BP centrally reduces efferent sympathetic discharge to the heart, peripheral vasculature and the kidneys. This results in negative inotropy, vasodilation and reduced renin secretion. There is also enhanced vagal activity, resulting in lowering of the heart rate. Understanding of this mechanism has led to the development of implantable devices that stimulate the carotid baroreceptors, thus elucidating desired effects.

Central arteriovenous fistula

Hypertrophy of arteries make them stiff and less compliant causing increased vascular resistance. The ROX coupler device creates a 4-mm fistula between the iliac artery and vein with a controlled shunt flow of 800 ml/min, thus reducing systemic vascular resistance. This reduces effective arterial volume, systemic vascular resistance (SVR) and cardiac afterload, thus lowering the BP.

Deep brain stimulation (DBS)

Minimal data regarding the use of deep brain stimulation (DBS) as a treatment for hypertension has been found.

Median Nerve stimulation

A neurostimulator has been designed by Valencia Technologies (eCoin) ~2 cm in diameter, placed subcutaneously overlying the median nerve. It generates stimuli that communicate with multiple pathways in the brain which control the BP.

SUMMARY

True resistant hypertension is not uncommon. There should be proper assessment so as to rule out the secondary causes. A major concern currently is the non adherence and under optimization of anti hypertensive therapy. Identification of phenotypes, aggressive lifestyle management along with a step wise algorithm comprising ACE inhibitors/angiotensin receptor blockers + calcium channel blockers + diuretics and a mineralocorticoid receptor antagonist are the fundamental steps for management of resistant hypertension. Recently developed device therapies provide promising options in the future.

DAY 1 - SESSION 1 (11:00 am - 12:00 noon)

Tricks for pharmacological management of advanced heart failure



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ADVANCED HEART FAILURE

- It is commonly seen in clinical practice that a subset of patients with chronic heart failure (HF) continue to progress and develop persistently severe symptoms despite maximum guideline-directed medical therapy (GDMT).
- Several terminologies have been used to describe this group of patients who are classified with The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) stage D HF, including “advanced HF,” “end-stage HF,” and “refractory HF.”
- Patients with advanced HF may be characterized by presence of severe impairment of functional capacity as shown by one of the following:
 - Inability to exercise
 - 6-Minute walk distance \leq 300 m
 - Peak VO_2 <12 to 14 mL/kg/min

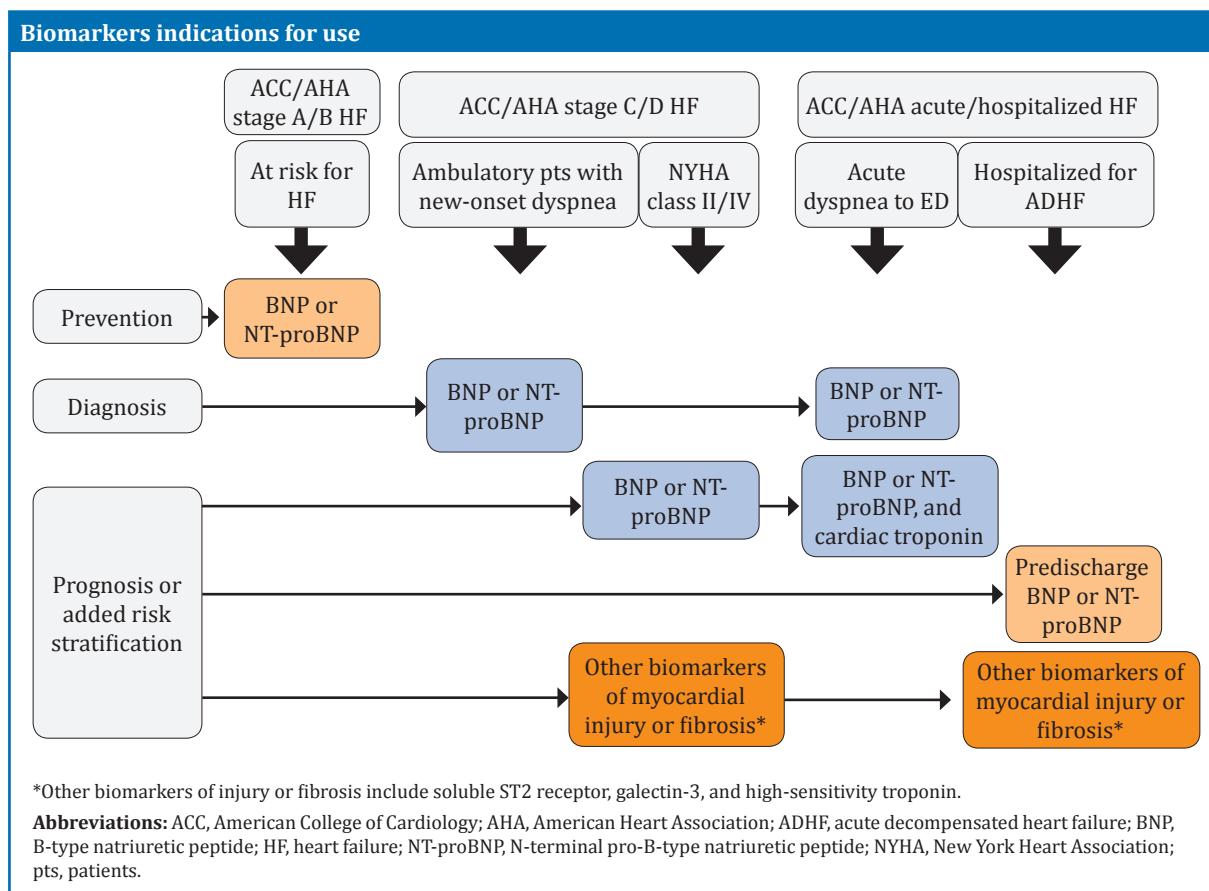
TREATMENT FOR PATIENTS WITH ADVANCED HF

- Patients with advanced HF have a range of treatment options, which vary from standard medical and device therapies to advanced device therapies to palliative care, dependent on the clinical status and requirement of the patient.
- In this event, the therapy related decision for individual patients could be facilitated by a variety of biomarkers, again dependent on the clinical setting.

PREDICTORS OF MORTALITY IN HF PATIENTS

a. Repeated hospitalizations

Repeated hospitalization for HF is a strong predictor of mortality in community HF patients, been found to be associated with a progressive decrease in survival period. In a study of over 14,000 patients, a



first hospitalization for HF associated with a median survival of only 2.5 years, with each subsequent hospitalization associated with worse survival. After a 3rd hospitalization for HF, the median survival dropped to less than 1 year.

b. An inability to tolerate HF medications

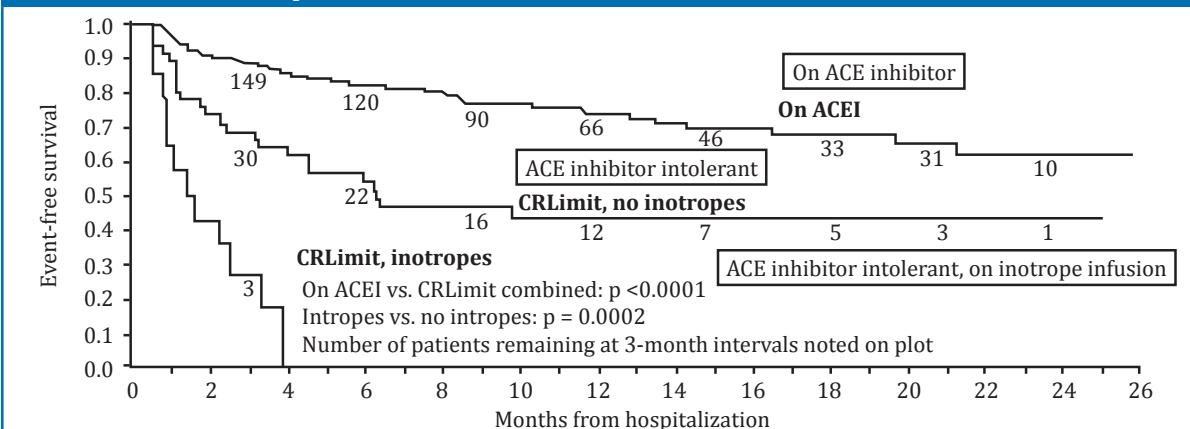
Similarly, an inability to tolerate HF medications is also an important predictor of mortality in HF. In a study of patients hospitalized for HF, those who could tolerate ACE-inhibitors had best outcomes, while those who could not tolerate them had <50% survival at 1 year following index hospital admission. Those patients who could not tolerate ACE-inhibitors and were inotrope dependent had the worst outcomes.

LIMITATIONS WITH CURRENT INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM

Inhibitors of the Renin-Angiotensin System (RAS) are widely used in patients with HF but have certain limitations, which affect their safety and efficacy.

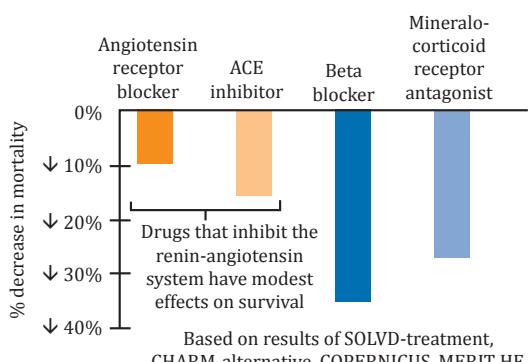
- New clinical trial data necessitated the recommendation on ANRI, seeing that increased activity of neprilysin, an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides, has adverse prognostic significance in HF. In ARNI, an ARB is combined with an inhibitor of neprilysin. The first approved ARNI is valsartan/sacubitril.
- It has been shown that angiotensin neprilysin inhibition almost doubles the effect on cardiovascular death of current inhibitors of the renin-angiotensin system.

Kaplan-Meier plot of survival without left ventricular assist device (LVAD) or transplant for 173 patients on ACE-inhibitors, 45 patients with circulatory-renal limitations (CRLimit) not on IV inotropes, and 14 patients with CRLimit on IV inotropes

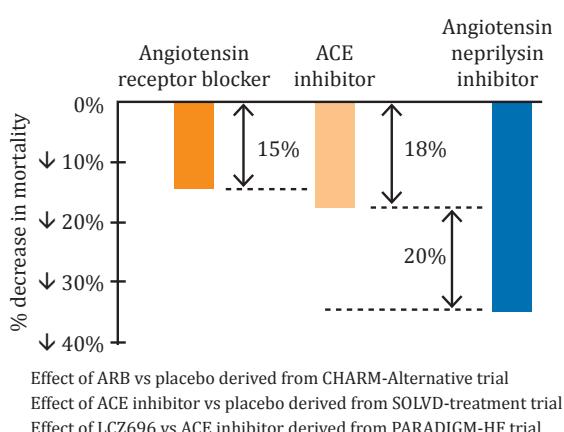


Patients on ACE-inhibitors had significantly longer survival time than patients with CRLimit. CRLimit patients who did not receive IV inotropes had significantly longer survival times than CRLimit patients who received IV inotropes.

Drugs that reduce mortality in HFrEF



Effect on cardiovascular death of current inhibitors of the renin-angiotensin system



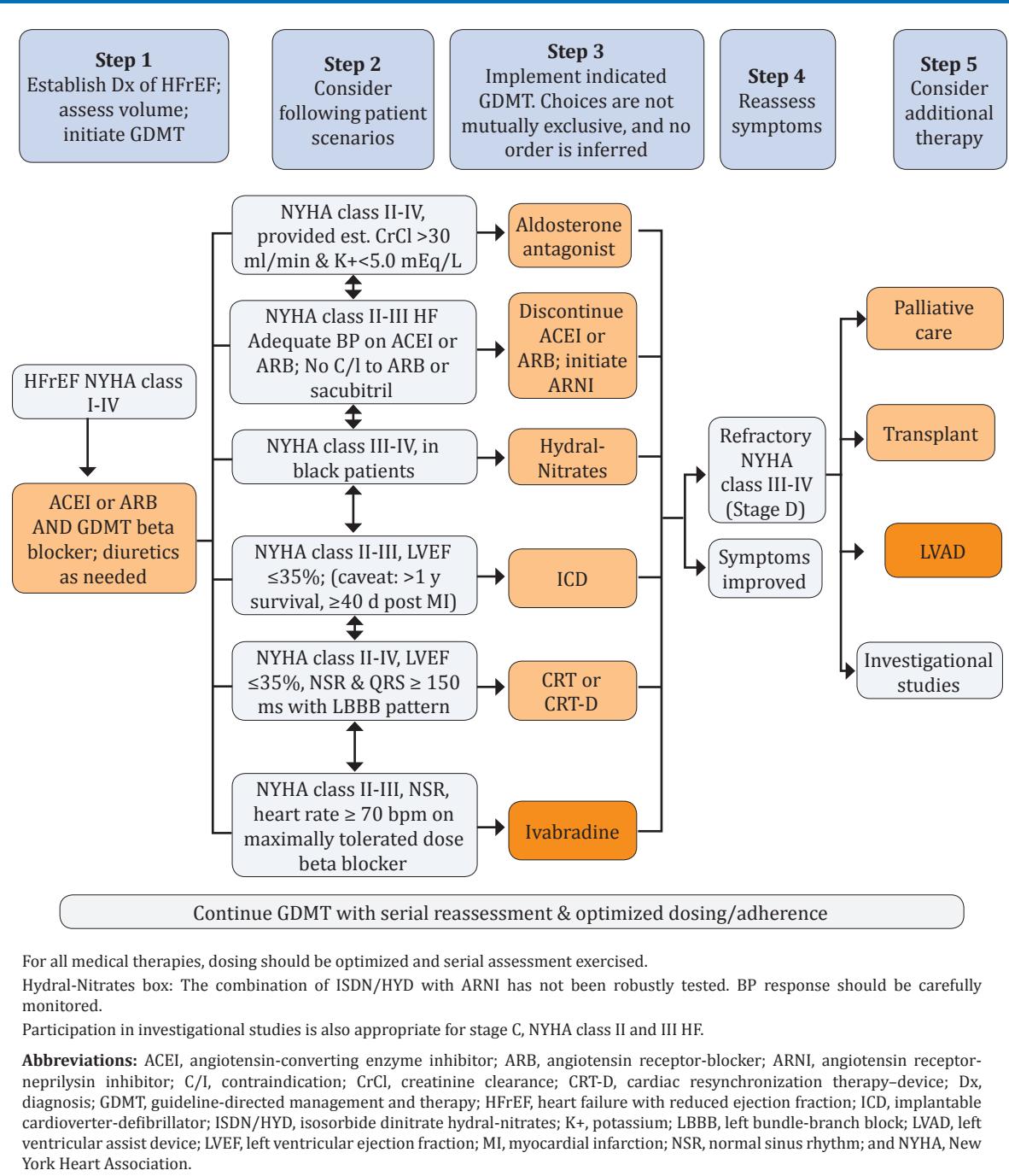
2017 update on guideline-directed medical therapy (GDMT)

ACE-I	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors, OR ARBs, OR ARNI in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
ARB	
ARNI	
ARNI	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality
ACE-inhibitor, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; ANRI, angiotensin receptor-neprilysin inhibitor	

ANRI - Sacubitril Valsartan - Key Messages

- Approved for chronic systolic heart failure (HFrEF)
- Reduces cardiovascular death and hospitalization for heart failure
- Reduces symptoms and improves physical function; reduces overall mortality
- Guidelines recommend replacement by ARNI to further reduce mortality and morbidity

2017 Update-Treatment of HFrEF Stages C and D



SUMMARY

- Optimal management of patients with heart failure necessitates consideration of the following:
- Careful assessment for underlying treatable conditions
- Optimal guideline-directed medical therapy (GDMT)
- Shared decision making with the patient on goals and risk/benefits of advanced therapies
- Very close longitudinal follow-up

CRT optimisation – Can we get with response rates to go higher?



DR. NIRAJ VARMA

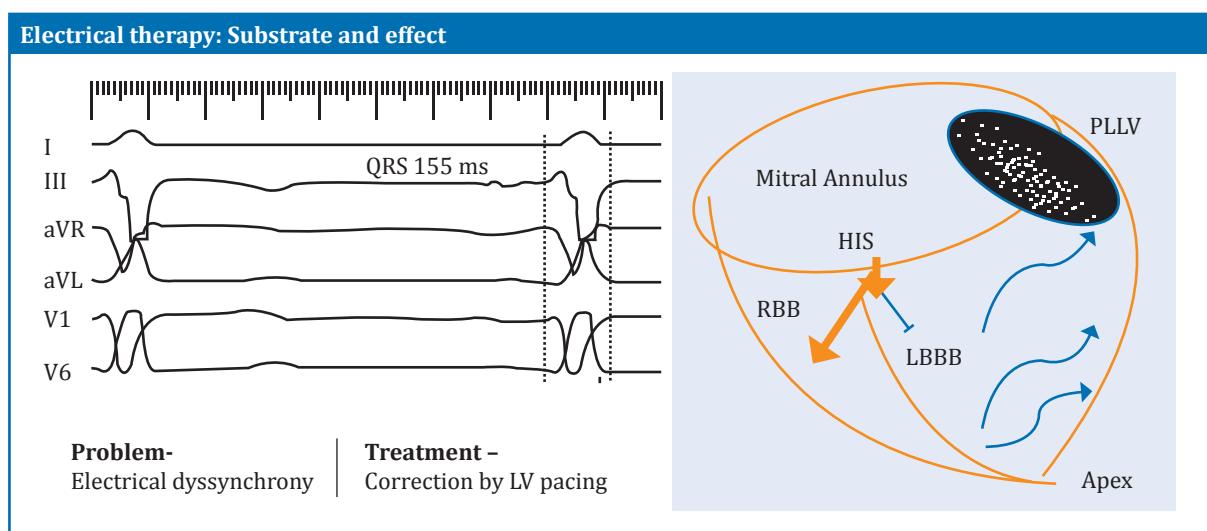
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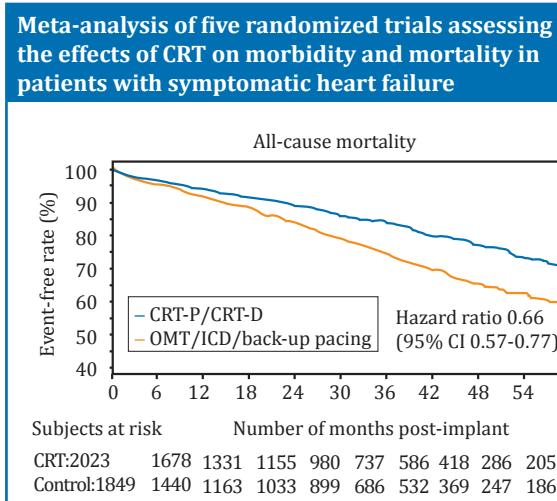
CARDIAC RESYNCHRONIZATION THERAPY (CRT)

- CRT in simple terms means the use of an electrical device to resynchronize and optimize aberrant electrical condition of the heart by electrical impulses. It is used in patients with heart failure and left bundle branch block (LBBB).
- Results of the CRT depend on several electrical parameters, and it is unlikely that any single set of parameters will fit every patient. This is manifested to some degree in the gradient of response to CRT.
- Wide QRS is an independent predictor of adverse prognosis in patients with heart failure.
- Positioning of electrodes may also impact the response desired from CRT in individual patients.

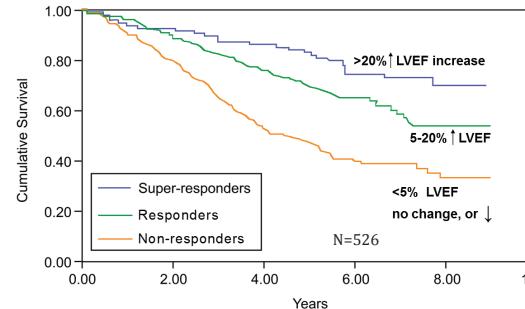
SURVIVAL BENEFIT OF CRT

- A meta-analysis of five randomized trials assessing the effects of CRT on morbidity and mortality in patients with symptomatic heart failure showed that CRT works well, and has survival benefit compared to medical therapy.





Durability of the survival effect of CRT by level of left ventricular functional improvement: fate of "non-responders"



- However, there are variations in the patients' response with some showing very good response to CRT while some showed no response, which affected survival. A clinical trial showed that those who responded to CRT had good 5-year survival, and its degree intimately tied to the level of improvement in ventricular function; whereas the non-responders had poor survival.
- There are several reasons for non-response to CRT, such as anemia, arrhythmia, QRS, and suboptimal AV timing.

LEVELS IN CRT

1. Pre-CRT: Candidate selection

Recommendations made for appropriate patient selection clearly signify the importance of QRS duration and morphology.

2. CRT: LV lead delivery

3. Post-CRT: Optimization

MEASURES TO INCREASE CRT EFFICACY

a. Pre Implant: Patient Selection

- LBBB and QRS duration >150 ms are criteria recommended for selection of patients for CRT. However, it is important to note that approximately 20% of patients matching these criteria do not respond.

b. At Implant: Lead Deployment

- Use of multipolar leads that reach more of the left ventricle and areas of late activation.
- However, it was observed that anatomical positioning of leads (anterior, posterior, lateral) did not show any difference.
- Electrical delay: qLV >95 ms used as a measure of activation delay has limited specificity and sensitivity.

Overall, it shows that despite taking measures at pre-implant (*Selecting the right candidate*) and at-implant (*optimizing the lead position*) stages, CRT has modest efficacy, showing the potential for measures at the post-implant stage.

Post pacing optimization (beyond patient selection and LV lead location)

1. Select ideal pacing configuration

- Echocardiographic
- Electrical resynchronization

2. Maintain BiV pacing “dynamically” through changing needs

- Quantity
- Consistency

For patients with <98% pacing, pacing loss commonly due to atrial fibrillation (AF), premature ventricular contractions (PVCs), but; inappropriately programmed sensed/paced atrioventricular (AV) intervals accounted for 34.5% of all ventricular sensing episodes.

CRT IN ATRIAL FIBRILLATION

- CRT depends on delivery of effective LV pacing
- Pacing counters may overestimate % effective LV pacing
 - E.g., Pseudofusion in AF: inconsistent paced QRS
- A study conducted in patients with AF undergoing CRT found that inconsistency of paced QRS morphologies decreased CRT efficacy despite high %BiV pacing; CRT response occurred in patients with effective CRT, i.e. only patients with complete capture responded clinically to CRT.
- Several devices are available that are designed for post-procedural dynamic programming and does this automatically at periodic intervals.; for e.g., the ADAPTive CRT re-optimize every minute.
- SyncAV is a new algorithm that provides the ability to (i) electrically resyncronize, and (ii) maintain % BiV pacing through changing needs (quantity and consistency)
 - Dynamically adjust AV delay according to patient's intrinsic rhythm
 - Maintains programmed resynchronization settings.

SUMMARY

- LBBB and optimized LV lead position is beneficial but not complete for electrical optimization, which requires attention to paced effects
- Nominal programmed settings may be suboptimal or even exacerbate electrical dyssynchrony
- CRT programming as an additional step is facilitated by:
 - Multipolar leads
 - Attention to:
 - » LV paced effects and use of MPP (individualization is key)
 - » Variability in intrinsic AV intervals
- Dynamic ambulatory adjustments increase dose of “Effective CRT”.

Class I recommendations
CRT is indicated for patients who have
LVEF ≤ 35%
Sinus rhythm
Left bundle branch block (LBBB)
QRS duration ≥ 150 ms
NYHA class II, III, or ambulatory class IV symptoms
Guideline-directed medical therapy
(Level of evidence: A for NYHA class III/IV; level of Evidence: B for NYHA class II)
Class IIa (Class 1 in ECS)
1. CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT.
2. CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, a non-LBB pattern with a QRS duration ≥ 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT.

Long-term DAPT: For whom and how long?

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DAPT – CURRENT RECOMMENDATIONS AND GUIDELINES

The estimated number of patients requiring dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and an oral inhibitor of the platelet P2Y₁₂ receptor for adenosine 5'-diphosphate (ADP), is considerable and has increased over time. Patients have an indication for DAPT after coronary intervention or myocardial infarction (MI), respectively.

Guidelines and Focused updates compiled with the support of the European Society of Cardiology's (ESC) Committee for Practice Guidelines (CPG) facilitate decision making of health practitioners in daily practice. However, the final decision regarding any patient should be made by the responsible health professional in consultation, with the patient and his/her family.

The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales.

Classes of recommendation	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective; and in some cases may be harmful	Is not recommended

Levels of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

2017 ESC FOCUSED UPDATE ON DAPT IN CORONARY ARTERY DISEASE (CAD)

Changes in recommendations in 2017

- Pre-treatment with P2Y₁₂ inhibitor when Percutaneous Coronary Intervention (PCI) is planned (Class I)
- Liberal use of Proton Pump Inhibitor (PPI) to mitigate minimum gastrointestinal bleeding (GI) risk (Class I)
- Elective surgery requiring discontinuation of the P2Y₁₂ inhibitor after 1 month (Class II)
- Ticagrelor interruption 3 days prior to elective surgery (Class II)
- Dual therapy as an alternative to triple therapy when bleeding risk outweighs the ischemic risk (Class II)
- Discontinuation of antiplatelet treatment in patients treated with DAC should be considered at 12 months (Class III)
- Routine platelet function testing to adjust therapy (Class III)

New recommendations in 2017

- The occurrence of actionable bleeding while on DAPT should prompt reconsideration of type and duration of DAPT regimen (Class I)
- The decision for DAPT duration should be dynamic and re-assessed during the course of the initially selected DAPT regimen (Class I)
- Discontinuation of P2Y₁₂ inhibitor therapy after 6 months when stenting ACS patients with PRECISE-DAPT ≥ 25 (Class II)
- 6-month DAPT regimen in patients with SCAD, treated with drug-coated balloon (Class II)
- Early administration of ticagrelor/clopidogrel in NSTE-ACS with invasive approach (Class II)
- Ticagrelor 60mg b.i.d. preferred over other oral P2Y₁₂ inhibitors for DAPT continuation > 12 months in post-MI (Class III)

New/revised concepts

- Metallic stent and DAPT duration
- Switch between P2Y₁₂ inhibitor
- Risk scores to guide DAPT duration
 - PRECISE DAPT score
 - DAPT score
- Specific profiling
 - Definition of complex PCI
 - Unfavorable profile for OAC and APT
 - Gender considerations and special populations

- DAPT duration without stenting
 - Medical management
 - CABG or cardiac surgery
- Anticoagulation and DAPT
 - Acute and chronic setting
 - Dosing regimen

SMART-DATE

6-month versus 12-month or longer DAPT after PCI in patients with acute coronary syndrome - a randomised, open-label, non-inferiority trial

The study involved 2712 patients in total: 1357 in the 6-month DAPT group and 1355 in the 12-month or longer DAPT group. Clopidogrel was used in over 80% of patients. The trial failed to show significant differences in the primary endpoint which occurred in 4.7% in the 6 month group vs. 4.2% in the 1 year group ($p=0.51$) with significance for the non-inferiority margin of $p=0.027$. Although there were no differences in the other individual secondary endpoints, 6-month therapy was associated with an excess myocardial infarction compared to 1 year. Bleeding was numerically higher but not statistically significant with 1 year vs. 6-month groups.

Take on the trial: Based on the findings of SMART-DATE, 6 months of dual antiplatelet therapy with clopidogrel is not recommended for ACS patients undergoing drug eluting stenting given the occurrence of excess MI with this strategy. In current practice, the “novel” antiplatelets that are more potent than clopidogrel are now standard of care for ACS patients. Several studies are underway evaluating shorter duration of novel agents in the setting of ACS and stenting with drug eluting stents which might be of relevance in the current contemporary care era, and the results of these trials are awaited.

Optimising results of PCI – Is imaging guidance an essential way of doing on what is the evidence?



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ANGIOGRAPHY LIMITATIONS

Angiographic imaging suffers from many limitations which may distort the diagnostic information obtained from coronary arteriograms:

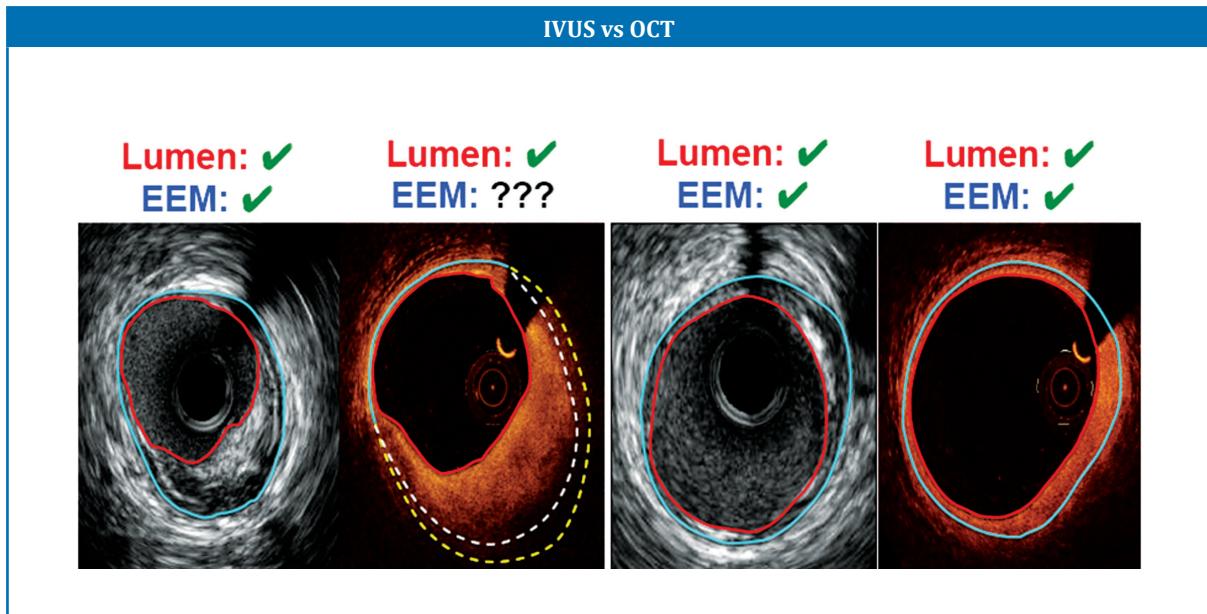
- Radiographic features limiting precise coronary stenosis measurement are caused by the x-ray source, the image intensifier, and the chemical properties of the cinefilm
- Biologic variations are introduced by fluctuations in angiographic contrast concentration and flow- or contrast-dependent coronary dilation
- Random errors are also introduced by the selection of the radiographic projection and frame to be analyzed and the digitization of cineangiograms

These limitations and their significance in distorting quantitative information obtained from coronary angiograms

INTRAVASCULAR ULTRASOUND (IVUS) AND OPTICAL COHERENT TOMOGRAPHY (OCT) IN COMPARISON

Both systems offer an anatomic assessment of the vasculature and allow visualization into the living, beating hearts. Both of these techniques are used to make measurements for lesion length and lumen size. Although IVUS is an appropriate method of choice for this scenario, IVUS has certain limitations which can be overcome by using optical coherent tomography (OCT).

Intravascular ultrasound (IVUS)	Optical coherent tomography (OCT)
<ul style="list-style-type: none"> Used to evaluate the extent and distribution of the neointima tissue within the stented segment but is limited to visualize its complex tissue structure as can be documented by histopathology IVUS emits sound waves 	<ul style="list-style-type: none"> It provides high-definition color images and is a leap forward in assessing coronary vessels from an anatomic standpoint. It has much better resolution, with 10x the axial and lateral resolution of IVUS OCT uses light waves OCT is able to produce a resolution 10 times greater than IVUS and is able to show much more information. OCT allows us to determine vessel sizing, stent under-expansion, dissection, thrombus, and gives us a good



HOW TO DETERMINE THE LANDING ZONE: IVUS

IVUS can assess true vessel (external elastic membrane) size to facilitate (and maximize) stent-size selection based on the largest reference lumen, midwall (halfway between the lumen and the external elastic membrane), or media-to-media dimensions. Stent length is based on identification of proximal and distal landing zones as the largest lumen with the least plaque within the same coronary artery segment avoiding areas of calcification, attenuation, and large plaque burden and measuring the distance between proximal and distal landing zones when IVUS is performed using motorized transducer pullback.

OCT CAN BE USED LIKE IVUS TO OPTIMIZE STENTS

OCT CAN BE USED LIKE IVUS TO OPTIMIZE STENTS!

MUSIC - criteria

If minimal stent area <9.0 mm²:

- Minimal stent area ≥ 90% of the mean reference lumen area
- Or Minimal stent area ≥ 100% of lumen lowest reference lumen area
- Proximal stent entrance ≥ 90% of proximal reference lumen area

If minimal stent area > 9.0 mm²:

- Minimal stent area ≥ 80% of the mean reference lumen area
- Or Minimal stent area ≥ 90% of lumen lowest reference lumen area
- Symmetric stent expansion defined by Stent Dmin/Dmax >0.7
- Complete stent apposition against the vessel wall

RESIST - criteria

- Minimal stent area > 80% of the mean reference lumen area
- TULIP - criteria
- Minimal stent diameter 80% of the mean reference diameters
- Minimal stent area (MLA) \geq 100% of distal reference lumen area
- Complete stent apposition

DIPOL - criteria

- Minimal stent area > 80% of mean reference lumen area or minimal stent area $> 7.5 \text{ mm}^2$ with full stent apposition

AVID - criteria

- Minimal stent area \geq 90% of distal reference lumen area
- Stent fully opposed to vessel wall
- Dissections covered by stent

HOME DES - criteria

- Minimal stent area $> 5 \text{ mm}^2$ or $> 90\%$ of distal reference lumen area
- Apposition of all sent struts
- No edge dissections

PCI OPTIMIZATION USING OCT

- **Acquire the image:** High quality image planning for PCI optimization
- **Assess plaque composition:** Determining vessel preparation
- **Identify references segments:** Stent from normal to normal
- **Choose stent size:** Size by the smallest mean EEL to EEL diameter of reference segment
- **Determine expansion/MSA:** Small increase in MSA lead to major improvements in outcomes
- **Rule out geographic miss:** Angiographic co-registration can eliminate geographic miss
- **Determine apposition:** Treatment is based on location (ostial) and relationship to under expansion
- **Identify edge dissection:** Treatment is based on location (proximal vs distal), arc, length and flow
- **Identify tissue protrusion**

SUMMARY

- The development of optical coherence tomography (OCT) provides new opportunities for the evaluation of coronary stents
- Having a much higher spatial resolution than intravascular ultrasound (IVUS), OCT is currently used for long-term assessment of stent implantation. In the immediate future, however, it is quite likely that OCT will be used synergically with IVUS to optimise stent deployment; the criteria for optimising stent implantation using OCT will be clearly indebted to the evidence gathered with IVUS, with an added value in contexts like ambiguous images presenting after stenting, or in complex percutaneous coronary interventions (PCI) procedures like bifurcation stenting
- However, since OCT is capable of identifying, during PCI, findings of potential relevance beyond the resolution IVUS, such as thrombus or tissue protrusion, intra-stent or edge dissections, or specific patterns of hyperplasia in restenotic lesions, it is foreseeable that new OCT-specific recommendations for optimal stent implantation will be made in the near future.

Remote monitoring of cardiac implantable electronic devices – Should this be standard of care?



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INTRODUCTION

- Cardiac implantable electronic devices (CIEDs) comprise pacemakers, implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT) devices, and implanted rhythm monitors and have evolved significantly over the past few decades in a number of ways
- Firstly the indications for their use have expanded, and access to these technologies has improved such that CIEDs have become increasingly prevalent all over the world
- Secondly, CIEDs have an ever-improving capability for remote monitoring (RM) of device function and patient health. By leveraging existing communication technologies (e.g., cellular, satellite, etc.), the tremendous wealth of information recorded and stored by CIEDs has become increasingly available to health care providers without face-to-face interaction.

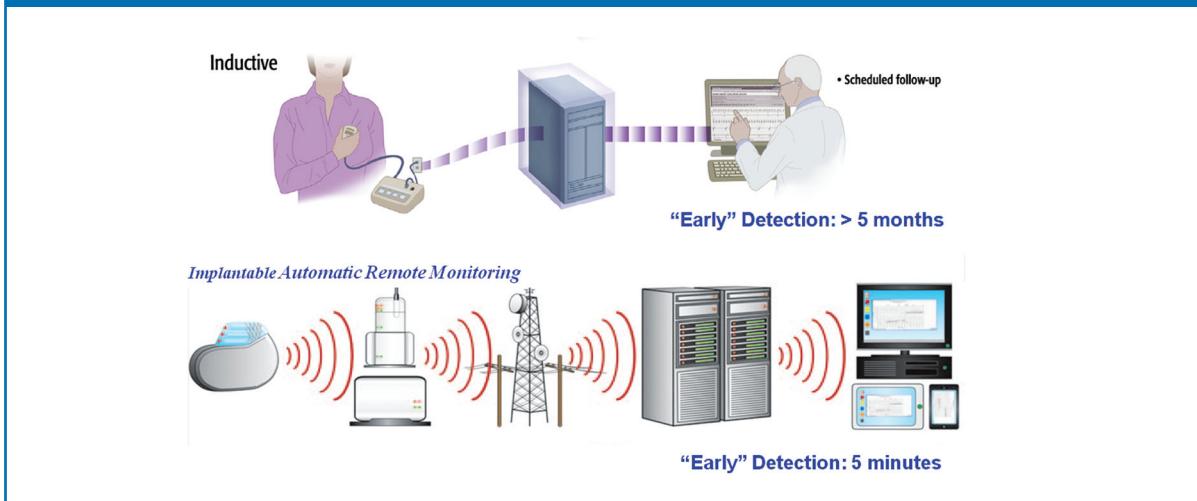
NEED OF REMOTE MONITORING FOR CHRONIC ILLNESSES

- Lack of hospital setting
- Attenuate the growing burden on hospital setting across the globe
- Reducing the overgrowing burden on the existing hospital
- To be able to monitor a large number of patients with chronic illnesses
- Maintain a connection and only bring in the patient to the hospital when they need to be seen
- To use hospital resources and own time more efficiently
- To cover a large patient population by maintaining patient and physician connection in the out-patient facility, out-patient setting and community setting
- To prevent crisis by efficient monitoring

WHAT WE HAVE WITH IMPLANTABLE DEVICES IN REMOTE MONITORING?

The technology has evolved significantly before it used to be patient-driven transmitted data that required coordination between patients, physicians and clinics. Both physicians and clinics are vulnerable to

Evolution of Implantable Device Technology



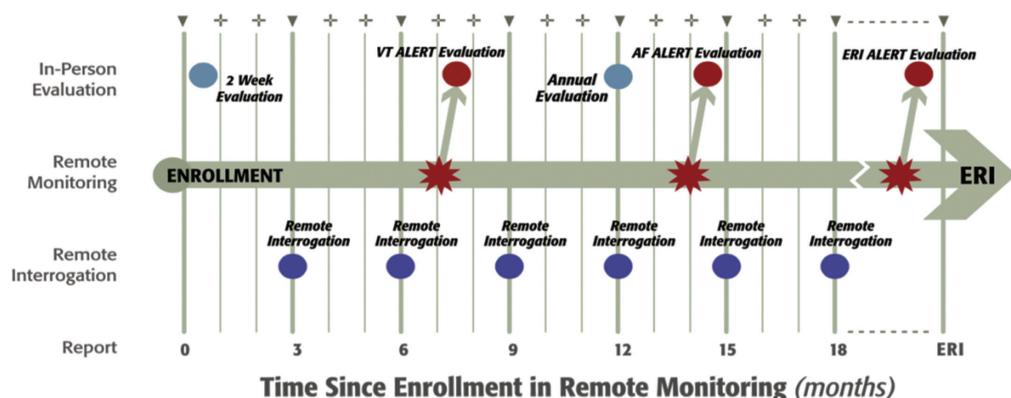
compliance and attrition. An early detection of this method sometimes to be modified to be seen once a year perhaps occasionally transmitting seen every 5 months. But the new technology implantation automate remote monitoring offers a better and improved window for management of patients with implants. Patients seldom have any connection with clinic and the data is transmitted automatically by the device via a telecommunication on daily basis. The collected data is well arranged, filtered and reviewed based on the requirement and further discretion over preventive and treatment strategies.

TRUST TRIAL

The TRUST trial is the first large-scale assessment of ICD follow-up either conventionally or with remote monitoring. Home monitoring (HM) permitted safe extension of face-to-face encounters, improved adherence to scheduled checks, significantly reduced the need for in-hospital device evaluation (without a detrimental effect on safety), yet enabled prompt evaluation of symptomatic or silent problems. The Lumos-T Safely Reduces Routine Office Device Follow-Up (TRUST) trial tested the hypothesis that remote HM with automatic daily surveillance is safe and effective for implantable cardioverter-defibrillator follow-up for 1 year and enables rapid physician evaluation of significant events.

HRS Expert Consensus Statement on Remote Monitoring – May 2015

Standard of Care: Continuous Monitoring With Event-Based Follow-Up



HRS Remote Monitoring Consensus Statement Recommendation

Device Follow-Up Paradigm

A strategy of remote CIED monitoring and interrogation, combined with at least annual IPE, is recommended over a calendar-based schedule of in-person CIED evaluation alone (when technically feasible).

All patients with CIEDs should be offered RM as part of the standard follow-up management strategy.

Before implementing RM, it is recommended that each patient be educated about the nature of RM, their responsibilities and expectations, potential benefits, and limitations. The occurrence of this discussion should be documented in the medical record.

It is recommended that all CIEDs be checked through direct patient contact 2 – 12 weeks postimplantation.

It may be beneficial to initiate RM within the 2 weeks of CIED implantation.

All patients with an implantable loop recorder with wireless data transfer capability should be enrolled in an RM program, given the daily availability of diagnostic data.

It is recommended that allied health care professionals responsible for interpreting RM transmissions and who are involved in subsequent patient management decisions have the same qualifications as those performing in-clinic assessments and should ideally possess IBHRE certification for device follow-up or equivalent experience

It is recommended that RM programs develop and document appropriate policies and procedures to govern program operations, the roles and responsibilities of those involved in the program, and the expected timelines for providing service.

CIED = cardiac implantable electronic device; HRS = Heart Rhythm Society; IBHRE = International Board of Heart Rhythm Examiners; IPE = in-person evaluation; RM = remote monitoring.

Device and Disease Management

RM should be performed for surveillance of lead function and battery conservation.

Patients with a CIED component that has been recalled or is on advisory should be enrolled in RM to enable early detection of actionable events.

RM is useful to reduce the incidence of inappropriate ICD shocks.

RM is useful for the early detection and quantification of atrial fibrillation.

The effectiveness of RM for thoracic impedance alone or combined with other diagnostics to manage congestive heart failure is currently uncertain

CIED = cardiac implantable electronic device; ICD = implantable cardioverter-defibrillator; RM = remote monitoring

SUMMARY

- Remote Monitoring technologies continue to evolve; patients connect to a system that allows transmission of stored CIED information to a provider
- If technological barriers and privacy concerns can be adequately addressed, there may be opportunity to program CIEDs remotely
- This may be particularly important for patients in remote geographic locations, those with urgent/emergent need based on a clinical event, and for the administration of software upgrades or execution of advisories and recalls amenable to reprogramming.

Sudden cardiac death – Is it preventable – drugs or device – A critical appraisal



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SCD BURDEN IS LARGE

- Sudden cardiac death (SCD) is usually defined as death due to cardiac causes occurring within 1 hour of the onset of symptoms
- 10% of total mortality – 7 lakh SCD every year
- Mean age – 61 yrs
- SCD as 1st manifestation of CAD is common
- SCD in the young is most devastating

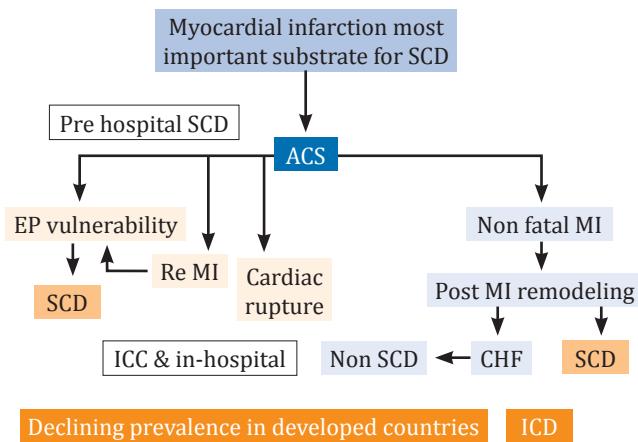
RISK STRATIFICATION FOR SCD IN HYPERTROPHIC CARDIOMYOPATHY

- Hypertrophic cardiomyopathy (HCM) remains one of the common causes of SCD in young individuals.
- An integral component of clinical investigation and management of patients with HCM is the assessment of risk of sudden death.
- At present, considerations for ICD therapy to prevent sudden death in patients with HCM should be confined to those judged to be in the high-risk subset, based on the presence of one or more of the acknowledged risk factors.
- Myocardial infarction (MI) constitutes the commonest cardiovascular substrate for sudden cardiac death.
- Strongest SCD risk factors includes- Cardiac arrest/sustained VT, family history of sudden death, malignant genotype, recurrent syncope, multiple-repetitive NSVT, exercise hypotension and massive LVH.

MORTALITY REDUCTION

- There has been reduction in the mortality; following reasons may be responsible for this reduction.

Myocardial infarction: Most important substrate for Sudden cardiac death



Primary prevention

- Smoking Cessation
- Hypertension & Diabetes control
- Cholesterol reduction

Treatments

- Acute myocardial infarction reperfusion
- Secondary prevention drugs
- Revascularization

VARIOUS CLASSES OF DRUGS WITH SCD MORTALITY BENEFIT

- Beta blockers reduce SCD in HF; various trials such as, US carvedilol, CIBIS II, and MERIT HF have shown relative reduction in SCD ranging from 40-50%.
- The effects of angiotensin-converting enzyme inhibitors (ACEI) in post myocardial infarction heart failure were evaluated by various trials. In a reanalysis of SOLVD-P, enalapril with beta-blockers, compared to enalapril alone, significantly reduced total (4.3% vs. 5.6%), p <0.01 and sudden death mortality (1.3% vs. 1.8% p <0.05).
- According to EPHESUS 2003 and RALES 1999, aldosterone antagonists decrease occurrence of SCD.
- Elite I, the only ARB trial, showed SCD mortality benefit i.e., 36% reduction over 4 weeks.

SUMMARY

- SCD is Global clinical problem
- Beta blockers, ACEI, Aldosterone antagonists, are used in maximally tolerated doses have resulted in decline in SCD burden
- Defibrillator devices have added incremental value to SCD prevention.
- Guideline-directed medical therapy (GDMT) with devices is the prescription for SCD prevention.

Atrial fibrillation – Drugs or ablation, how to decide and which has a better outcome?



DR. NIRAJ VARMA

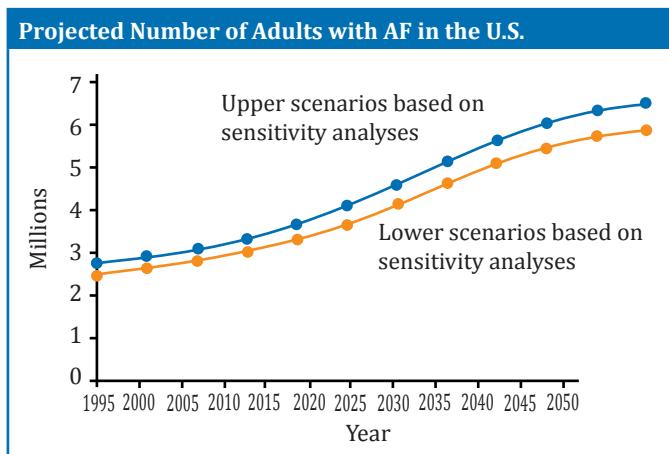
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EPIDEMILOGY OF ATRIAL FIBRILLATION

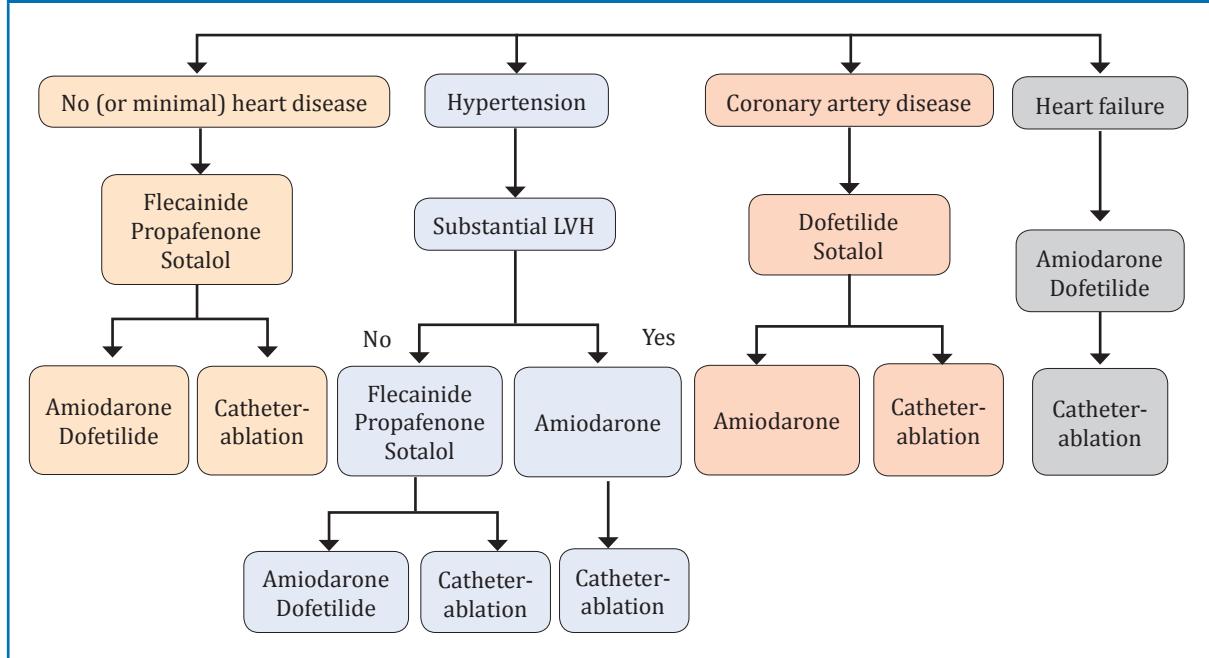
Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical function. Atrial fibrillation is the most common arrhythmia in elderly persons and a potent risk factor for stroke. The number of patients with atrial fibrillation is likely to increase 2.5-fold during the next 50 years, reflecting the growing proportion of elderly individuals.

MAINTENANCE OF SINUS RHYTHM IN AF PATIENTS

- Management of patients with AF requires knowledge of its pattern of presentation (paroxysmal, persistent, or permanent), underlying conditions, and decisions about restoration and maintenance of sinus rhythm, control of the ventricular rate, and antithrombotic therapy.
- Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or atrioventricular (AV) node dysfunction unless they have a functioning electronic cardiac pacemaker.



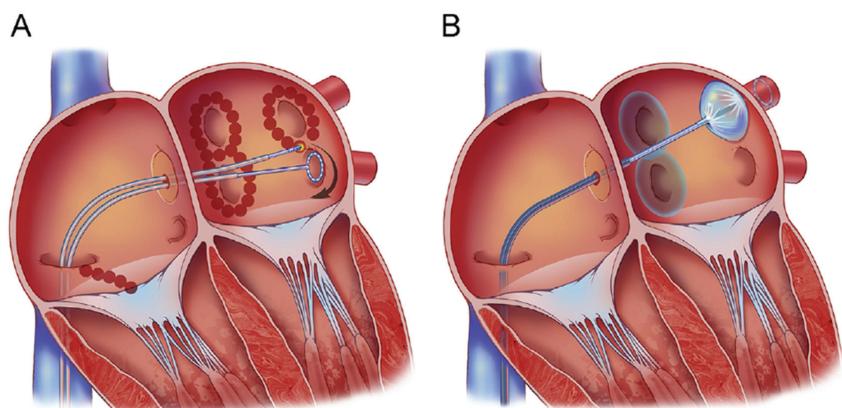
Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation



ABLATION: ATRIAL FIBRILLATION

- Management of AF by ablation is effective for both rate and rhythm. Catheter ablation should be considered to maintain sinus rhythm in selected patients who failed to respond to antiarrhythmic drug therapy control. Techniques of ablations are as follows:
 - Circumferential ablation cryoballoon
 - Double transeptal puncture

Circumferential ablation cryoballoon



COMPLICATIONS

Overall complication rate is 1% - 2% when performed by an experienced operator.

Various complications and their prevalence	
Complications	Prevalence
Stroke	0.2% - 1%
Cardiac perforation/tamponade	0.5% - 2%
Vascular injury/bleeding	1.0% - 2%
Phrenic nerve injury	0.1% - .5%
PV stenosis	0.2% - 0.5%
Atrial esophageal fistula	<0.1%
Cerebral embolic event	0.1% - 0.5%
Death	<0.1%

AF ABLATION VS. ANTIARRHYTHMIC DRUGS

According to CABANA trial, treatment strategy of percutaneous left atrial catheter ablation for purpose of eliminating AF is superior to current state-of-the-art medical therapy with either rate control or rhythm control drugs for reducing total mortality (primary endpoint) and decreasing composite endpoint of total mortality, disabling stroke, serious bleeding or cardiac arrest (key secondary endpoint) in patients with untreated or incompletely treated AF warranting therapy.

SUMMARY

- AF ablation is a well established treatment
- Since first developed safety and efficacy have improved
- Technically challenging
- Outcomes:
 - Single procedure efficacy varies from 30% to 80%
 - The major complication rate ranges from 1% to 3%
- The indications for AF ablation are defined in the 2017 consensus document on AF ablation
- First line ablation is appropriate for small but important subsets of patients

Transcatheter aortic valve replacement, Status in 2018



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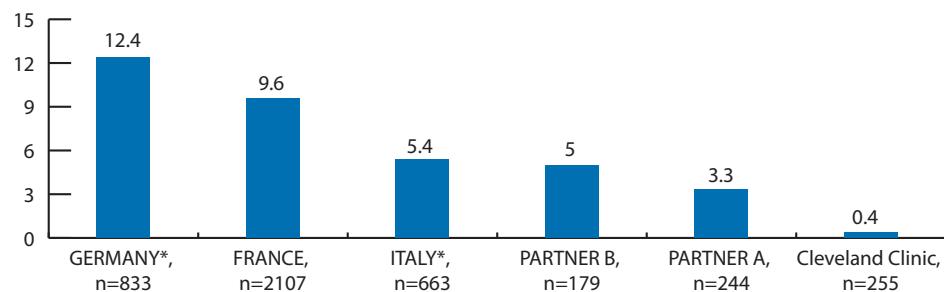
AORTIC STENOSIS

- Aortic stenosis is the most common of all valvular heart diseases in the developed nations of the world
- A typical case of aortic stenosis would be:
 - An old age patient who presents with complaint of shortness of breath with exertion
 - There would no prior cardiac history, no lightheadedness, no jugular vein distension (JVD), no edema, and lungs would be clear
 - Upon examination the BP and HR will be normal
 - Upon echocardiography – Normal S1 sound, but A2 will not be heard and there will be late peaking systolic pressure
- Aortic valve surgery is the recommended treatment for this, and it can now be performed safely and effectively using transcatheter techniques, potentially revolutionizing the approach to this potentially fatal disease

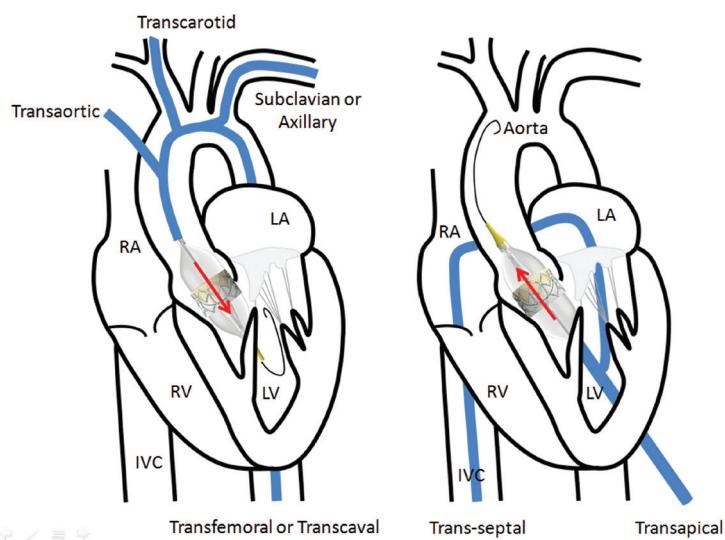
TRANSCATHETER AORTIC VALVE REPLACEMENT

- Transcatheter aortic valve replacement (TAVR) is an effective way to treat patients with symptomatic severe aortic valve stenosis who are deemed high risk or inoperable
- It is an easy and reproducible surgery and is associated with low mortality rates

30-day mortality rates with transcatheter aortic valve replacement in several trials



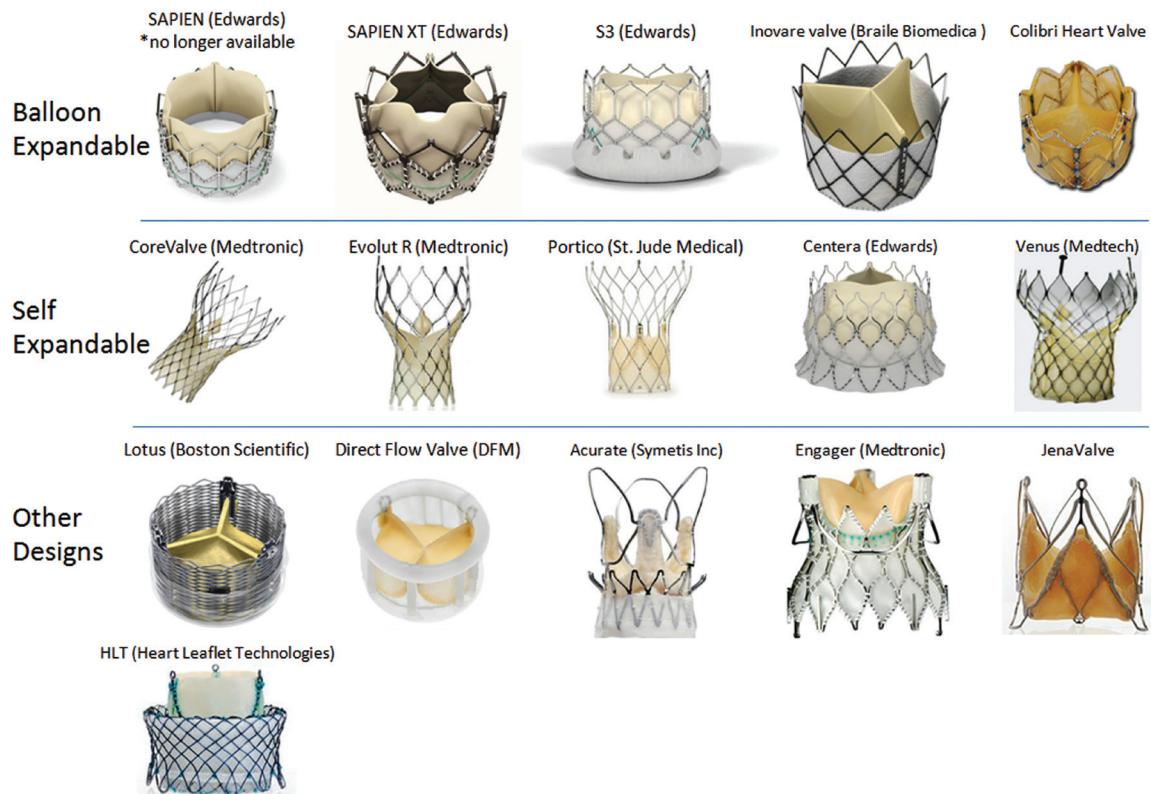
Different approaches for transcatheter aortic valve replacement



DIFFERENT TYPE OF VALVES AVAILABLE FOR TAVR

- There are several types of valves available such as balloon expandable, self expandable and other designs.

Different type of valves for transcatheter aortic valve implantation



MAJOR TAVR TRIALS

- Trials for TAVR include extremely high risk trial, followed by high risk, intermediate and low risk trials and various randomized control trials (RCTs) namely, Partner 1 B trial, comparing standard therapy with TAVR; Partner 1B (Core valve) trial; S3i SURTAVI trial; and NOTION P3 and CoreValve trial, all comparing surgical aortic valve replacement (SAVR) with TAVR
- The results of these trials demonstrate superiority of TAVR in comparison to SAVR in terms of reducing complications with time
- TAVR outcomes in P1A, P2A and S3i trials demonstrate procedural deaths to be reducing from 0.9% to 0.2%, valve embolization to be reducing from 2% to nil, number of major vascular complications to be reducing from 7.9 to 5.6, number of life-threatening bleeding to be reducing from over time 9.3 to 5.4, number of acute kidney injury (AKI) to be reducing from 2.9 to 0.5 and number of new AKI to be reducing from 8.6 to 5.

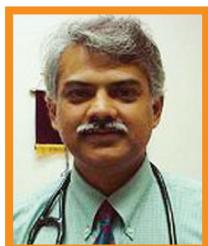
TAVR outcomes in P1A, P2A and S3i trials			
Outcomes	P1A	P2A	S3i
Procedural deaths (%)	0.9	1.2	0.2
Valve embolization (%)	2.0	1.0	0
Major vascularization (n)	7.9	7.9	5.6
Life-threatening bleeding	9.3	10.4	5.4
AKI (stage III)	2.9	1.3	0.5
New AKI	8.6	9.1	5.0

TAVR-transcatheter aortic valve replacement; AKI-acute kidney injury

SUMMARY

- Aortic stenosis is the most common of all valvular heart diseases in the developed nations of the world
- Aortic valve surgery using transcatheter techniques (TAVR) can be performed safely and effectively
- Results from various trials have shown that TAVR is associated with decreased risk of complications such as stroke in comparison to SAVR
- Considering these results, TAVR has become a standard of care for patients who are at high or intermediate risk and also for those who are inoperable (Class I A or II A recommendation depending in risk of patient)
- Trials are being conducted to assess the use of anticoagulants in such patients and results including durability data will take TAVR to a next level.

Will NOACs replace Vit K antagonists, Status in 2018



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ATRIAL FIBRILLATION AND STROKE

- Nearly 20-30% stroke episodes are attributed to Atrial fibrillation (AF)
- In AF, the stroke risk is 5-folds greater in comparison to that in sinus rhythm (SR)
- In cryptogenic stroke cases, 1/3rd of patients have AF
- Chronic AF is associated with decline in cognitive function
- Clinical AF affects about 35-40 million patients globally and is associated with high morbidity and mortality
- Besides, there are several cases of silent and subclinical AF as well

DRUG THERAPY FOR AF AND STROKE

- Vitamin K antagonists (VKA) such as warfarin are commonly prescribed in the prevention of stroke
- A meta-analysis showed that adjusted-dose warfarin was associated with reduced incidence of stroke by 64% when compared to control
- However, due to the limitations associated with its use, it is believed that nearly 50% of patients eligible for treatment receive no anticoagulant treatment.

Limitations of warfarin

- Unpredictable response
- Narrow therapeutic window
- Routine coagulation monitoring
- Frequent dose adjustments
- Slow onset/offset of action
- Numerous food-drug interactions
- Numerous drug-drug interactions
- Risk of Bleeding Complications

Warfarin use is associated with intracranial hemorrhage

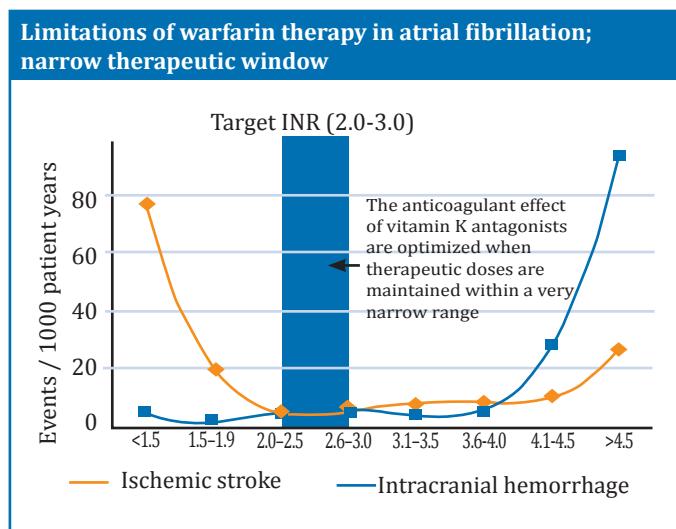
- Warfarin was ranked no. 1 in 2003 and 2004 in the number of mentions of “deaths for drugs causing adverse effects in therapeutic use”
- Warfarin is the commonest cause of anticoagulant-associated intracerebral hemorrhage (ICH)
- Warfarin use in ICH patients is associated with significant mortality

STROKE PREVENTION IN ATRIAL FIBRILLATION

- Over-anticoagulation [International Normalized Ratio (INR) >3] can lead to an increased risk of bleeding and under-anticoagulation (INR <2) can lead to increased risk of stroke.
- The anticoagulant effect of VKAs is optimized when therapeutic doses are maintained within a very narrow therapeutic range

BARRIERS TO WARFARIN

- Patient's bleeding risk is assessed to be too high for warfarin treatment (89%-91%)
- Doctor's lack of awareness about guidelines for Stroke Prevention in Atrial Fibrillation (SPAF) Management(69%) (Combination therapy, use of antiplatelet monotherapy, low dose warfarin)
- Lack of patient access to pathology labs for INR monitoring (67%)
- Patients refuse warfarin treatment (84%)
- Patient's comorbidities do not permit warfarin treatment (71%)



WARFARIN UNDERUSE

- Underuse of warfarin is greatest in elderly patients who are at the highest risk of stroke
- Warfarin is used in only 50% of the eligible patients with AF.

NEWER ORAL ANTICOAGULANTS (NOACs)

Newer oral anticoagulants:

- Are at least as effective as warfarin
- Have a predictable response
- Have wide therapeutic window
- Are associated with low incidence and severity of adverse effects
- Have oral fixed dose
- Have low potential for food or drug interactions
- Have fast onset and offset of action
- Are cost-effective

Comparison of VKA (warfarin) versus NOAC pharmacokinetics

Features	Warfarin	NOAC
Onset of action	Slow	Rapid
Dosing	Variable	Fixed
Food effects	Yes	No
Drug interactions	Yes	No
Monitoring	Yes	No
Half-life	Long	Short
VKA-vitamin K antagonist; NOAC-newer oral anticoagulants		

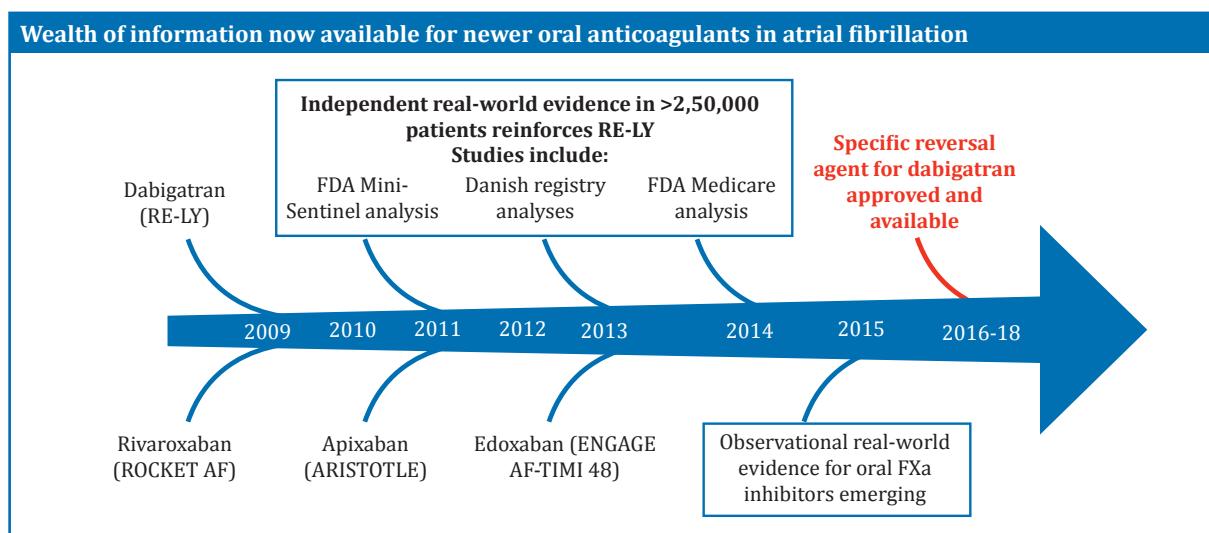
Dabigatran Etxilate

- Dabigatran etexilate is a NOAC that is a potent and reversible oral direct thrombin inhibitor 1 (DTI1) that inhibits both clot bound and free thrombin 1
- It has a predictable and consistent pharmacokinetic profile with rapid onset of action (peak plasma levels within 2 hours)

- Importantly, anticoagulation monitoring is not required with dabigatran etexilate
- It has a half-life of 12-17 hours (dose twice daily)
- Drug-drug interactions associated with dabigatran etexilate are low; it is not metabolized by cytochrome P450 (CYP450)
- It is not associated with any drug-food interaction
- Its dosing is independent of meals or dietary restrictions
- It has 6.5% bioavailability, ~80% renal excretion

COMPARISON OF VKA (WARFARIN) VS. NOAC PHARMACOKINETICS

- NOAC demonstrates superior pharmacokinetic profile than warfarin
- Now there is wealth of information available for NOACs which suggests its use in AF.



SUMMARY

- NOACs will possibly replace VKA; however VKAs must be continued for
 - Metallic prosthetic valves & RVHD
 - Well managed on VKAs with low risk of bleeding
- Indian context:
 - Cost – steadily coming down
 - However difficult measuring compliance
- VKA naïve patients should be offered NOACs
- NOACs: acid-peptic symptoms; Stroke/bleeding – learn to manage

Management pearls for heart failure with preserved EF management



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HEART FAILURE WITH PRESERVED EJECTION FRACTION

- Heart failure with preserved ejection fraction (HFpEF) is also called diastolic heart failure
- This disorder is associated with significant mortality and morbidity similar to HF with reduced ejection fraction (HFrEF)
- Patients with HFpEF show signs and symptoms of HF, have left ventricular EF $\geq 50\%$, have raised levels of natriuretic peptides { B-type natriuretic peptide (BNP) >35 pg/ml and/or N-terminal pro b-type natriuretic peptide (NT-proBNP) > 125 pg/ml}, and have at least one of the following criteria:
 - Relevant structural heart disease (left ventricular hypertrophy and/or left atrial enlargement)
 - Diastolic dysfunction.

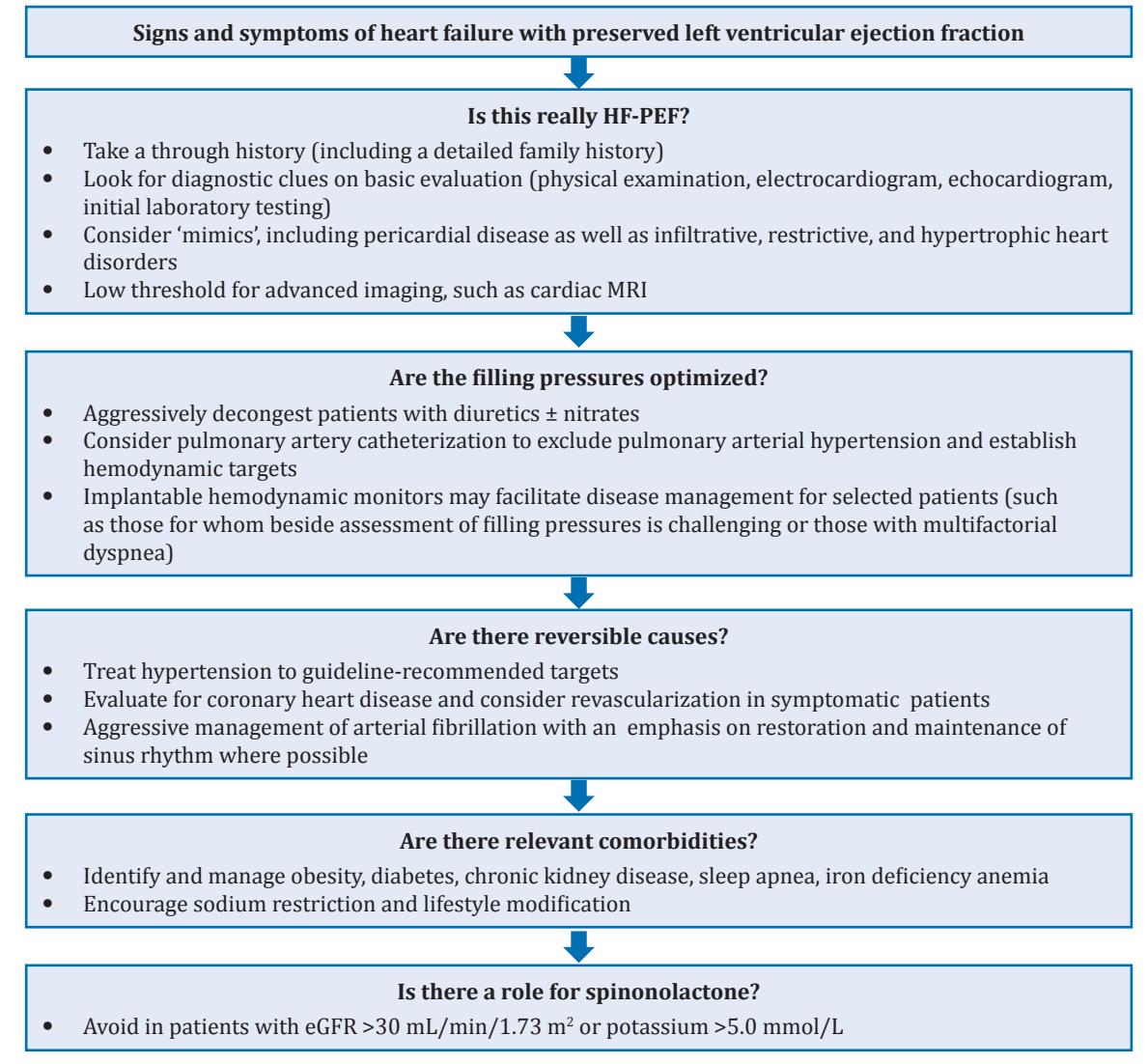
CLASSIFICATION AND PATHOPHYSIOLOGY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

- HFpEF is considered a heterogeneous disorder with varied phenotypes and multiple pathophysiological mechanisms
- A phenotype-based classification of HFpEF has been proposed
- The etiology of the disorder is diverse, and multiple comorbidities have been suggested to be associated with the pathophysiology of HFpEF
- These comorbidities cause a sequence of events leading to the myocardial remodeling and dysfunction in HFpEF

COMMON FINDINGS AND DIFFERENTIAL DIAGNOSIS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

- Echocardiography in HFpEF reveals left ventricular hypertrophy, left atrial dilatation, EF $\geq 40-50\%$, elevated E/e' ratio, increased left ventricular stiffness and raised left ventricular end-diastolic pressure
- Laboratory findings show modestly elevated BNP and NT-proBNP
- Differential diagnosis of HFpEF includes restrictive and hypertrophic cardiomyopathies, pericardial disease, right ventricular failure and storage diseases like fabry disease or LAMP2 and PRKAG2 diseases.

Clinical approach for the management of HFrEF



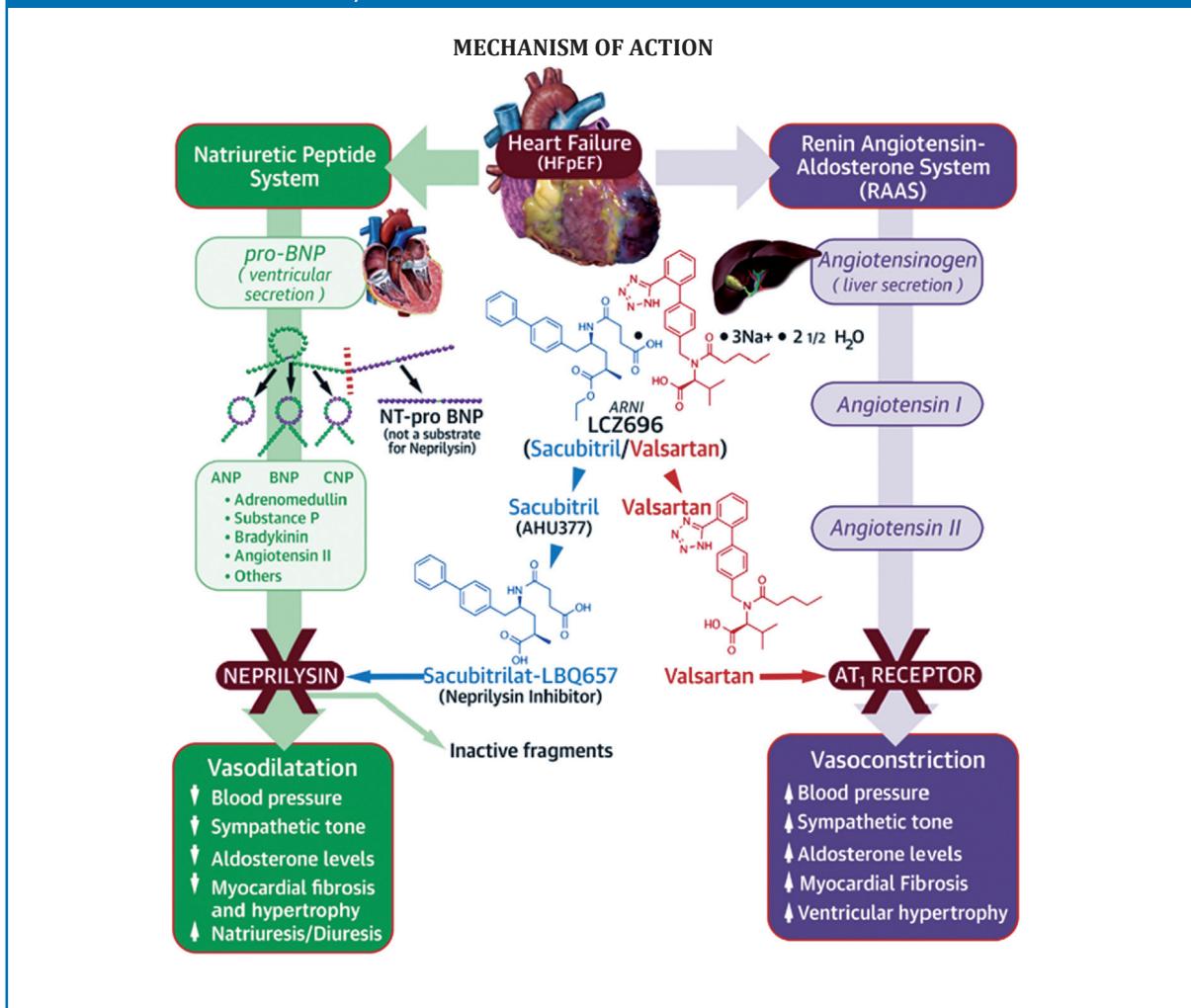
MANAGEMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

- At present, there is a lack of proven optimal treatment regimen for HFrEF
- Traditional management therapies have not been effective in treating HFrEF. However, a clinical approach for the management of HFrEF has been proposed
- Many clinical trials on HFrEF treatment have failed possibly because of improper recruitment and endpoint selection, limited knowledge of the disorder's pathophysiology, underestimation of the importance of comorbidities and focusing on inappropriate targets.

Role of sacubitril valsartan in the management of heart failure with preserved ejection fraction: The ongoing paragon HF trial

- Sacubitril/valsartan exhibits the novel mechanism of an angiotensin receptor neprilysin inhibitor
- The efficacy and tolerability of sacubitril valsartan in patients with HFrEF is being evaluated in this phase III trial

Mechanism of action of sacubitril/valsartan



- Patients with EF ≥ 45%, NYHA II–IV, and those having left atrial enlargement and/or left ventricular hypertrophy have been recruited
- The primary outcome of the trial is the composite of cardiovascular death and total HF hospitalizations. Additional treatment strategies of HFpEF include aggressive management of hypertension and all cardiac and non-cardiac comorbidities. Future development of successful therapies for HFpEF will require better understanding of the HFpEF phenotypes and discovery of specific therapy targeting the unique pathophysiological mechanisms.

SUMMARY

- Heart failure with preserved ejection fraction is associated with significant mortality and morbidity
- Multiple comorbidities have been associated with the pathophysiology of HFpEF
- There is a lack of proven optimal treatment regimen for HFpEF
- The efficacy and tolerability of sacubitril valsartan in patients with HFpEF is being evaluated in the paragon HF trial
- Additional treatment measures of HFpEF include aggressive management of hypertension and all cardiac and non-cardiac comorbidities.

Percutaneous treatment of functional mitral regurgitation



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SPECTRUM OF MITRAL REGURGITATION

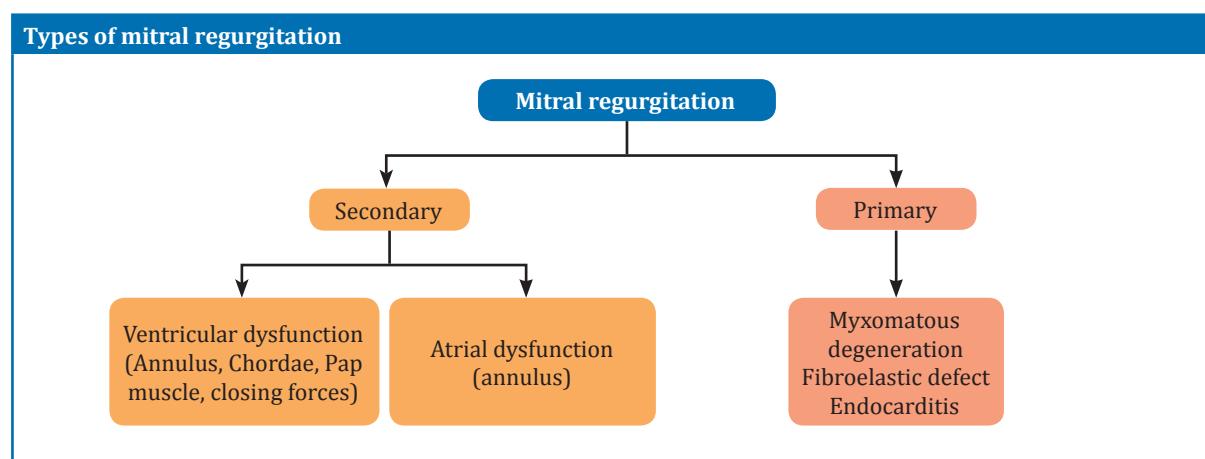
- Mitral regurgitation (MR) can be classified into two main categories: primary or secondary
- Primary MR can be caused due to myxomatous degeneration, fibroelastic deficiency or endocarditis
- Secondary MR occurs either due to atrial dysfunction or ventricular abnormalities.

MANAGEMENT OF MITRAL REGURGITATION

- Several medical society practice guidelines do not recommend mitral valve surgery in certain patients
- A randomized controlled trial evaluated the four-year survival rates in patients of mitral regurgitation following percutaneous repair and surgery

Outcomes from TTV registry-based dataset

- Data from the TTV registry on patients treated with mitral valve repair were analyzed
- The study population consisted of 2,952 patients treated between November 2013 and September 2015
- The rate of primary MR was 85.9%



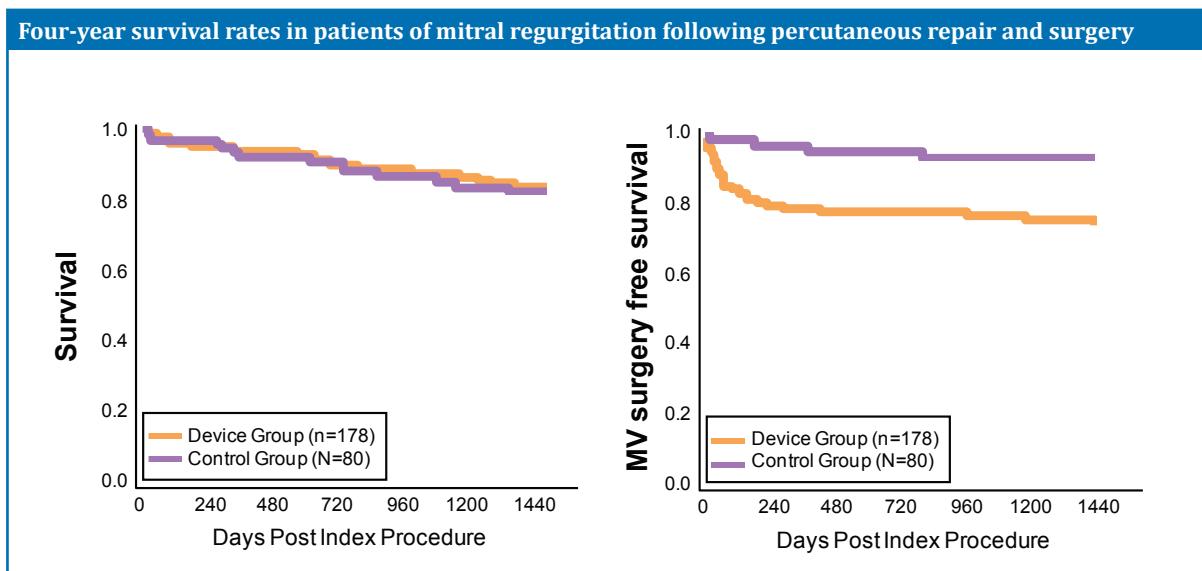
Guideline recommendations for mitral valve surgery

Heart Failure Guidelines	ACC/AHA	The effectiveness of mitral valve repair or replacement is not established for severe secondary mitral regurgitation in refractory end-stage HF.
	HFSA	Isolated mitral valve repair or replacement for severe mitral regurgitation secondary to ventricular dilatation in the presence of severe left ventricular systolic dysfunction is not generally recommended.
	ESC	Surgery may be considered in selected patients with severe functional MR and severely depressed LV function, who remain symptomatic despite optimal medical therapy.
Valvular Heart Disease Guidelines	ACC/AHA	MV repair may be considered for patients with chronic severe secondary MR due to severe LV dysfunction (LVEF < 30%) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing.
	ESC	Patients with severe MR, LVEF .30%, no option for revascularization, refractory to medical therapy, and low comorbidity.
Other	ISHLT	In patients with heart failure and low LVEF, ventricular restoration surgery or mitral valve repair may be considered.

Devices developed for the management of functional mitral regurgitation

Device design	Developmental phase
Leaflet techniques	
Edge-to-edge leaflet repair	
MitralClip™ (Evalve, Menlo Park, CA)	Phase III trials
MOBIUS (Edwards, Lifesciences, Irvine, CA)	Development halted
MitraFlex (TransCardiac Therapeutics, Altanta, GA)	Preclinical phase
Leaflet Space Occupiers	
Percu-Pro (Cardiosolutions, Stoughton, MA)	Phase I trials
Annuloplasty	
Indirect (via coronary sinus)	
Viacor PTMA (Viacor, Wilmington, MA)	Development halted
CARILLONTM Mitral Contour System (Cardiac Dimensions, Kirkland, WA)	First-in-human
MONARCTM (Edwards Lifesciences, Irvine, CA)	CE mark granted
St.Jude adjustable annuloplasty ring (St. Jude Medical, St. Paul, MN)	Development halted
NIH-Cerclage technology	Animal models
Direct	
Mitralign Percutaneous Annuloplasty System (Mitralign, Tewksbury, MA)	First-in-human
GDS Accucinch Annuloplasty System (GDS)	First-in-human
Kardium Cinch (Kardium)	Feasibility phase
Millipede Percutaneous Annuloplasty Ring (MC3, Ann Arbor, MI)	Preclinical phase
QuantumCor device (QuantumCor, Bothell, WA)	Preclinical phase
ReCor (ReCor Medical, Ronkonkoma, NY)	Feasibility phase

Adjustable Annuloplasty Ring (Mitral Solutions, Fort Lauderdale, FL)	First-in-human
Dynamic Annuloplasty Ring System (MiCardia, Irvine, CA)	First-in-human
PS3 System (Ample Medical Inc., Foster City, CA)	Development halted
Left ventricular remodeling	
iCoapsysTM (Myocor, Maple Grove, MN)	Development halted
BACE device (Phoenix Cardiac devices, Northbrook, IL)	First-in-human



The COAPT trial

- The trial evaluates the MitraClip system in patients with MR
- Approximately 610 MR patients have been enrolled at 100 investigational sites with about 305 subjects targeted to receive the study device
- Inclusion criteria is patients with symptomatic heart failure who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery
- Primary end point of the trial includes hospitalization for heart failure within 2 years
- Outcomes are evaluated at baseline and following treatment at 1-week, and after 1, 6, 12, 18, 24, 36, 48 and 60 months.

Scenario in United States

- MitraClip system is indicated in patients with primary MR and in those who are at high risk for surgery
- Other future approaches include:
 - Use of MitraClip for functional MR
 - Neochord and Harpoon (TA approach)
 - Carillon (coronary sinus device)
 - Pivotal trial in US

Clinical outcomes at 30 days and 1 year following mitral valve repair in patients with mitral regurgitation				
	Number of events	30 days	Number of events	1 year
Death	96	5.2	336	25.8
Myocardial infarction	3	0.2	27	2.5
Stroke				
Any stroke	17	1.0	36	2.7
Hemorrhagic	6	0.4	8	0.6
Heart failure hospitalization	80	4.7	254	20.2
Mitral valve surgery	9	0.4	10	2.1
Repeat mitraClip	23	1.3	80	6.2

Values are % unless otherwise indicated. Each variable was linked to U.S. Center of Medicare and Services data among 1,867 patients with linkage data.

- Direct annuloplasty
 - » Cardioband – Pivotal trial
 - » Millipede – Feasibility trial
- Early feasibility trials of TMVR
 - » Tendyne, CardiAQ, Tiara, Twelve, Caisson, Navigate
- Pivotal
 - » Intrepid, Tendyne

SUMMARY

- Mitral regurgitation can be categorized as primary or secondary
- Several medical practice guidelines disapprove surgery in certain MR patients
- Non-invasive devices are being developed as treatment option for MR
- In the US, MitraClip is an approved treatment option for percutaneous mitral valve repair in patients with primary MR
- The ongoing trials can help identify clinical and anatomical characteristics of different devices used in MR
- Percutaneous mitral valve replacement and repair can be considered in MR patients based on their efficacy and tolerability data.

Ethics in coronary revascularisation



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ETHICS: IS IT RELATED TO

- What your consent says right or wrong?
- Religious beliefs?
- Following law?

“Branch of philosophy dealing with values pertaining to human conduct, considering the rightness and wrongness of actions, motives and the ends of such actions”

ETHICS VS. LAW

Ethics is a standard of behavior where moral values serve as basis for ethical conduct whereas a law is a rule of conduct or action. Ethics concerns itself with why and how one ought to act where as law describe the way in which people are required to act with each other in a society.

THE RELEVANCE OF ETHICS

- Patients competing with scarce resources.
- Conflict of interest
- Perceptive decline in ethical standards of clinicians
- Fading of positive doctor-patient relationship

Ethical Decision Making Includes:

- Honesty
- Integrity
- Fairness
- Respect

Principles of Ethic:

- Non- Maleficence : “do no harm”
- Beneficence : “do good”
- Autonomy: “respect for persons”
- Justice & Equity : “to be fair”

CONSENT

Three sets of elements characterize informed consent:

- Preconditions (capacity and voluntariness)
- Information (disclosure and recommendations)
- Consent (decision and authorization)

PRINCIPLES ADOPTED BY THE AMERICAN MEDICAL ASSOCIATION ARE NOT LAWS, BUT STANDARDS OF CONDUCT WHICH DEFINE THE ESSENTIALS OF HONORABLE BEHAVIOR FOR THE PHYSICIAN

- A physician shall be dedicated to providing competent medical care, with compassion and respect for human dignity and rights.

- A physician shall uphold the standards of professionalism, be honest in all professional interactions, and strive to report physicians deficient in character or competence, or engaging in fraud or deception, to appropriate entities.
- A physician shall respect the law and also recognize a responsibility to seek changes in those requirements which are contrary to the best interests of the patient.
- A physician shall respect the rights of patients, colleagues, and other health professionals, and shall safeguard patient confidences and privacy within the constraints of the law.
- A physician shall continue to study, apply, and advance scientific knowledge, maintain a commitment to medical education, make relevant information available to patients, colleagues, and the public, obtain consultation, and use the talents of other health professionals when indicated.
- A physician shall, in the provision of appropriate patient care, except in emergencies, be free to choose whom to serve, with whom to associate, and the environment in which to provide medical care.
- A physician shall recognize a responsibility to participate in activities contributing to the improvement of the community and the betterment of public health.
- A physician shall, while caring for a patient, regard responsibility to the patient as paramount.
- A physician shall support access to medical care for all people

CHALLENGES: THE ECONOMIC IMPACT HAS LED TO PRESSURES FROM SEVERAL DIRECTIONS

- Seeking increased revenues, hospitals and departments of medicine exert pressure on cardiologists (for more procedures and higher fees).
- National and state credentialing standards for minimal procedural volumes influence cardiologists in case selection especially low-risk cases.
- Competition for technology creates an incentive to participate in clinical research, often sponsored by industry, another potential source of revenue for individuals, departments, and hospitals.
- The sponsorship by industry of both formal and informal educational seminars presents potential ethical conflicts to both invited lecturers and invited audiences.

RELATIONSHIP OF INVASIVE CARDIOLOGIST TO PATIENT

The invasive cardiologist is ultimately responsible for informing the patient of the various options, the risks and benefits of therapy, as well as for determining the appropriateness and timing of each invasive procedure.

- His ethical judgment for the patient must not be clouded by any conflict with money, prestige, academic advancement, patient ethnicity, socioeconomic status, or any other factor.
- There are many areas in which there can be a conflict between the patient's best interest and the physician's own personal interest. The cardiologist's commitment to his patient takes precedence over his allegiance to an institution.
- A cardiologist who has an ownership or other financial interest in a facility in which he performs his procedures must disclose this interest to the patient before performing the procedure
- Referral fees and fee splitting or sharing are unethical as well as illegal irrespective of the sources of the funds, other physicians, hospitals, or equipment vendors should not interfere with decision making in coronary revascularization.

CASE 1

A 62 yr old lady came with complaints of atypical chest pain and HTN (160/90). Her TMT was done which depicted mild positive response. Treatment was initiated with aspirin, atrovastatin, metoprolol 25 mg and telmisartan 40 mg. The patient was then referred to the cardiologist for angiography. The angiography

revealed 60% distal LAD disease and 80% OM 3 lesion measuring about 2 mm. The cardiologist explained the relative that the patient requires PTCA and stent placement because of disease in 2 arteries which if remain untreated may lead to heart attack later. The relative agreed and were told that they are going to use American stent. After FFR which was non-conclusive, PTCA and stent placement of LAD and OM3 was performed. The stent placed for LAD led to distal dissection (because over-sized stent was used as proper sized stent was not available) for which IVUS done and another stent was put. Now in the process there was small dissection in LM ostium, where another stent was put. Meanwhile chief of the lab noted that the 4 mm balloon used for post dilatation of LM has broken in the guiding and is not retrieved. Luckily doctor was able to retrieve whole assembly and further the angiography showed good result. However there was suspicion of incomplete expansion of LM stent. Rewiring was done and IVUS showed satisfactory result. The patient was sent to CCU and then was discharged on day 3. The family was convinced that PTCA was difficult but he has successfully managed the case and the patient is fine. Total 500 ml contrast, 4 balloon, 4 wire 1 IVUS and 4 stent was used and Patient was discharged on ticagrelor + aspirin.

Now the question arises whether:

- The Diagnosis was correctly made? – NO
- The TMT interpretation was correctly done? – No
- Adequate drug was advised – No
- The patient was informed about the need of angiography before performing? - No
- Doing adhoc angioplasty in distal disease was justified? – No
- LAD dissection, LM dissection and balloon break could have been avoided – Yes
- LAD and OM stent was unnecessary ? – Yes

CASE 2

A 30 year old patient with STEMI was asked for PPCI and was told that it's urgent and lifesaving. The patient's family was trying to arrange money. Thrombolysis was not offered until 3 hours, finally after 3 hours the procedure was done. The next day when family arranged the money PCI of distal RCA was done.

Now the question arises whether:

- The unrealistic amplified benefit of PPCI was told to the family? – Yes
- In anticipation that family might arrange money, Thrombolysis was delayed? – Yes
- Next day PCI of distal RCA in pain free stable patient was justified? – No

"Backed by some scientific data, amplified by unrealistic expectations of ill informed patients, some hospitals/doctors are avoiding Initial emergency treatment of acute MI. Instead they waste time in securing the finance for the costly invasive procedures. In the ensuing emotional and financial melee many of the ill-fated patients lose vital time window of thrombolysis as well."

SUMMARY

What should be done:

- Identify ethical issues and problems
- Identify & analyze available alternatives
- Select one alternative
- Justify the selection
- Risk benefit of treatment should be explained in a simple way.
- Should disclose information to the patient as far as possible
- Must take informed consent
- 'Competent' patients have the right to refuse treatment
- Never influence your decision for any other except the benefit of patient.

Rule in/Rule out AMI – Troponin timings are having impact on ER timings



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MYOCARDIAL INFARCTION

The diagnosis of acute myocardial infarction (MI) entails a combination of criteria that includes the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin, with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

- Symptoms of ischemia
- New or presumed new significant ST-T wave changes or left bundle branch block on 12-lead electrocardiogram (ECG)
- Development of pathological Q waves on ECG
- Imaging evidence of new or presumed new loss of viable myocardium or regional wall motion abnormality
- Intracoronary thrombus detected on angiography or autopsy.

TYPES OF MYOCARDIAL INFARCTION

- Type 1: Spontaneous MI due to atherosclerotic plaque rupture, ulceration, fissure, or erosion
- Type 2: MI secondary to an ischemic imbalance
- Type 3: MI resulting in death and biomarkers are unavailable
- Type 4:
 - 4a: MI associated with percutaneous coronary intervention (PCI)
 - 4b: MI associated with stent thrombosis
- Type 5: MI associated with coronary artery bypass graft surgery (CABG)

SENSITIVE AND HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

- With advancement in assay technology, there has been an improvement in cardiac troponin (cTn) assays and therefore the clinical ability to detect and quantify cardiomyocyte injury.
- Sensitive (detection of cTn in almost 20–50% of healthy individuals) and high-sensitivity cTn (hs-cTn, detection of cTn in almost 50–90% of healthy individuals) assays have two characteristic features that differentiate them from conventional cTn assays:
 - Detection of cTn in a substantial number of healthy persons and
 - A more precise definition of what is ‘normal’ (= the 99th percentile) with a precision of the assay expressed as the coefficient of variability which should be <20% and preferably <10%.
- These features are of major importance as a cTn value above the 99th percentile of a normal reference population is a ‘condition sine qua non’ for the diagnosis of acute MI.

CLINICAL IMPLICATIONS OF HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

- Compared with standard cTn assays, high-sensitivity assays:
 - Have greater negative predictive value for acute MI
 - Decrease the “troponin-blind” interval leading to earlier detection of acute MI
 - Result in approximately 4% absolute and about 20% relative increase in the detection of type 1 MI and a corresponding reduction in the diagnosis of unstable angina
 - Are associated with a 2-fold increase in the detection of type 2 MI.
- Levels of hs-cTn should be interpreted as quantitative markers of cardiomyocyte damage; it means that the higher the level of hs-cTn, the greater the likelihood of MI:
 - Elevations more than 5-fold the upper reference limit have high (>90%) positive predictive value for acute type 1 MI
 - Elevations up to 3-fold the upper reference limit have only limited (50–60%) positive predictive value for acute MI and may be associated with various conditions
 - It is quite usual to detect circulating levels of cTn in healthy individuals
 - Rising and/or falling cTn levels differentiate acute from chronic cardiomyocyte damage; the more pronounced the change, the higher the likelihood of acute MI.

‘RULE-IN’ AND ‘RULE-OUT’ ALGORITHMS

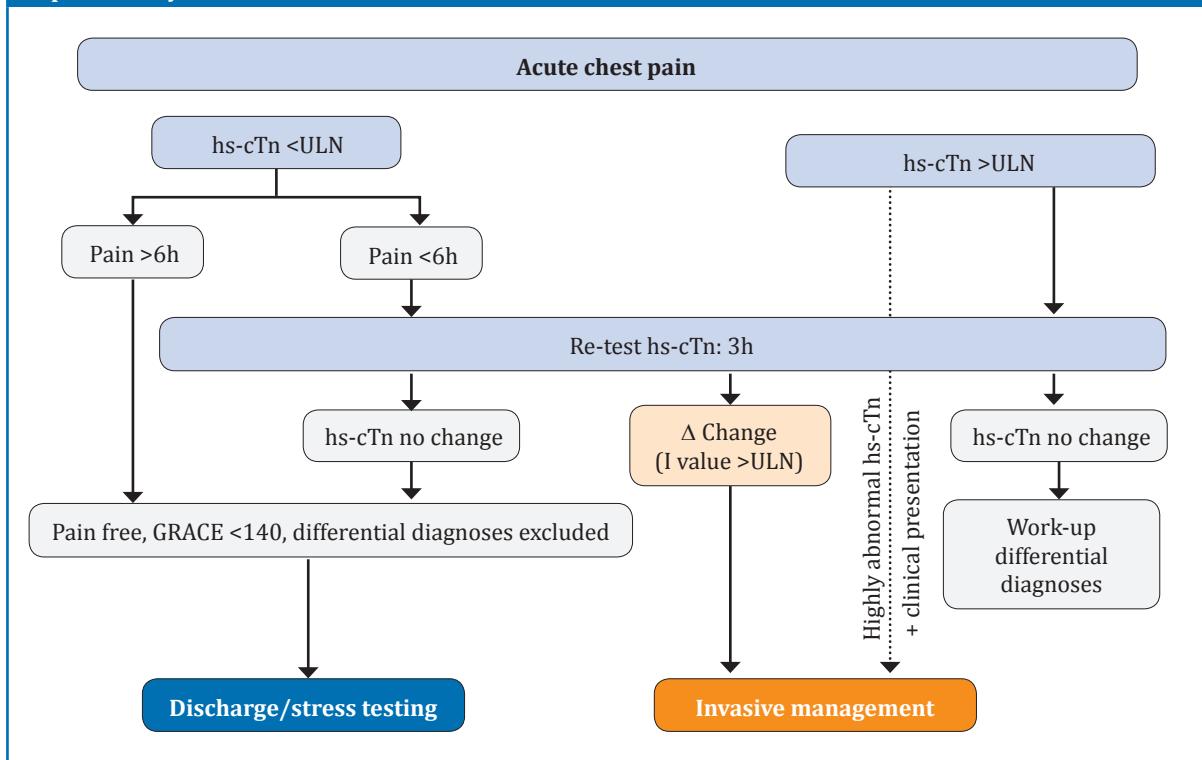
It is recommended to use the 0 h/3 h algorithm. As an alternative, 0 h/1 h algorithms are recommended when hs-cTn assays are available.

- In several large validation cohorts, the negative predictive value for MI in patients assigned ‘rule-out’ exceeded 98%. The 0 h/1 h algorithm, used in combination with clinical and ECG findings, may allow the identification of candidates for early discharge and outpatient management.
- Likewise, the positive predictive value for MI in those patients meeting the ‘rule-in’ criteria was 75–80%. A majority of the ‘rule-in’ patients with diagnoses other than MI did have conditions that usually necessitate inpatient CAG for accurate diagnosis, including Takotsubo cardiomyopathy and myocarditis.

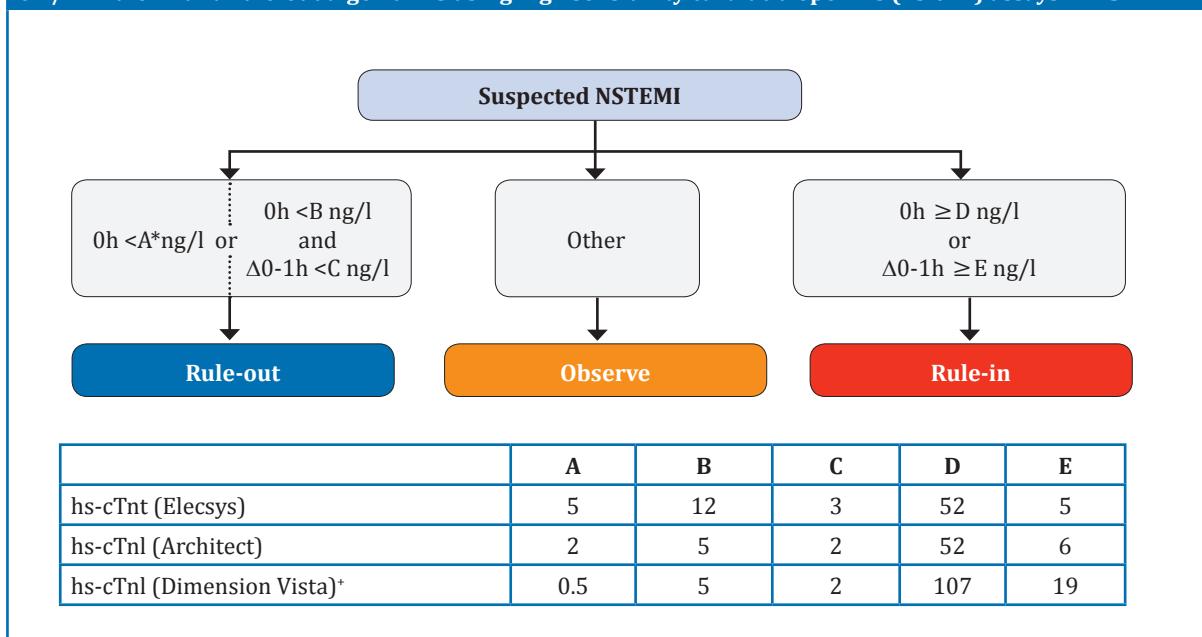
FOR ‘RAPID RULE-OUT’, TWO ALTERNATIVE APPROACHES TO THE 0 H/1 H OR 0 H/3 H ALGORITHMS MAY BE CONSIDERED:

- A 2 h rule-out protocol that combines the Thrombolysis in Myocardial Infarction (TIMI) risk score with ECG and high sensitivity cardiac troponin at presentation; this approach is associated with a safe rule-out in up to 40% of patients

0 h/3 h rule-out algorithm of non-ST-elevation acute coronary syndromes using high-sensitivity cardiac troponin assays

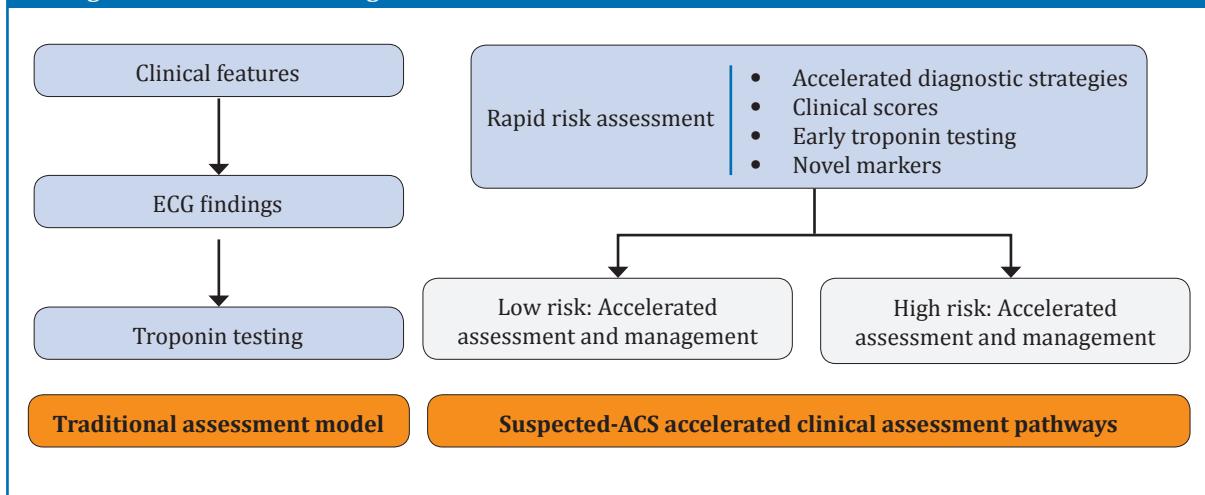


0 h/1 h rule-in and rule-out algorithms using high sensitivity cardiac troponins (hs-cTn) assays in NSTEMI



- A dual-marker strategy combining normal levels of cardiac troponin together with low levels of copeptin (<10 pmol/L) at presentation; this approach exhibited very high negative predictive value for MI, precluding the need for serial testing in selected patients.

Making Sense out of the Challenge



SUMMARY

- The traditional model of assessment of patients with suspected acute coronary syndromes (ACS) is based upon a combination of the key elements of clinical presentations, ECG findings, and cardiac troponin testing
- New suspected-ACS accelerated clinical assessment pathways also include all such elements
- Additionally, these may include risk scores, early troponin testing, novel markers, and accelerated diagnostic strategies that are customized toward refined evaluation of the likelihood of acute MI.

Antidiabetic medications and CV outcomes – What have recent trials taught us?



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CARDIOVASCULAR RISK IN DRUGS INTENDED TO TREAT TYPE 2 DIABETES

The Food and Drug Administration announces new recommendations on evaluating cardiovascular risk in drugs intended to treat type 2 diabetes

- In the year 2008, the FDA recommended that studies should demonstrate that all new drugs developed for the treatment of type 2 diabetes do not increase the risk of cardiovascular (CV) events, especially when the drugs are used by patients of advanced age, diabetes or renal impairment
- The new recommendations were issued in the wake of the acknowledgement that rosiglitazone therapy significantly increases the risk of myocardial infarction (MI) in patients with type 2 diabetes
- The FDA defined more robust and adequate design and data collection approaches for Phase 2 and Phase 3 trials and mandated that all new antidiabetic drugs should undergo cardiovascular outcome trial (CVOT).

COMPARISONS BETWEEN TRIALS

- After the new FDA recommendations, there is an increased interest in interpreting the data from various trials and comparing them. However, comparisons between CVOTs are complicated by differences in:
 - Populations
 - Trial designs
 - Analytic approaches
 - Drug effects
- Therefore, comparisons can be risky, subject to bias, and may be confounded by multiple uncontrolled factors.

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

As regards to DPP-4Is, there are five dedicated CVOTs:

- Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in myocardial infarction (SAVOR-TIMI)
- Examination of CV Outcomes with alogliptin versus Standard of Care (EXAMINE)
- Trial Evaluating CV Outcomes with Sitagliptin (TECOS)
- Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA)
- CARdiovascular Outcome Trial of LINagliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA)

Comparison between three dedicated CVOTs			
Parameters	SAVOR-TIMI	TECOS	EXAMINE
Number of patients	16,492	14,735	5,380
Clinical scenario	<ul style="list-style-type: none"> • Stable • Established CVD (78%) • Multiple risk factors (22%) 	<ul style="list-style-type: none"> • Stable • All with established CVD 	15-90 days post-ACS (median 45 days)
Median follow-up	2.1 years	2.8 years	1.5 years
Primary endpoint	CV death, MI, ischemic stroke	CV death, MI, stroke, hospitalization for unstable angina	CV death, MI, Stroke
A1c entry criteria	6.5-12%	6.5-8.0%	6.5-11%
Concomitant diabetes medications	Anything except incretin, including treatment-naive	Mono/dual oral therapy or insulin ± metformin	At least one other non-incretin medication
Premature study drug discontinuation	20%	25%	21%

SAFETY OF DPP-4Is AND THE RISK OF HEART FAILURE

To date, the DPP4 inhibitors are the most thoroughly evaluated class of diabetes drugs. Overall, they are well-tolerated without any increase in cardiovascular death, myocardial infarction, or stroke. Of the 3 DPP-4Is, sitagliptin seems to have the safest cardiovascular profile.

SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITORS

- Empagliflozin Reducing Excess Glucose (EMPA-REG)
- Canagliflozin Cardiovascular Assessment Study (CANVAS)

Key differences in CANVAS vs. EMPA-REG		
Parameters	CANVAS	EMPA-REG
Patient Number	10,142	7,020
Study duration	<ul style="list-style-type: none"> • ~6 years duration (Longer term) • Median 3.6 Yr 	<ul style="list-style-type: none"> • ~4 years duration (Medium term) • Median 3.1 Yr
<ul style="list-style-type: none"> • 1° Prevention • 2° Prevention 	<ul style="list-style-type: none"> • 35% • 65% 	<ul style="list-style-type: none"> • 1% • 99%
Duration of diabetes (mean)	13.5 years	>1 to 5 years: 15.2% >5 to 10 years: 25.1% >10 years: 57.0%
Use of anti-thrombotic	73%	83%
Use of beta-blockers	52%	65%

Comparison of cardiovascular deaths		
Parameters	CANVAS	EMPA-REG
CV Death	0.87 (0.72–1.06)	0.62 (0.49–0.77)
- CV Deaths in Placebo arm	12.8/1000 patient-years	20.2/1000 patient-years
- CV Deaths in Treatment arm	11.6/1000 patient-years	12.4/1000 patient-years
Nonfatal MI	0.85 (0.69–1.05)	0.87 (0.70–1.09)
Nonfatal Stroke	0.90 (0.71–1.15)	1.24 (0.92–1.67)

Outcome comparison between CANVAS and EMPA-REG		
Critical analysis	EMPA-REG Outcome	CANVAS Program
CV Death	↓↓ 0.62 (0.49–0.77)	↓ 0.87 (0.72–1.06)
Nonfatal MI	↓ 0.87 (0.70–1.09)	↓ 0.85 (0.69–1.05)
Nonfatal Stroke	↑ 1.24 (0.92–1.67)	↓ 0.90 (0.71–1.15)
Fatal and nonfatal stroke	↑ 1.18 (0.89–1.56)	↓ 0.87 (0.69–1.09)

HOW DO THESE TRIALS AND THEIR OUTCOMES MAKE DIFFERENCE FOR AN INDIAN PATIENT WITH TYPE 2 DIABETES?

- Effect of smoking cessation: Patient's life expectancy increases by 2.1 years
- Effect of good HbA1c control: Patient's life expectancy increases by 1.1 years
- Effect of good lipid control: Patient's life expectancy increases by 1.2 years
- Effect of good blood pressure control: Patient's life expectancy increases by 1.5 years
- Effect of multiple risk-factor control: Patient's life expectancy increases by 4.9 years
- Further benefit of adding empagliflozin above all these standards of care: Estimated mean survival increases by 2.8 years

SUMMARY

- Addressing cardiovascular outcomes constitutes an important part of type 2 diabetes management
- CV outcome studies have underscored the significance of newer anti-diabetic agents in the management of type 2 diabetes
- Using these newer anti-diabetic agents offers CV outcome benefits over and above standard of care.

Revascularization in stable angina – when and how?



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This presentation discussed the best suited management option for a patient with stable angina. The decision for management option is made in the light of various seminal clinical trials including the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial, and the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial.

CORONARY ARTERY DISEASE

Approaches to reduce the risk of CAD include lifestyle changes, such as eating a healthy diet, regularly exercising, maintaining a healthy weight, and not smoking along with occasional use of medications for diabetes, high cholesterol, or high blood pressure. In severe cases, procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) may be used. However, it is still not clear whether PCI or CABG, in addition to the other treatments, improves life expectancy or decreases risk of heart attack in patients with stable CAD.

COURAGE TRIAL

The COURAGE trial was a randomized trial involving 2287 patients with objective evidence of myocardial ischemia and significant CAD. The patients were randomized to PCI with optimal medical therapy (OMT) versus OMT alone. Intensive, guideline-driven medical therapy and lifestyle intervention were used in both groups. The primary outcome was death from any cause and nonfatal MI during a follow-up period of 2.5 to 7.0 years (median, 4.6). Secondary outcomes included health care economics and health related quality of life (HRQoL).

Overall survival

- The estimated 4.6-year rate of death from any cause was 7.6% in the PCI group and 8.3% in the OMT group
- Estimated 4.6-year rate of acute myocardial infarction was 13.2% in the PCI group and 12.3% in the OMT group

BARI 2D TRIAL

This was a prospective randomized trial involving 2368 patients with both type 2 diabetes and mild to moderate CAD. Patients were randomized to undergo either prompt revascularization with OMT or OMT alone and to undergo either insulin-sensitization or insulin-provision therapy. Primary end point was the rate of death from any cause and secondary endpoint was composite of death, MI, or stroke. Randomization was stratified according to the choice of PCI or CABG as the more appropriate intervention.

BARI-2D outcomes

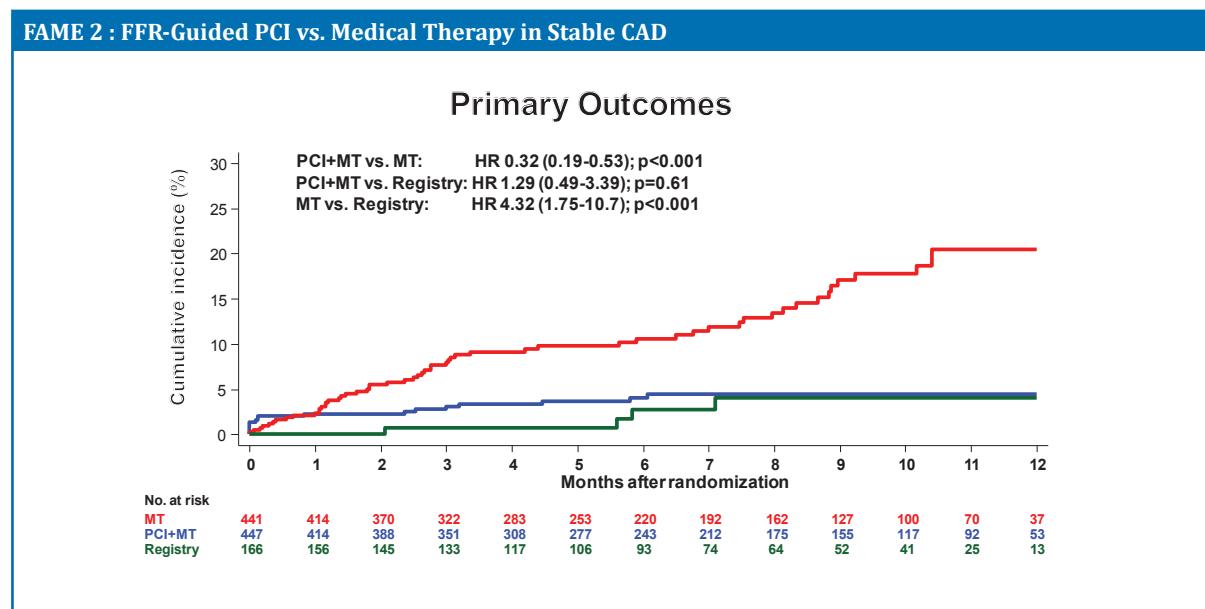
There was no considerable difference in rates of survival between the two groups among patients who were selected for the PCI stratum (Panel A) or among those who were selected for the CABG stratum (Panel B).

THE FRACTIONAL FLOW RESERVE VS. ANGIOGRAPHY FOR MULTIVESSEL EVALUATION 2 (FAME 2) STUDY

The FAME 2 trial included 1220 patients with stable coronary artery disease for whom PCI was being considered. Patients with at least one stenosis ($\text{FFR} \leq 0.80$; n=888) were randomly assigned to FFR-guided PCI plus medical therapy (MT) or MT alone. Patients in whom all stenoses had an $\text{FFR} > 0.80$ (n=332) were entered into a registry and received MT.

Primary outcomes

The percentage of patients who had a primary end-point event was lower in the PCI group than in the MT group (hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; $p<0.001$).

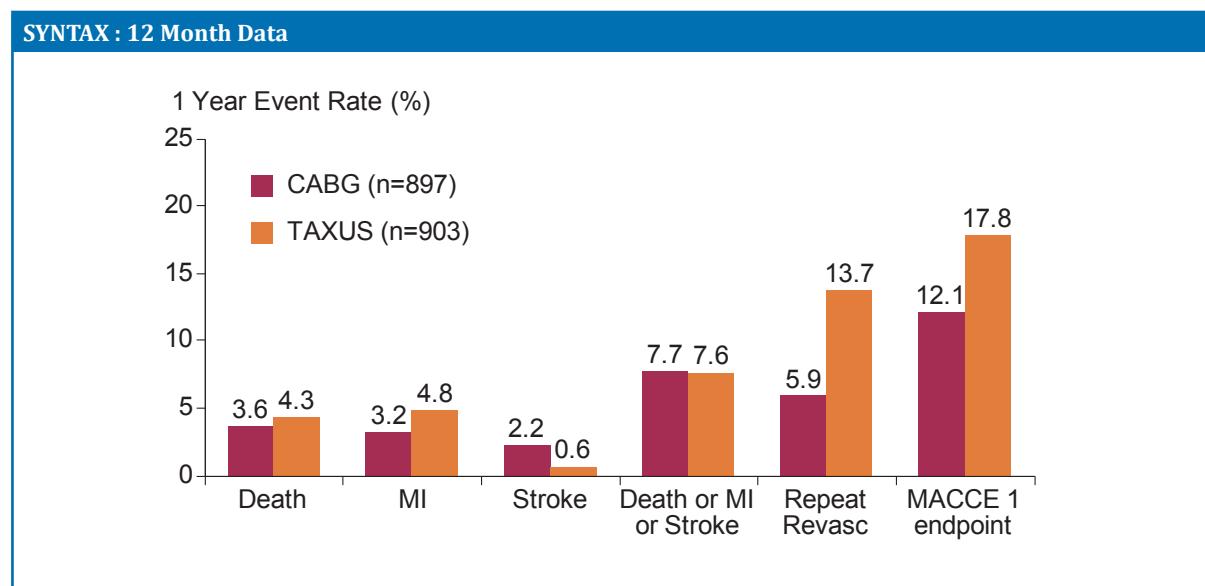


THE SYNERGY BETWEEN PCI WITH TAXUS AND CARDIAC SURGERY (SYNTAX) TRIAL

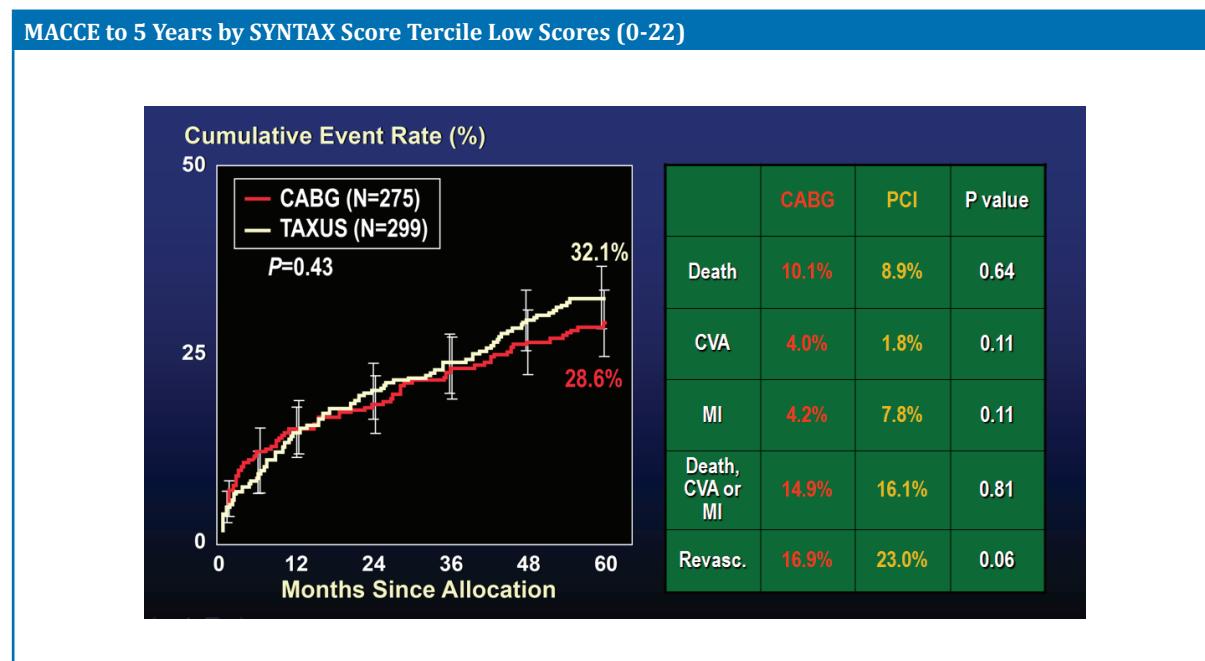
The SYNTAX trial included 1800 patients with three-vessel disease (3VD) or left main coronary artery disease (LM) to undergo CABG (n=897) or PCI with Taxus (n=903). Patients who were amenable for only one of the two treatment approaches were entered into a parallel two registry arms; CABG (n=1077) or PCI (n=198).

SYNTAX: 12 month data

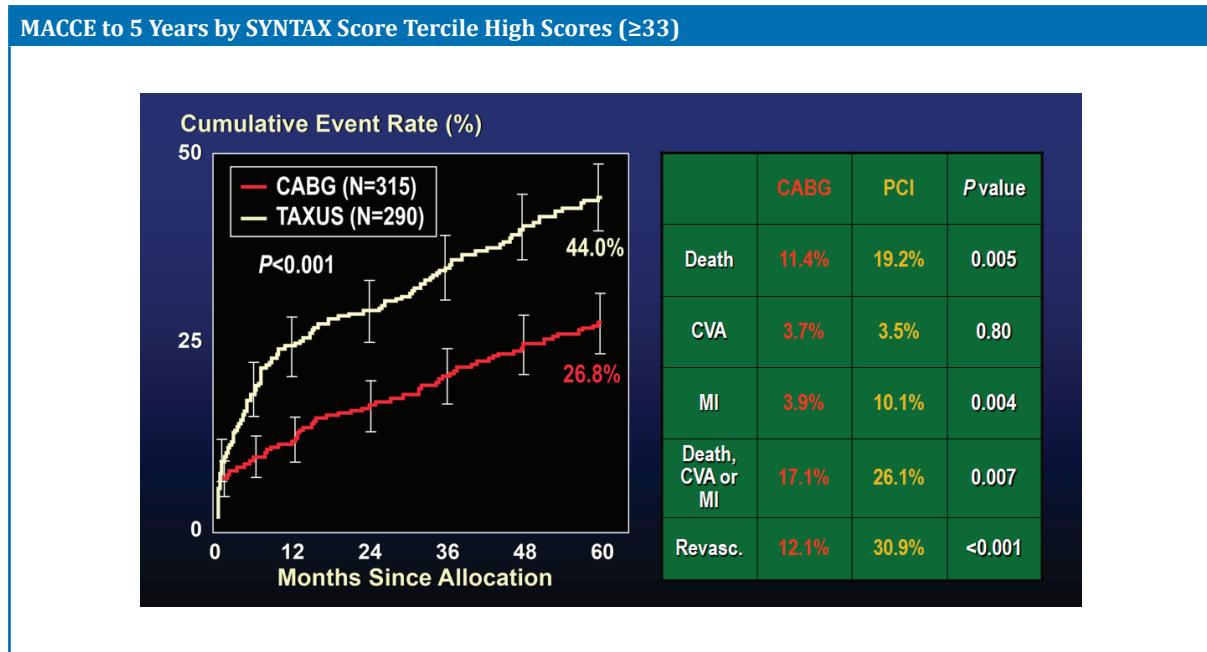
Rates of major adverse cardiac or cerebrovascular events (MACCE) at 12 months were considerably higher in the PCI with Taxus group (17.8% versus 12.1% for CABG). PCI with Taxus was also associated with an increased rate of repeat revascularization (13.7% versus 5.9% for CABG). At 12 months, the rates of death and myocardial infarction were similar between the two groups (7.6 for PCI with Taxus versus 7.7 for CABG). Stroke was considerably more likely to occur with CABG (2.2% versus 0.6% with PCI).



- In patients with low SYNTAX score, PCI and CABG offer similar benefit for death and MI



- CABG is more effective than PCI for patients with anatomically complex coronary disease (high SYNTAX score)



SUMMARY

- Optimal medical therapy is very effective strategy for majority of patients with stable coronary artery disease
- PCI saves lives in acute myocardial infarction and unstable angina (USA)/NSTEMI
- PCI prevents spontaneous MI particularly in patients with severe functionally severe lesions subtending significant myocardium
- CABG is more effective than PCI for patients with anatomically complex coronary disease (high SYNTAX score) especially in patients with diabetes and when IMA is used
- In patients with low SYNTAX score, PCI and CABG offer similar benefit for death and MI
- CABG is associated with higher incidence of stroke
- Patient co-morbidities, LV function, anatomy of lesions and target vessels determine the best revascularization approach.

Revascularization in LV dysfunction – Is there a benefit – How to select patients for medical management, PCI or surgery?



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INTRODUCTION

- Chronic congestive heart failure with reduced ejection fraction (HF-REF) is associated with increased hospitalization and shortened survival. Despite a plethora of available causative agents, ischemic heart disease remains the most common etiology of HF-REF in the developed world, and are with >60% of diagnoses.
- Patients with ischemic causes of left ventricular (LV) systolic dysfunction have been associated with higher death counts in comparison to patients with nonischemic etiologies.
- Treating patients with multivessel coronary artery disease and low ejection fraction (EF) with LV dilatation presents a challenge to medical fraternity.

TREATMENT FOR PATIENTS WITH SEVERE LV DYSFUNCTION

- Patients with severe Lv dysfunction have a range of treatment options available :CABG, PCI, Medical management, Devices - CRT, ICD, ASSIT DEVICES and Transplant
- This event provides a brief overview on Surgical Treatment for Ischemic Heart Failure Trial (STICH) and shed light on the therapy related decision for individual patients on the basis of various guidelines proposed by internationally acclaimed bodies such as *ESC Guidelines 2012*.

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class III and ambulatory class IV heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy

Recommendations

LBBB QRS morphology

CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥ 120 ms, LBBB QRS morphology, and an EF $\leq 35\%$, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.

Non-LBBB QRS morphology

CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥ 150 ms, irrespective of QRS morphology, and an EF $\leq 35\%$, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.

CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; EF = ejection fraction; HF = heart failure; LBBB = left bundle branch block; NYHA = New York Heart Association.

Recommendations for myocardial revascularization in patients with chronic HF and systolic LV dysfunction

Recommendations

CABG is recommended for patients with angina and significant left main stenosis, who are otherwise suitable for surgery and expected to survive >1 year with good functional status, to reduce the risk of premature death.

CABG is recommended for patients with angina and two- or three-vessel coronary disease, including a left anterior descending stenosis, who are otherwise suitable for surgery and expected to survive >1 year with good functional status, to reduce the risk of hospitalization for cardiovascular causes and the risk of premature death from cardiovascular causes.

Alternative to CABG:

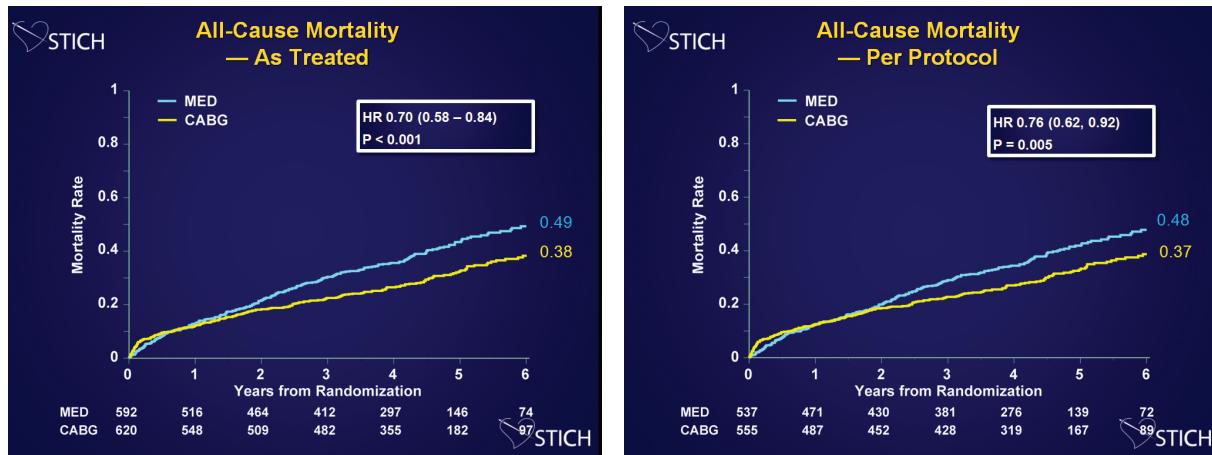
PCI may be considered as an alternative to CABG in the above categories of patients unsuitable for surgery.

CABG and PCI are NOT recommended in patients without angina AND without viable myocardium.

CABG = coronary artery bypass graft; EF = ejection fraction; HF = heart failure; LV = left ventricular; PCI = percutaneous coronary intervention.

CORONARY ARTERY BYPASS GRAFT SURGERY IN PATIENTS WITH ISCHEMIC HEART FAILURE – STICH TRIAL

- In this event, the two following hypothesis was proposed in Surgical Treatment for Ischemic Heart Failure Trial (STICH):
 - Hypothesis 1 - Role of surgical revascularisation in patients with ischemic cardiomyopathy
 - Hypothesis 2 - Role of SVR with CABG in patients with Ischemic cardiomyopathy.
- In patients with HF, LVD and CAD amenable to surgical revascularization, CABG added to intensive MED will decrease all-cause mortality compared to MED alone.
- The end points of the trials included:
 - Primary Endpoint: All-cause mortality
 - Major Secondary Endpoints: Cardiovascular mortality and Death (all-cause) + cardiovascular hospitalization
- The important inclusion criterias were:
 - LVEF ≤ 0.35 within 3 months of trial entry, CAD suitable for CABG (Absence of left main CAD as defined by an intraluminal stenosis of $\geq 50\%$, Absence of CCS III angina or greater (angina markedly limiting ordinary activity) and MED eligible



- The STICH revascularisation hypothesis included a total of 1212 patients who received treatment. Subsequently, a group of 1212 were evaluated who reviewed treatment as per protocol. The entire study population was last followed up from August – November 2010. Final follow-up ascertained: 1207 (99.6%). Overall duration of follow-up: 56 months.
- Results of the study divulged as following:
 - As treated the hazard ratio for all cause mortality with CABG was 0.70 and corresponded to a p value of less than 0.001
 - When comparing the 537 patients who remained on medical therapy only as per protocol and the 555 patients who received CABG per protocol the hazard ratio for all cause mortality with cabg was 0.76 and corresponded to a p value of less than 0.001

Note: Despite the medical adherence and operative results achieved, STICH-like patients remain at substantial risk (5-year mortality risk with MED only = 40%)

SUMMARY

- There was no remarkable statistical difference in all cause mortality between medical therapy alone and medical therapy with CABG in patients randomized to STICH.
- Medical therapy with CABG compared to medical therapy alone reduces cardiovascular mortality and morbidity.
- However, patients were exposed to an early risk when randomized to CABG.

Primary pulmonary hypertension – Beginning of a new era in the management



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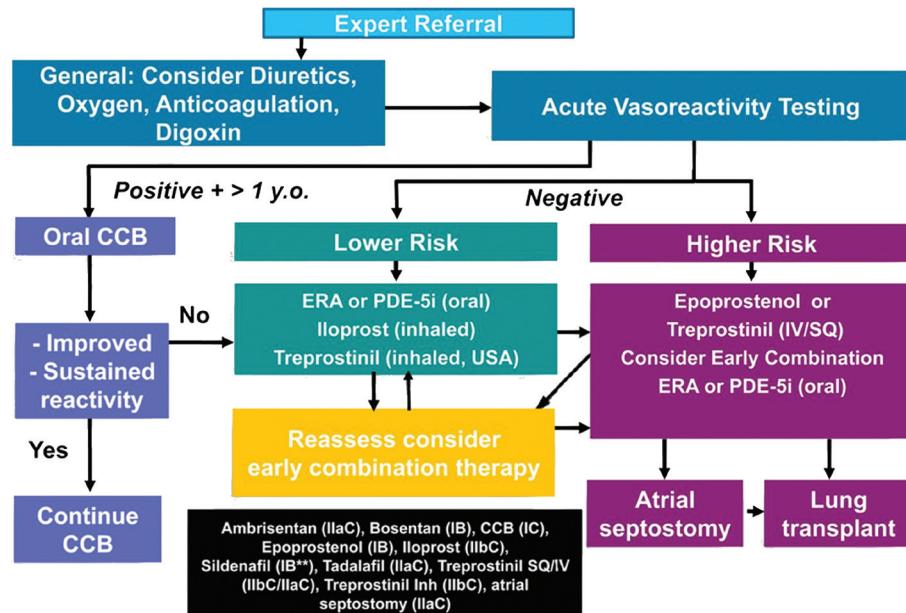
INTRODUCTION

- Despite recent advancements in the field of health care; pulmonary hypertension remains a serious public problem.
- This event intends to provide brief overview on pulmonary arterial hypertension (PAH) management.

THE SERAPHIN STUDY-STUDY WITH ENDOTHELIN RECEPTOR ANTAGONIST IN PULMONARY ARTERIAL HYPERTENSION TO IMPROVE CLINICAL OUTCOME

- It was a multicentre double-blind, randomized phase III clinical trial with a novel and robust primary endpoint designed to evaluate long term benefits of macitentan in patients with PAH.
- Characteristic properties of macitentan
 - Optimised physicochemical properties
 - Enhanced affinity for endothelin (ET) receptors, long-lasting receptor occupancy
- Superior pre-clinical *in vivo* efficacy compared with other endothelin receptor antagonists (ERAs)
- No relevant interaction with bile salt export pump
- No relevant interaction with hepatic organic anion transporter protein (OATP)
- The entire study was thoroughly formulated and both primary and secondary endpoints were measured and summarized below.
 - Primary endpoint: Time from treatment initiation to the first morbidity or mortality event up to end of treatment and other worsening primary endpoints of PAH
 - Secondary endpoints: Change in 6-minute walk distance (6-MWD) and WHO functional class (FC) at month 6; mortality due to PAH or hospitalisation for PAH; all-cause mortality up to end of treatment and study and safety and tolerability.

Pulmonary arterial hypertension (PAH) management

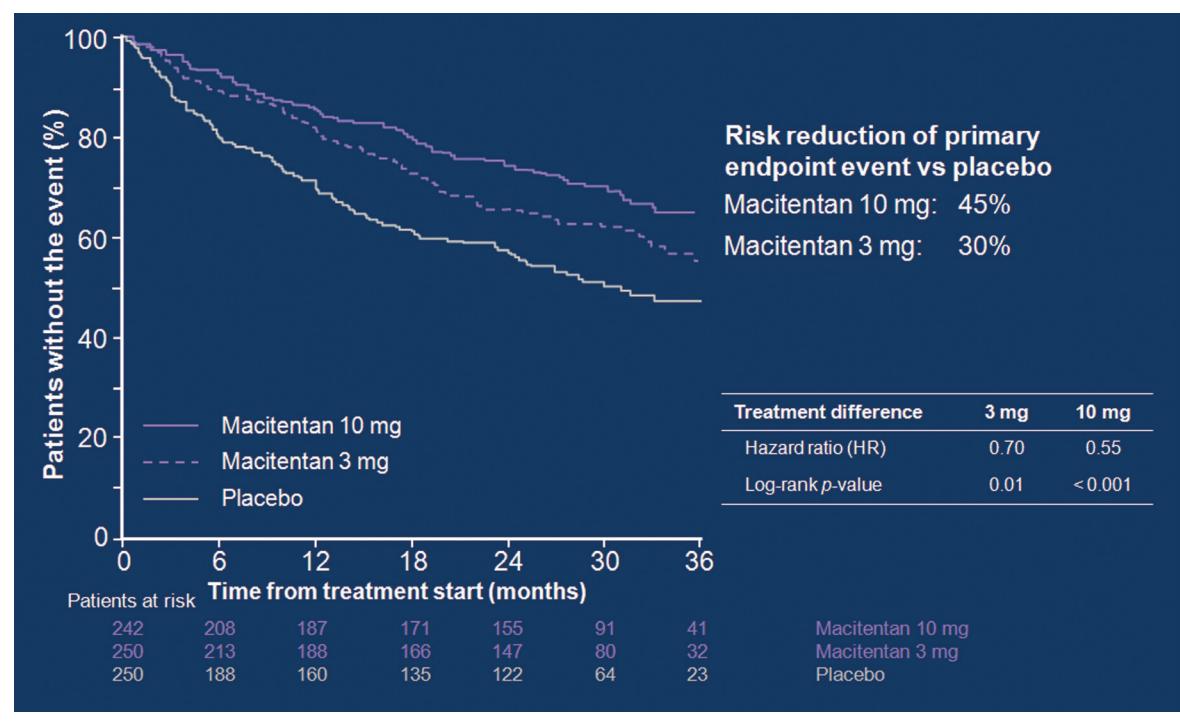


- Study population included diagnosed PAH patients or patient with symptomatic PAH in FC II to IV. In addition inclusion criteria involved those patients who had 6MWD: 6-minute walking distance ≥ 50 m.
- After 28 days of screening the participants of the study with matched demographic and baseline characteristics received concomitant therapy and were randomized from May 2008 to December 2009 into Macitentan 10 mg, Macitentan 3 mg and placebo.

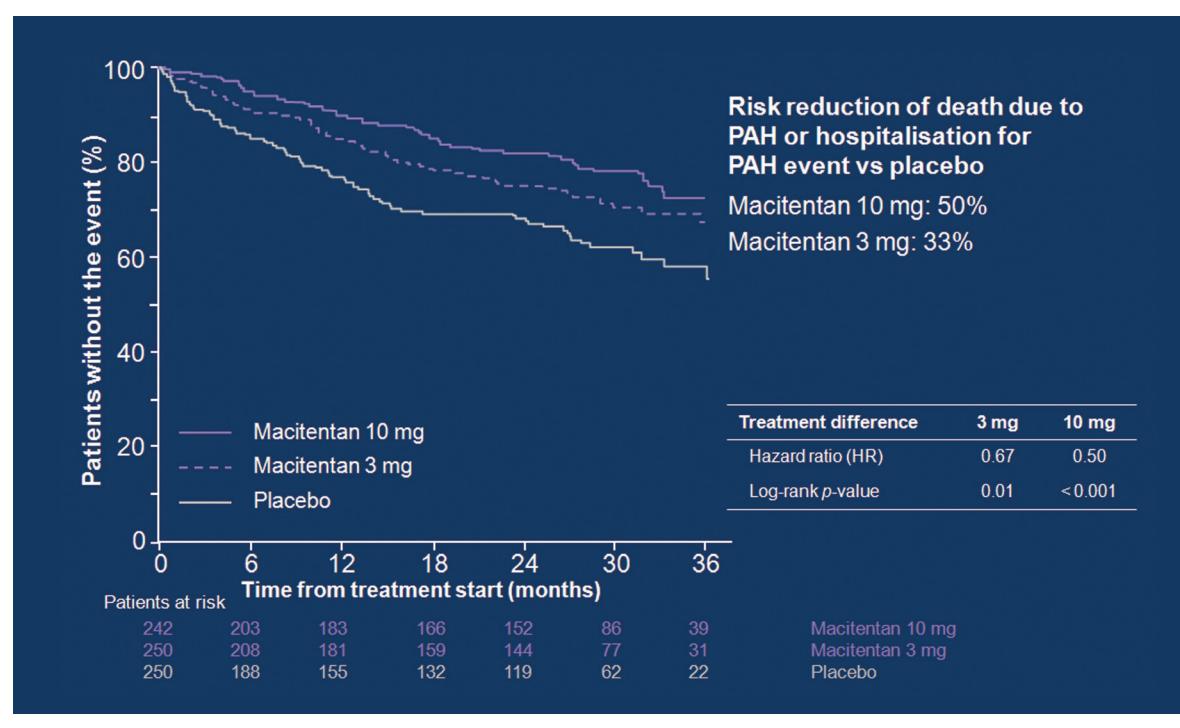
Result divulged at the end of study (285 events; March 2012) were as follows:

1. Macitentan effect on the Composite Primary End Point of a First Event Related to PAH or Death from Any Cause: A remarkable treatment effect in favor of macitentan at a once-daily dose of 3 mg and at 10 mg versus placebo were recorded. The hazard ratio at once-daily dose of 3 mg and at 10 mg versus placebo was 0.70 and 0.55, respectively
2. Macitentan on the Composite Secondary End Point of Death Due to PAH or Hospitalization for PAH as a First Event: Findings showed favorable treatment effects with 3-mg and 10-mg dose of macitentan versus placebo with hazard ratio of 0.67 and 0.50, respectively
3. Both the primary and secondary endpoints were studied
4. Macitentan remarkably improves health-related quality of life (HRQoL) in patients with PAH compared with placebo.

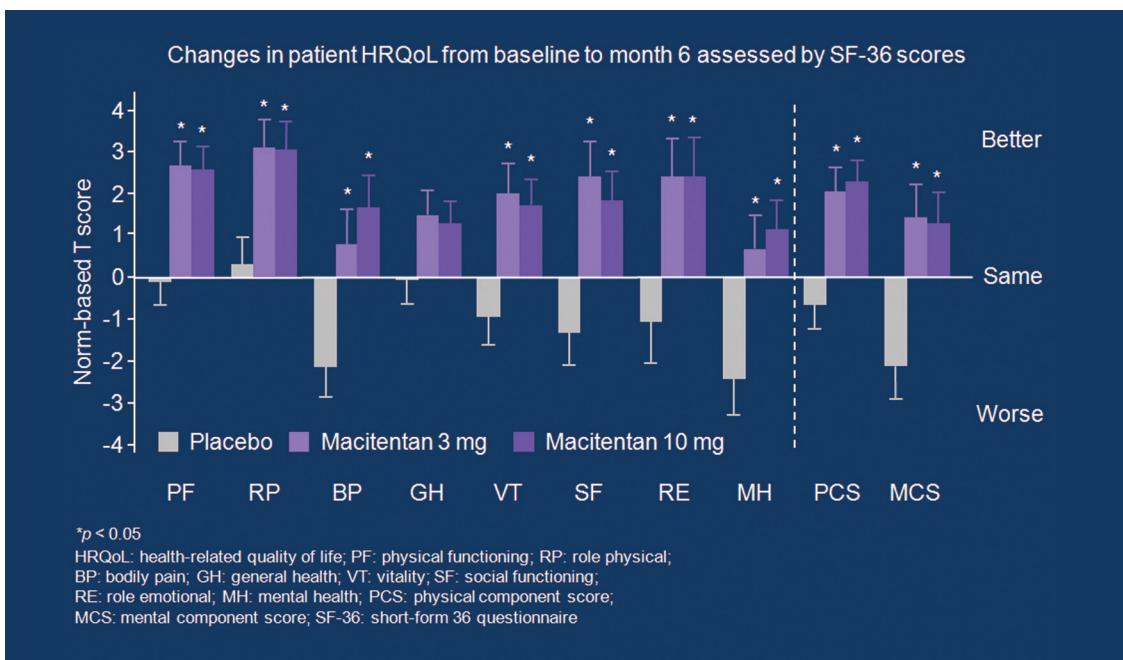
Primary endpoint: Morbidity and mortality up to end of treatment



Secondary endpoint: Death due to PAH or hospitalisation for PAH



Macitentan improves HRQoL in patients with PAH



SUMMARY

- The global, event-driven SERAPHIN study has fostered a new paradigm in PAH trial design.
- Macitentan 10 mg treatment effects was consistent and independent of background PAH therapy.
- Macitentan 10 mg remarkably reduced the risk of morbidity and mortality events up to 45% vs placebo.
- Macitentan significantly improved quality of life, 6MWD, WHO FC, and hemodynamic parameters and was generally well tolerated during long term therapy.

Pulmonary hypertension in heart failure – Implications for management



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PULMONARY HYPERTENSION

- It is a common scene for cardiologists to encounter patients with vasoconstriction, vascular remodeling and or thrombosis, which eventually leads to elevated pressure in the pulmonary artery that is also known as pulmonary hypertension (PH).
- Pulmonary hypertension group-2 is classified as following:
 - Pulmonary hypertension with left heart disease
 - PA mean >25 with PCWP >15 with normal or reduced CO
 - » Passive = Transpulmonary gradient (TPG) < 12
 - » Reactive = TPG ≥ 12
 - » (Post-Capillary Pulmonary Hypertension)
- Heart failure (HF) and PH are serious health concerns worldwide, usually associated with right ventricular (RV) dysfunction. Both Pulmonary vascular resistance (PVR) and RV function affects exercise capacity and prognosis. Despite of recent advancements in the field of medicine, pharmacologic agents have been disappointing in treating heart failure and pulmonary hypertension.
- Right Heart Catheterization in group 2 Pulmonary Arterial Hypertension(PAH) diagnosed PAH as:
 - Mean Pulmonary Artery pressure ≥ 25 mmHg
 - Pulmonary Capillary Wedge Pressure > 15 mmHg
 - Further differentiation was based on PVR > 3, TPG > 12 and Diastolic pressure gradient (DPG). Herein, proposed use of diastolic pressure gradient was:
 - » DPG = diastolic PA – mean PCWP
 - » DPG < 7 post capillary PH
 - » DPG ≥ 7 pre and post capillary PH
- This event aims to provide comprehensive clinically relevant information focusing on treatment of PAH.

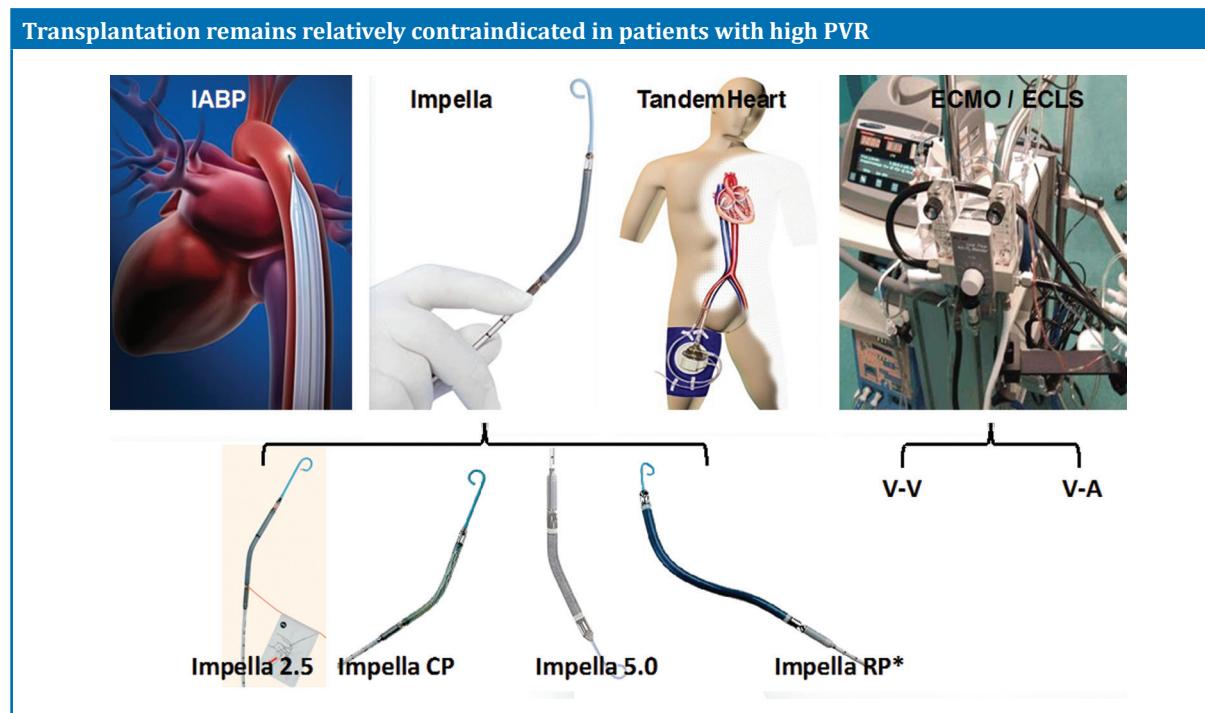
TREATMENT OF GROUP 2 PH

- The concern of pulmonary vasodilators in HF: Reduce PVR leads to increase left sided filling pressure which eventually results in increased pulmonary congestion.
- The parameters that need to be focus in Treatment of PH in Group 2 PH involves:
 - Treatment of underlying heart disease
 - Optimize LV function
 - Treat high LV filling pressures
 - Vasodilators, diuretics

PH IN ADVANCED HEART FAILURE AND IMPACT ON THERAPIES

Transplantation remains relatively contraindicated in patients with high PVR. In this context, multiple interventions were introduced that may reduce PVR, which includes:

- Vasodilators
- PDE-5 inhibitors
- Mechanical Circulatory Support
 - Left Ventricular Assist Device; durable and temporary
 - Total Artificial Heart; infrequent



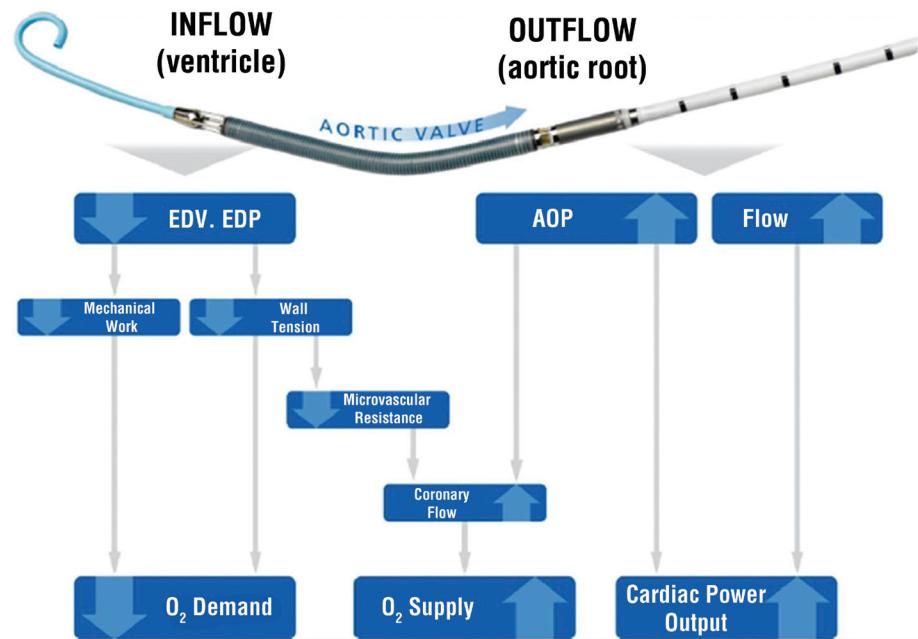
IMPELLA

- Physiology impact of Impella was thoroughly evaluated.

LVAS: LEFT VENTRICULAR ASSIST SYSTEMS

- The Heartmate II LVAS is a mechanical bearing axial continuous pump, and was approved for both Bridge-To- Transplant (BTT) and Destination therapy (DT) patients.

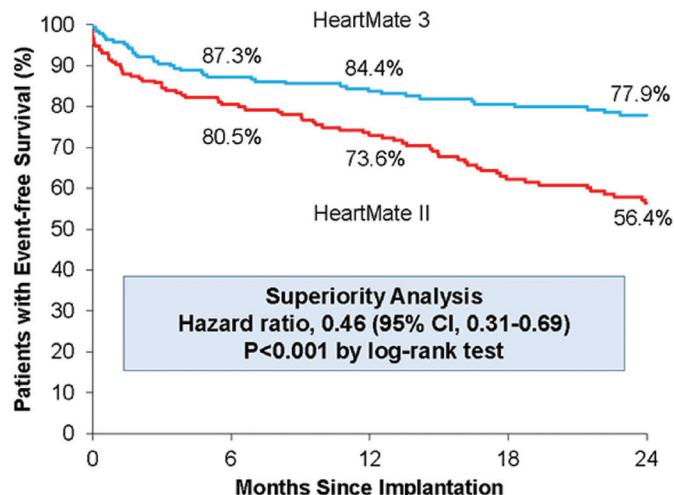
Physiology impact of Impella



- Patients with advanced HF refractory to medical therapy who received continuous flow LVAS had shown improved survival rate and quality of life.
- However, LVAS-HeartMateII was associated with high risk of pump thrombosis and major adverse effects such as stroke, bleeding and device related infections.
- Thus, LVAS-HeartMate3 achieved higher success and was approved by FDA for short term use, ascribed to its following properties:
 - Wide blood flow passage
 - Frictionless with absence of mechanical bearings
 - Intrinsic pulse design
- In this context, a two year outcome of a magnetically levitated cardiac pump in heart failure was assessed
 - Primary end point of survival at 2 years free of disabling stroke or reoperation to replace/remove a malfunctioning device was evaluated
 - » Primary component-1: Overall survival
 - » Primary component-2: Freedom from disabling stroke
 - » Primary component-3: Freedom from reoperation to replace or remove pump
 - Adversities like pump thrombosis, bleeding and neurological events were thoroughly determined
 - Stroke severity: A total of 12 subjects were evaluated, and score of most severe stroke was recorded as 1.6% HeartMate3 (n=3) and 5.2% HeartMate2 (n=9) and had a modified Rankin score of 0 at 60 days post stroke (CI= confidence interval).

Primary end point analysis (ITT)

Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device

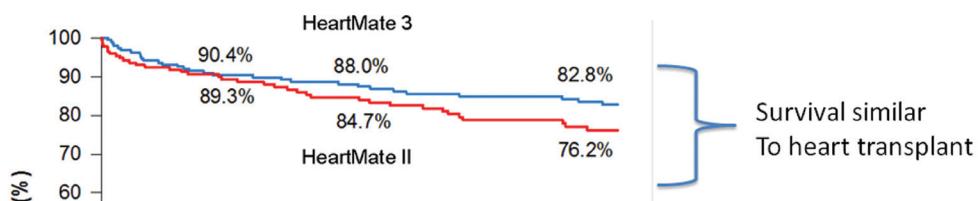


Superiority Analysis
Hazard ratio, 0.46 (95% CI, 0.31-0.69)
P<0.001 by log-rank test

No. at Risk

	0	6	12	18	24
HeartMate 3	190	161	141	122	111
HeartMate II	176	134	114	90	75

Primary endpoint component 1 overall survival



HR = 0.71 (95%CI: 0.44 - 1.15)

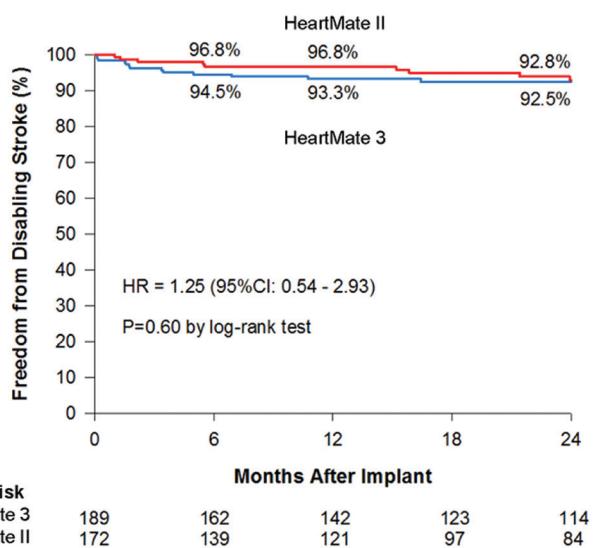
P=0.16 by log-rank test

Survival similar
To heart transplant

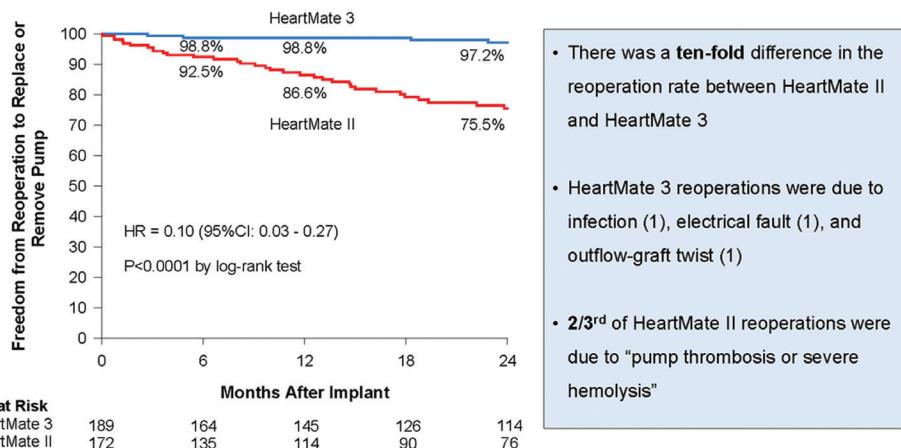
No. at Risk

	0	6	12	18	24
HeartMate 3	189	165	146	127	117
HeartMate II	172	141	121	98	86

Primary endpoint component 2 freedom from disabling stroke



Primary endpoint component 3 freedom from reoperation to replace or remove pump



- At 2 years, HeartMateII axial-flow pump was recorded clinically inferior than HeartMate3 LVAS
- HeartMate3 LVAS founded to be more efficient attributing to its lower respiration rate
- A significant reduced rate of strokes were observed with HeartMate3 LVAS

SUMMARY

It is common to encounter PH in HF patients. This association is related to high death counts. Advancements in technologies helped us resolve numerous medical challenges; however effectiveness of pulmonary vasodilators is still variable. In addition, registered data supports their effectiveness in successful treatment of Group 2 PH; but not as much as for Group 1 PH. LVADs have been shown to decrease PVR. Moreover, in cases of fixed PH, the speaker advocates consideration on addition of PDE-5 to LVAD therapy.

Indications for left atrial appendage occlusion in patients with atrial fibrillation



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This presentation provides an insight into the use of left atrial appendage occlusion (LAAO) in patients with atrial fibrillation. In context to this, a case report of a 78 year old male patient with paroxysmal atrial fibrillation has been discussed, who has been treated with watchman percutaneous LAAO procedure. In addition to this, the presentation also throws light on data from various trials performed on watchman including 5 year outcomes of the PREVAIL and PROTECT AF TRIALS.

INTRODUCTION

Left atrial appendage closure (LAAC) is a treatment strategy, to reduce the risk of left atrial appendage blood clots from entering the bloodstream, and causing a stroke in patients with non-valvular atrial fibrillation (NVAF).

LAA CLOSURE

The closure of LAA can be done in patients with AF to prevent clot formation. The LAAO closure techniques are as follows:

1. Surgical
2. Percutaneous
 - Lariat
 - Watchman
 - Amulet
 - Others

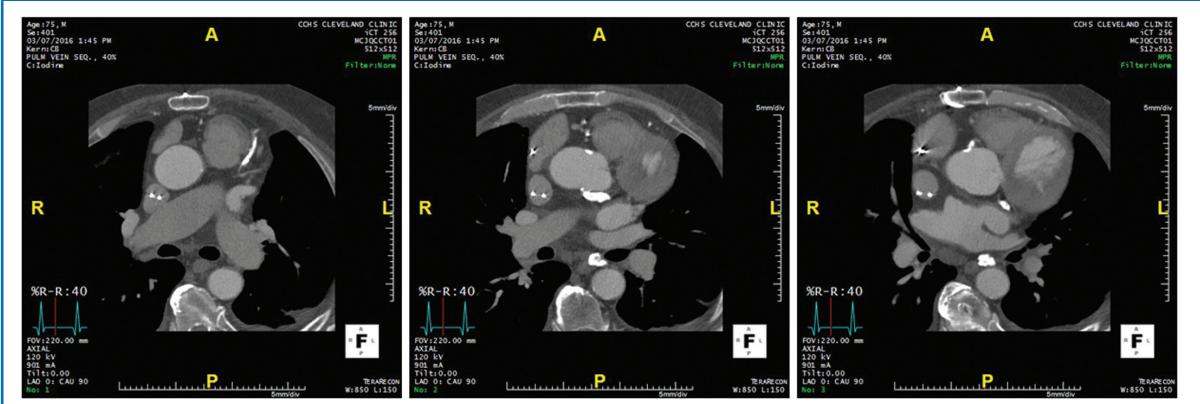
CASE PRESENTATION

- A 78-year-old male patient with paroxysmal atrial fibrillation
- Unstable angina 11/2015 from severe ISR of LMT-LCx stent so repeat PCI with 4.0 x 23 mm Xience Alpine EES
- Discharged on ASA/Clopidogrel/Warfarin x 1 month followed by Clopidogrel/Warfarin x 1 year with plan to downgrade to ASA/Warfarin thereafter (WOEST)
- PMH: CAD s/p CABG (L-LAD) 1999 and PCI to LMT-LCx 2011 H/o GI bleeding, ESRD on HD, HFpEF, DM2, HTN, CHB s/p PPM
- Angiogram shows thrombus in LMT, Angiojet thrombectomy, Well expanded stent on OCT
- ASA/Clopidogrel resistance panel obtained and demonstrated Clopidogrel resistance.
- Changed to ASA/Ticagrelor/Warfarin
- Given need for long term DAPT and risk of bleeding as well as risk of stroke from AF he was referred for consideration of Watchman LAA closure
- The CHA₂DS₂-VASc score was 5 and HAS-BLED score was 4
- Pre procedure TEE:
 - EF: 50% (LAD WMA at rest)
 - 2+ MR
 - No LA/LAA thrombus
 - 15 degrees - 1.9 x 1.6 cm
 - 30 degrees - 1.7 x 3.2 cm
 - 45 degrees - 1.9 x 2.8 cm
 - 60 degrees - 1.9 x 3.2 cm
 - 90 degrees - 1.5 x 3.3 cm
 - 100 degrees - 1.8 x 3.4 cm
 - 120 degrees - 1.5 x 4.1 cm
- CT Scan for Procedure Planning: LAA courses superiorly and anteriorly with two main lobes
- On the basis of these findings, the size of the watchman device was planned. In this case a plan for #27 v #30 Watchman device was considered.

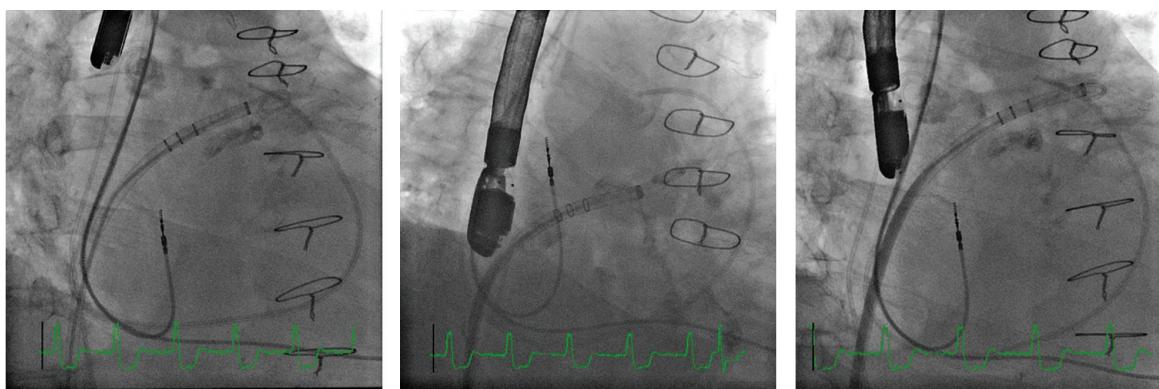
PROCEDURAL PLANNING:

- Superior and Anterior Lobe

CT Scan for Procedure Planning: This LAA courses superiorly and anteriorly with two main lobes



Pigtail in smaller of two lobes (A,B) and Pigtail repositioned in larger, more anterior lobe (C)

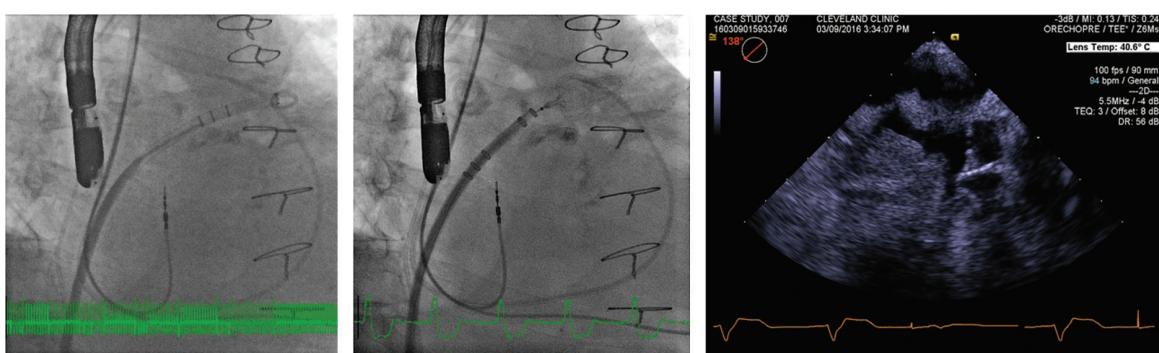


- Post – inferior puncture, double curve
- Anterior *but not* Superior
 - Slightly anterior puncture, double curve
 - Posterior puncture, single curve
- Pigtail in smaller of two lobes (A,B) and Pigtail repositioned in larger, more anterior lobe (C)
- Watchman Deployment 30 mm (D) and Deployment Deep where smaller inferior lobe is filling with contrast and not covered by Watchman device (E,F)
- **Clinical Course:** - Discharged on ASA/Ticagrelor/Warfarin for 45 days
 - Repeat TEE 45 days post-implant confirmed sealing so Warfarin discontinued
 - ASA/Ticagrelor indefinitely
- 5 Year Data from PREVAIL and PROTECT AF trials: This data was based on the results of 1114 randomized patients
- Post Approval Data: After the approval of LAAC by USFDA a study was performed on 3822 Patients

NON-VALVULAR ATRIAL FIBRILLATION

- **PROTECT-AF:** “The subject has not been diagnosed with rheumatic mitral valvular heart disease”
- **ACP Trial :** “Nonvalvular AF refers to cases without rheumatic mitral valve disease, prosthetic heart valve, or valve repair.”

Watchman Deployment 30 mm (D) and Deployment Deep where smaller inferior lobe is filling with contrast and not covered by Watchman device (E,F)



5 Year Data from PREVAIL and PROTECT AF trials : This data was based on the results of 1114 randomized patients

	PROTECT AF			PREVAIL			Combined Cohort		
	Device (n = 463)	Control (n = 244)	p Value	Device (n = 269)	Control (n = 138)	p Value	Device (n = 732)	Control (n = 382)	p Value
Age, yrs	71.7±8.8	72.7±9.2	0.18	74.0±7.4	74.9±7.2	0.26	72.6±8.4	73.5±8.6	0.09
Male	70.4	70.1	0.93	67.7	74.6	0.15	69.4	71.7	0.42
CHADS2 score	2.2±1.2	2.3±1.2	0.07	2.6±1.0	2.6±1.0	0.48	2.3±1.1	2.4±1.2	0.06
Risk factors									
CHF	26.8	27.0	0.94	23.4	23.2	0.96	25.5	25.7	0.97
Hypertension	89.6	90.2	0.82	88.5	97.1	0.003	89.2	92.7	0.06
Age \$75 yrs	36.9	41.4	0.25	46.5	46.4	0.99	40.4	43.2	0.38
Diabetes	24.4	29.5	0.14	33.8	29.7	0.4	27.9	29.6	0.55
Prior stroke/ TIA	17.7	20.1	0.44	29.7	29.7%	1.0	22.1	23.6	0.59
CHA2DS2-VASc score	3.4±1.5	3.7±1.6	0.02	4.0±1.2	4.1±1.2	0.4	3.6±1.4	3.9±1.5	0.02
AF pattern									
Paroxysmal	43.2	40.6	0.50	48.7	51.4	0.6	45.2	44.5	0.82
Persistent	21.0	20.5	0.89	31.6	28.3	0.49	24.9	23.3	0.56
Permanent	34.6	38.1	0.35	15.6	15.9	0.93	27.6	30.1	0.38
Unknown	1.3	0.8	0.72	1.5	0.7	0.5	1.4	0.8	0.56
Paced	0	0	—	2.6	3.6	0.55	1.0	1.3	0.56

- Non-valvular AF = “Non-rheumatic AF”
- However = AVA <1.0 cm² was an exclusion criterion

SUMMARY

- LAAO is a very important treatment option for patients with high risk of AF and increased risk of bleeding
- Safety and efficacy data should be carefully presented to patients for shared decision making
- Careful attention to details is necessary for safe and effective implantation of the devices
- On going trials will help to clarify specific indications better
- Newer devices will allow effective treatment for more anatomical variations.

Post Approval Data : After the approval of LAAC by USFDA a study was performed on 3822 Patients

Procedural parameters	Aggregate clinical data
Number of procedures	6,720
Implantation success, %	94.9%
Complication rates	
Pericardial tamponade	1.24%
Procedure-related stroke	0.18%
Device embolization	0.25%
Procedure-related death	0.06%

Angiography vs. hemodynamic assessment to predict the natural history of CAD



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This presentation provides a comparison between coronary angiography and hemodynamic assessment techniques used to predict the nature of coronary artery disease. It also provides an insight on the results of the FAME study, DEFER study and FAME 2 trial ultimately concluding hemodynamic index (FFR) to be a more reliable source in predicting the natural history of stable coronary artery disease.

DECISION-MAKING IN CAD

- Coronary artery disease (CAD) is the most common form of heart disease and affects millions of people globally, accounting for 30% of all global deaths
- Coronary angiogram is gold standard for anatomical assessment.

Anatomical (Quantitative)	Morphological (Qualitative)
<ul style="list-style-type: none">• Lesion quantification in at least 2 orthogonal views:• Reference vessel size• Bifurcation/trifurcation stenosis• Identifying and quantifying coronary collaterals	<ul style="list-style-type: none">• Severity/calcification/degree of tortuosity• Presence of ulceration/thrombus• Distal vessels (graftable or not)• Grading TIMI myocardial perfusion blush grade

PITFALLS OF CORONARY ANGIOGRAPHY

- Limitation of the angiographic views
 - a. Inferior image quality: Inadequate opacification, vessel overlap, unknown LM severity
 - b. Inter observer variability
 - c. Lesion eccentricity
- Distal microvasculature
- Ischemia producing vessel in MVD

WHAT TO TREAT AND HOW TO TREAT IN CAD?

- Myocardial ischemia is the most powerful prognostic factor in patients with CAD
- Benefit of revascularization over OMT is known when the extent of reversible ischemia exceeds 10%

HOW TO DETERMINE ISCHEMIC LESIONS - CORONARY HEMODYNAMICS

Non invasive test:

- Excercise ECG: Info per patient (Sens ~ 65%, Spec ~ 65%)
- Nuclear SCAN: Info per artery (Sens ~ 80%, Spec ~ 80%)

Invasive Test:

- FFR: Info per lesion (The gold standard offering the best spatial resolution)

WHAT IS FFR?

- Fractional flow reserve (FFR) is a technique used to measure pressure differences across a coronary artery stenosis in order to determine its hemodynamic severity during period of maximum hyperemia
- Fractional flow reserve is defined as the pressure distal to a stenosis relative to the pressure proximal the stenosis.

UNIQUE FEATURES OF FFR

- FFR specifically relates the influence of the epicardial stenosis to the myocardial perfusion area and blood flow
- Normal value = 1.0 for every patient and every artery
- FFR has a circumspect threshold value (0.80) to indicate ischemia
- FFR is easy to measure (success rate 99%) and extremely reproducible
- FFR is not influenced by changing hemodynamic conditions (heart rate, blood pressure, contractility).

HOW TO KNOW FFR IS SIGNIFICANT OR NOT?

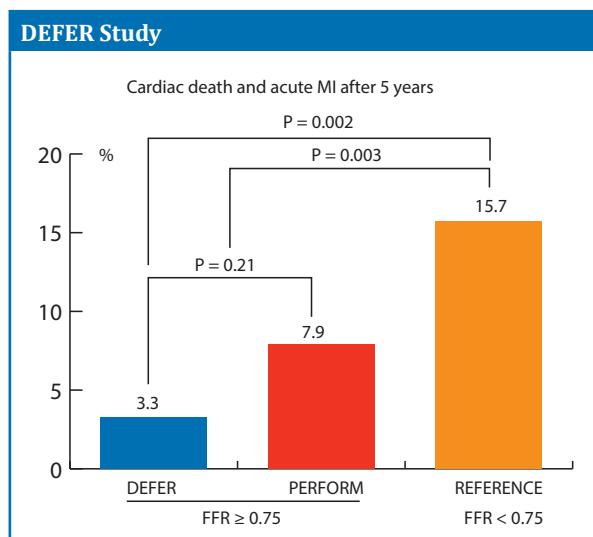
- FFR < 0.8 – Always ischemia (specificity 100%)
- FFR > 0.8 – Ischemia very unlikely (sensitivity 88%).

FAME STUDY

CONCLUSION: Do not rely purely on angiogram.

DEFER STUDY

- At 2-year follow up: 89% of patients in the deferral group experienced no adverse events
- At 5 year follow-up (92% patients): Deferral of PCI associated with a favorable very long term follow-up with reduced rate of AMI
- Risk of death or AMI being for FFR > 0.75 is < 1% per year
- Hence, the results of this trial prove that stenting a “non-ischemic” stenosis does not benefit patients with stable angina



CONCLUSION: Do not revascularize functionally non-significant lesions.

FAME 2: TRIAL DESIGN

- 2 Year Results
 - I⁰ end point in FFR guided PCI less than half that in OMT group
 - 79% relative risk reduction for urgent revascularization
- 3 year Results
 - FFR-guided PCI strategy noted to be cost-effective at 3 years

CONCLUSION: Do revascularize all the functionally significant stenoses.

VISUAL FUNCTIONAL MISMATCH BETWEEN FFR AND ANGIOGRAPHY

The probable reason of Mismatch between FFR and Angiography is based on:

- Reference diameter cannot predict the quantum of myocardium supplied by vessel
- Angiogram does not provide any clue about morphologic details of lesion and vasodilatory capabilities of the microvasculature
- Inaccuracies of pressure measurement and angiographic lesion definition.

WHAT PREDICTS THE NATURAL HISTORY OF CAD? ANGIOGRAPHIC APPEARANCE OR HEMODYNAMIC SIGNIFICANCE

- Recently published FAME 2 sub study throws some light on this subject
- The results of this study demonstrated that among the stenoses with mismatch between DS and FFR, more than half had a low FFR in the presence of an angiographically mild stenosis (orange – PM)

CONCLUSION: Hemodynamics triumphs Anatomy.

SUMMARY

- Hemodynamic index (FFR) is more reliable in predicting the natural history of stable CAD
- Visual evaluation (Anatomy) of coronary arteries cannot sufficiently predict presence of the obstructive CAD
- PCI should be guided by the hemodynamic considerations and not solely by anatomic ones.



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