MYOCARDIAL ISCHEMIA
from traditional beliefs to new concepts

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Ischemic heart disease; a worldwide significant clinical burden

IHD
1st cause of death
7.4 million

¾ of IHD deaths in Low & middle income countries

WHO fact sheet No. 310 – updated May 2014
Ischemic heart disease mortality rates

High mortality rate in Egypt ranges from 240 - 480 per 100,000

Angina pectoris; where are we now?

Stable angina: A common and disabling disorder that is prevalent in 20 000 to 50 000 per one million in general population

Angina pectoris - most prevalent manifestation of IHD, often preceding more serious problems (hospitalization, death) and thus providing a “window of opportunity” for prevention of morbidity and mortality.

Economic impact

x 3 fold higher risk of DISABILITY
x 1.5 fold higher risk of JOB LOSS
x 4 fold higher risk of DEPRESSION

Personal impact
What is the traditional believes?

2006 ESC guidelines on the management of stable angina pectoris

**Myocardial ischemia:**

*Myocardial ischaemia is caused by an imbalance between myocardial oxygen supply and myocardial oxygen consumption.*

Coronary obstruction

Angina management focused on hemodynamic therapies BB, CCB, Nitrates, Nicorandil
Challenges:

# Are traditional hemodynamic therapies providing complete answer for angina management?

# Is it only a matter of coronary obstruction? Do we have another mechanisms responsible for angina?

Traditional hemodynamic therapies !!!

- Limited efficacy in combination.

**Akhras and Jackson**
- β-blocker
- β-blocker + CCB
- β-blocker + ISMN
- β-blocker + ISMN + CCB

“Combination offers no substantial advantage over optimum beta-blockade as monotherapy.”

**TIBET**
- β-blocker
- CCB
- β-blocker + CCB

“Little advantage gained from using combination therapy”
Traditional antianginal therapies !!!

- Even with the use of traditional antianginal therapies (β-blockers, CCBs, nitrates and nicorandil), significant proportion of patients are not well controlled.

- A significant number of patients have relative intolerance to full doses of β-blockers, nitrates, and nicorandil.

- β-blockers and many CCBs have similar depressive effects on BP, HR and/or AV nodal conduction.

Is it only coronary obstruction?
the American College of Cardiology
National Cardiovascular Data Registry

398,987 patients

there is no consistent relation
between coronary obstruction and angina symptoms

CONFIRM Registry 2011

CAD (>50%):
1. Incidence is less than expected
2. more related to age than angina symptoms
IHD may result from a number of mechanisms,...

Myocardial cell metabolism is affected whatever the mechanism that leads to ischemia.

A new concept for myocardial ischemia

Myocardial ischemia:

Myocardial ischaemia and hypoxia in SCAD are caused by a transient imbalance between blood supply and metabolic demand.
Myocardial ischemia
• Impaired energy metabolism
• Na, Ca$^2+$ overload
• lactic acidosis
• Promotion of the programmed cellular death

Metabolic demands of myocardial cell during ischemia

How to correct?

Myocardial ischemia
• Better energy metabolism
• Less Na, Ca$^2+$ overload
• Less lactic acidosis
• Increased tolerance of cardiac cells to ischemia

TRIMETAZIDINE; fulfilling ischemic myocardial cell needs

Glucose oxidation
1 Oz mol. → 6.4 ATP

FFA oxidation
1 Oz mol. → 5.6 ATP

Less ATP production
Lactic acidosis and cell death
**TRIMETAZIDINE; fulfilling ischemic myocardial cell needs**

**Glucose oxidation**
- 1 O₂ mol. → 6.4 ATP

**FFA oxidation**
- 1 O₂ mol. → 5.6 ATP

**Less acidosis and more cardiac ATP**

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**Trimetazidine MR:** antianginal efficacy comparable to β. blocker (propranolol)

<table>
<thead>
<tr>
<th>Changes in</th>
<th>Propranolol</th>
<th>TRIMETAZIDINE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG units consumption per week</td>
<td>-2.4</td>
<td>-3.5</td>
<td>0.426</td>
</tr>
<tr>
<td>Time to onset of angina (s)</td>
<td>+64</td>
<td>+67</td>
<td>0.830</td>
</tr>
<tr>
<td>Time to 1-mm ST-segment depression (s)</td>
<td>+64</td>
<td>+50</td>
<td>0.481</td>
</tr>
<tr>
<td>Exercise duration (s)</td>
<td>+33</td>
<td>+33</td>
<td>0.982</td>
</tr>
</tbody>
</table>

TRIMETAZIDINE MR; proven efficacy Versus other antianginal agents

19,280 patients
Trimetazidine MR
is at least as effective as other antianginal agents

AA : Mean weekly number of angina episodes
SAN: Mean weekly short acting nitrate consumption


Trimetazidine MR; proven efficacy in combination with β-blockers

Time to 1-mm ST depression
Time to onset of angina

n=426
Stable angina patients
All on metoprolol (50 mg/day)

Significant improve in exercise capacity

Trimetazidine is an anti-ischaemic metabolic modulator, with similar anti-anginal efficacy to propranolol in doses of 20 mg thrice daily. The heart rate and rate × pressure product at rest and at peak exercise remained unchanged in the trimetazidine group, thus showing a non-mechanical anti-ischaemic action.

Trimetazidine (35 mg twice daily) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia, as reviewed by the EMA in June 2012.
Strong evidence in different clinical situations

**Angina patients**
- Glezer (2017)
- Peng (2014)
- Nesukay (2014)
- Xu (2014)
- Vitale (2012)
- Danchin (2011)
- Glezer (2007)
- Rosano (2005)
- Chazov (2005)
- Manchanda (1997)
- Michaelides (1997)
- Dalla-Volta (1990)
- Szwed - TRIMPOL I study (2001)
- Szwed - TRIMPOL II study (2001)
- Detry - TEMS study (1999)

**Diabetic patients**
- Shehata (2014)
- Xu (2014)
- Belardinelli (2008)
- Rosano (2007)
- Padial-DIETRIC study (2005)
- Fragasso (2003)
- Szwed-TRIMPOL I study (2001)
- Data for diabetics. If intolerance, consider clopidogrel.

**Patients undergoing angioplasty**
- Wang (2016)
- Zhang (2015)
- Shehata (2014)
- Xu (2014)
- Chen (2014)
- Xu (2013)
- Labrou (2007)
- Bonello (2006)
- Polonski (2002)
- Steg-LIST study (2001)
- Birand (1997)
- Kober (1992)

**Left ventricular dysfunction**
- Grajek (2015)
- Bubnova (2012)
- Zhang (2012)
- Fragasso (2012)
- Gao (2011)
- Tuunanen (2008)
- Sisakian (2008)
- Belardinelli (2008)
- Di Napoli (2007)
- Belardinelli (2007)
- Fragasso (2006)
- Di Napoli (2005)
- El Kady (2005)
- Belardinelli (2001)
- Lu-Chierchia (1998)
- Brottier (1990)

**Acute MI patients**
- Li (2016)
- Wang (2016)
- Demirell (2013)
- Kim - KAMIR study (2013)
- Steg - LIST study (2001)
- Boissel - EMIP FR study (2000)
- Di Pasquale (1999)

**Patients undergoing coronary bypass**
- Zhang (2015)
- Martins (2015)
- Lopatkin (2010)
- Iskensen (2009)
- Tunerir (1999)
- Fabiani (1992)
Angina with diabetics

**Diabetes**  ↓ insulin

↓ Cardiac glucose uptake & utilization

↓ Glucose oxidation  ↓ Cardiac glucose uptake & utilization

↓ Fatty acids oxidation  ↓ Glucose oxidation

Less O2 cost for energy production  More O2 cost for energy production

Cardiac energy sources in ischemic diabetics: 10% glucose  90% fatty acids

More oxygen consumption & less energy production

Metabolic consequences in ischemic diabetics

↑ Free radicals due to hyperglycemia & dyslipidemia

Endothelial dysfunction

Angiopathy

Big vessels
Coronaries

Smaller vessels
Nerves

Stable angina / Unstable angina / Silent ischemia

Acute MI  ➔ ischemic heart failure
Trimetazidine MR; Antianginal efficacy in ischemic diabetic patients

Mean number of angina attacks
- M0: Red
- M6: Gray

Exercise test duration (s)
- M0: Red
- M6: Gray

*P<0.001

Trimetazidine MR; Antianginal efficacy in ischemic diabetic patients

Time to 1-mm ST-segment depression
- W-1: Red
- W0: Gray
- W4: Red

P<0.01

Time to onset of angina
- W-1: Red
- W0: Gray
- W4: Red

P<0.01


Effect on silent & symptomatic ischemia in diabetic patients

Evaluation at baseline and 6 months by 24-h ambulatory ECG


Trimetazidine MR;
Cardio-protective effect of administration before PCI and CABG
Trimetazidine MR; Cardio-protective effect of administration before PCI and CABG

**Before PCI**

- n=266 patients undergoing PCI
- *** P<0.0001

**Before CABG**

- n=30 patients undergoing CABG
- * P<0.05

**Troponin I levels (ng/mL)**

- **-67%**

**Troponin T (ng/mL)**

- **Before CABG**
- **Hour 2**
- **Hour 18**
- **Hour 48**

Reduces risk of ischemic damage in cardiomyocytes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Bonello et al. 2007</td>
<td>1.10 (0.69, 1.76)</td>
<td></td>
</tr>
<tr>
<td>Labrou et al. 2007</td>
<td>0.59 (0.27, 1.28)</td>
<td></td>
</tr>
<tr>
<td>Polonski et al. 2002</td>
<td>0.57 (0.30, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Xu et al. 2013</td>
<td>0.58 (0.45, 0.75)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>0.69 (0.48, 0.99)</td>
<td>n=468  P=0.04</td>
</tr>
</tbody>
</table>

**Forest plots for serum cTnl levels**

Favors Trimetazidine  Favors control

Benefits after PCI in diabetic patients

**Early benefits**

Reduces the risk of recurrent angina

**Long term benefits**

At 2-years follow-up significant improvement of silent myocardial ischemia

Cumulative Angina pectoris-free Survival (%)

- Control
- Trimetazidine


Trimetazidine MR;
Significantly preserves LV function after revascularization

EF measurement (%)

- Placebo
- Trimetazidine

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

11.2 Angina and coronary artery disease

for stable angina patients with symptomatic HFrEF (NYHA Class II-IV)

"Effective anti-anginal treatment, safe in HF"
"Improves exercise duration and LV function"
"Improves NYHA functional capacity"

Moving from the traditional management to new horizons
• 900 angina patients
• Aspirin, Statin, Clopidogrel
• B. blocker alone or in combination with LAN, CCB or both.
• Mean weekly angina attacks (5/week)
• Mean walking distance eliciting angina = 336 m.

3 groups of background anti-ischemic / antianginal therapies

Patients treated with TRIMETAZIDINE MR, angina symptoms re-evaluated after 2 weeks, 2,4 and 6 months
**Trimetazidine MR**

significantly improve exercise capacity and quality of life

**CHOICE - 2**

Mean walking distance (m) eliciting angina

- Baseline: 336.9
- 1 week: 378.5
- 2 months: 460.9
- 4 months: 538.5
- 6 months: 593.6

* p<0.00001 Vs previous visit

Mean self rated well-being

- Baseline: 44
- 1 week: 52.8
- 2 months: 62.2
- 4 months: 69.6
- 6 months: 77.3

* p<0.00001 Vs previous visit

**TRIMETAZIDINE MR;**

continuous reduction of angina & nitrate consumption

**CHOICE - 2**

Mean weekly number of angina attacks

- Baseline: 5.4
- 2 weeks: 3.7
- 2 months: 2.4
- 4 months: 1.6
- 6 months: 1.1

P < 0.00001 Vs baseline

Mean weekly number of short acting nitrates

- Baseline: 5.1
- 2 weeks: 3.3
- 2 months: 2.0
- 4 months: 1.3
- 6 months: 0.9

P < 0.00001 Vs baseline
Trimetazidine MR is rapidly effective whatever the previous treatment

**Conclusion**

Early combination of Trimetazidine MR with B. blocker is the fastest and most efficient way to relief angina
The future

• Phase III, international, multicenter, randomized, double-blind, placebo-controlled trial

• 5,800 patients, 27 countries, 432 centers.

• 2 parallel and balanced arms
  Trimetazidine 35 mg b.i.d. Vs placebo

• On top of post-PCI recommended treatment for Coronary Artery Disease (as per normal practice of the investigator/current guidelines/patient’s clinical condition)

Study end points

- Superiority of trimetazidine over placebo on the time to first occurrence of an event in the composite of:
  • Cardiac death
  • Hospitalisation for a cardiac event
  • Recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies
  • Recurrent or persistent angina leading to performing a coronary angiography

- Secondary end points:
  Each component of the primary end points
Take home message

• Traditional belief that depends only on O2 supply / demand balance using hemodynamic therapies was not sufficient to control angina.

• The latest ESC guidelines established a new concept that depends on the balance between blood supply and metabolic demands for efficient control of angina.

• Ischemic myocardial cell requires better energy metabolism and less acidosis to augment its’ tolerance to ischemia.

• TRIMETAZIDINE MR acts directly on ischemic cardiac cells to keep them alive and functioning, it reduces acidosis and increase cardiac ATP production.

Take home message

• TRIMETAZIDINE MR is a strong tool in managing ischemic heart disease from the early stages of the disease up to Heart Failure.

• When applying new concepts targeting stenotic lesion as well as myocardial cell metabolic demands, we should consider early inclusion of TRIMETAZIDINE MR in the following situations:
  ▪ in combination with B.blocker for angina patients
  ▪ ischemic diabetic patients
  ▪ angina patient with heart failure
  ▪ Pre & post revascularization (PCI / CABG)

• We are waiting for ATPCI results, that could expand the horizons of TRIMETAZIDINE MR use in daily practice.
Thank You