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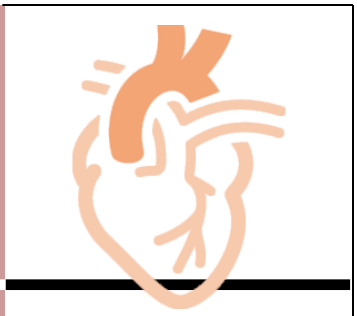
State of the HEART

A monthly cardiology news

INTAS MEDICAL AFFAIRS

Monthly Magazine Issue 15

State of the Heart



Dear Reader,

We are grateful to present you the 15th issue of "**State of the Heart**", which explores the clinical evidence supporting the new understandings and happenings in the field of cardiology.

In India, the epidemiological transition from predominantly infectious disease conditions to non-communicable diseases has occurred over a rather succinct period of time. Despite wide heterogeneity in the prevalence of cardiovascular risk factors across different regions, CVD has emerged as the leading cause of death in all parts of India, including poorer states and rural areas. In this research driven time, management of these disorders is also constantly evolving towards the betterment whether it's pharmacological or non-pharmacological.

Being a healthcare custodian of the society, clinicians are constantly thriving to be abreast with the novel understandings of disease and its management. In this context, this is our initiative to provide you a compiled and to the point information.

Present booklet comprises of recent and latest deeds in the field of cardiovascular diseases like dyslipidemia, coronary artery disease, heart failure and its management. We hope that it will facilitate increased cooperation and innovation, and enthuse commitment to prevent these life-threatening and disabling disorders and providing the best possible care for people who suffer from these conditions.

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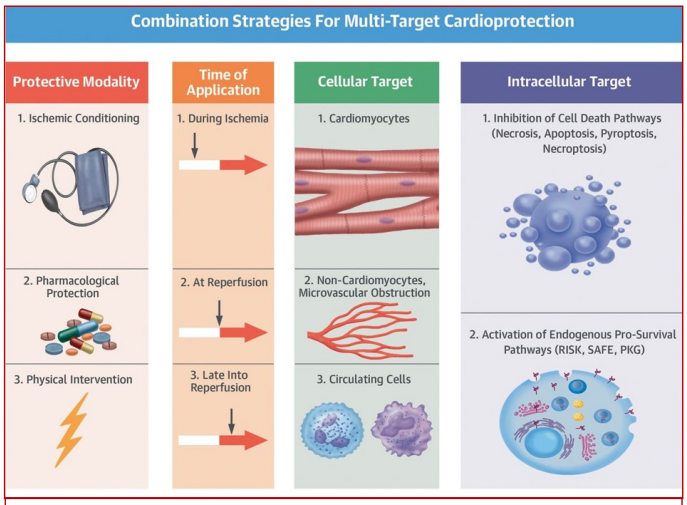
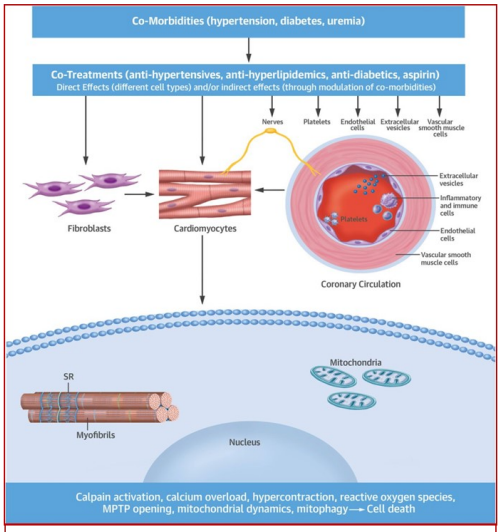
1. Multi-target Strategies to Reduce Myocardial Ischemia/Reperfusion Injury

Multi-target Strategies to Reduce Myocardial Ischemia/Reperfusion Injury



Cardio-protective strategies against myocardial ischemia–reperfusion injury (IRI) can be broadly divided into several categories based on the protective modality, time of application, cellular target, and intracellular target



Different comorbidities and co-treatments can influence protection via effects on different cellular and subcellular targets.

Optimal cardio-protection may require the combination of additive or synergistic multitarget therapies.

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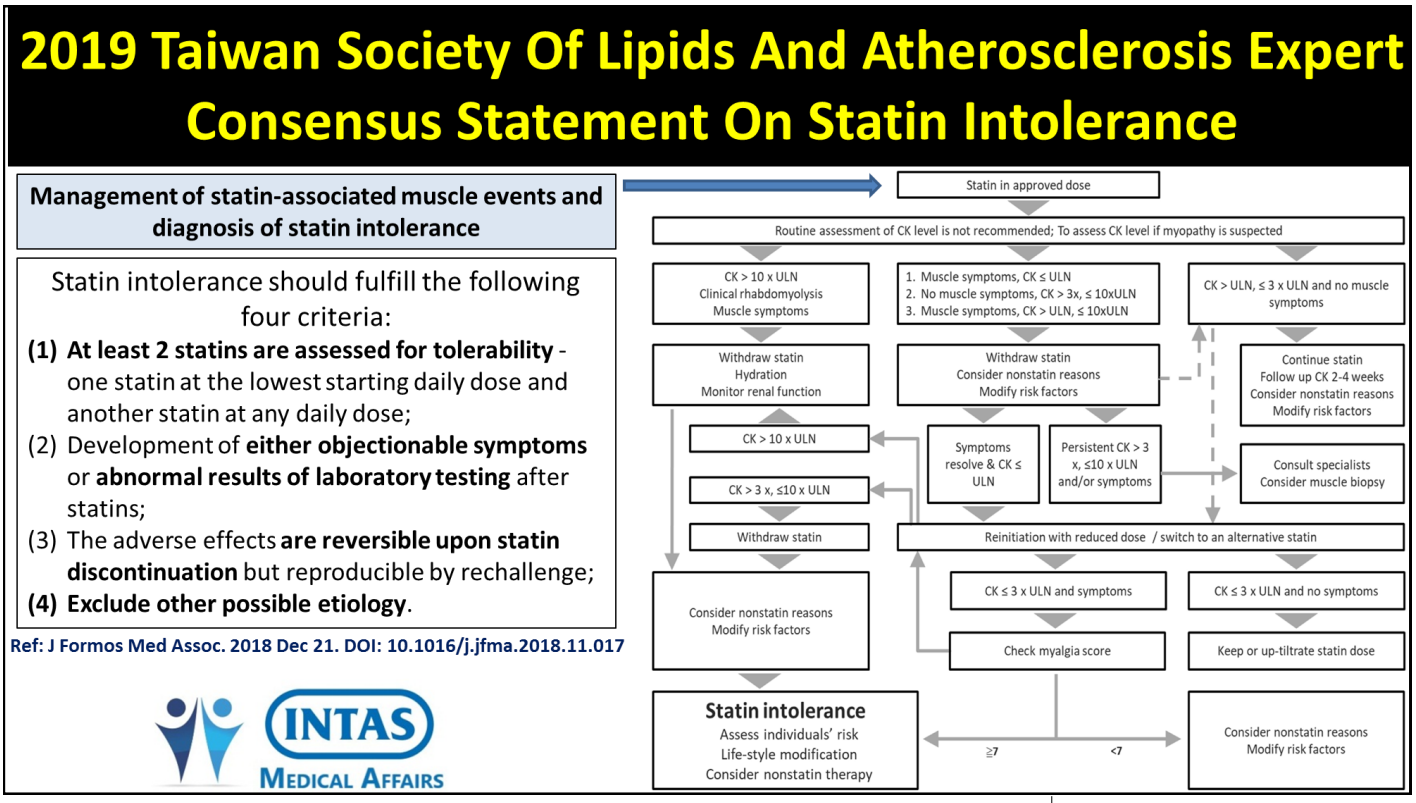
Many treatments have been identified that confer robust cardioprotection in experimental animal models of acute ischemia and reperfusion injury. However, translation of these cardioprotective therapies into the clinical setting of acute myocardial infarction (AMI) for patient benefit has been disappointing. One important reason might be that AMI is multifactorial, causing cardiomyocyte death via multiple mechanisms, as well as affecting other cell types, including platelets, fibroblasts, endothelial and smooth muscle cells, and immune cells.

Conceptually, the simplest approach to multitarget cardioprotection is to combine 2 or more agents or interventions, each of which has a distinct target within the cardiomyocyte. In this approach, it is important that each cardioprotective agent or intervention is at maximal "dose" (i.e., not subthreshold), and that the combination of agents or interventions confers additive benefit in terms of infarct size reduction. The intracellular targets can include prosurvival signaling pathways (e.g., the RISK, SAFE, and NO-cGMP-PKG cascades), cell death pathways (e.g., necrosis, apoptosis, autophagy, necroptosis, and pyroptosis), and cellular organelles (e.g., mitochondria, sarcoplasmic reticulum) As such, maximal cardioprotection may require activation of complementary prosurvival pathways and/or inhibition of deleterious cell death pathways, as recently proposed in the "multitarget hypothesis".

Many cardioprotective strategies act through common end-effectors and may be suboptimal in patients with comorbidities. In this regard, emerging data suggest that optimal cardioprotection may require the combination of additive or synergistic multitarget therapies.

"Optimal cardio-protection may require the combination of additive or synergistic multitarget therapies."

2. 2019 Taiwan Society Of Lipids And Atherosclerosis Expert Consensus Statement On Statin Intolerance



Statin reduces low-density lipoprotein cholesterol and improves clinical outcomes in high risk patients. In general, statin is a safe and well-tolerated medication. However, varieties of adverse effects are reported in some patients and may interfere long-term drug compliance.

Statin-associated muscle events and liver function change account for most of these adverse effects.

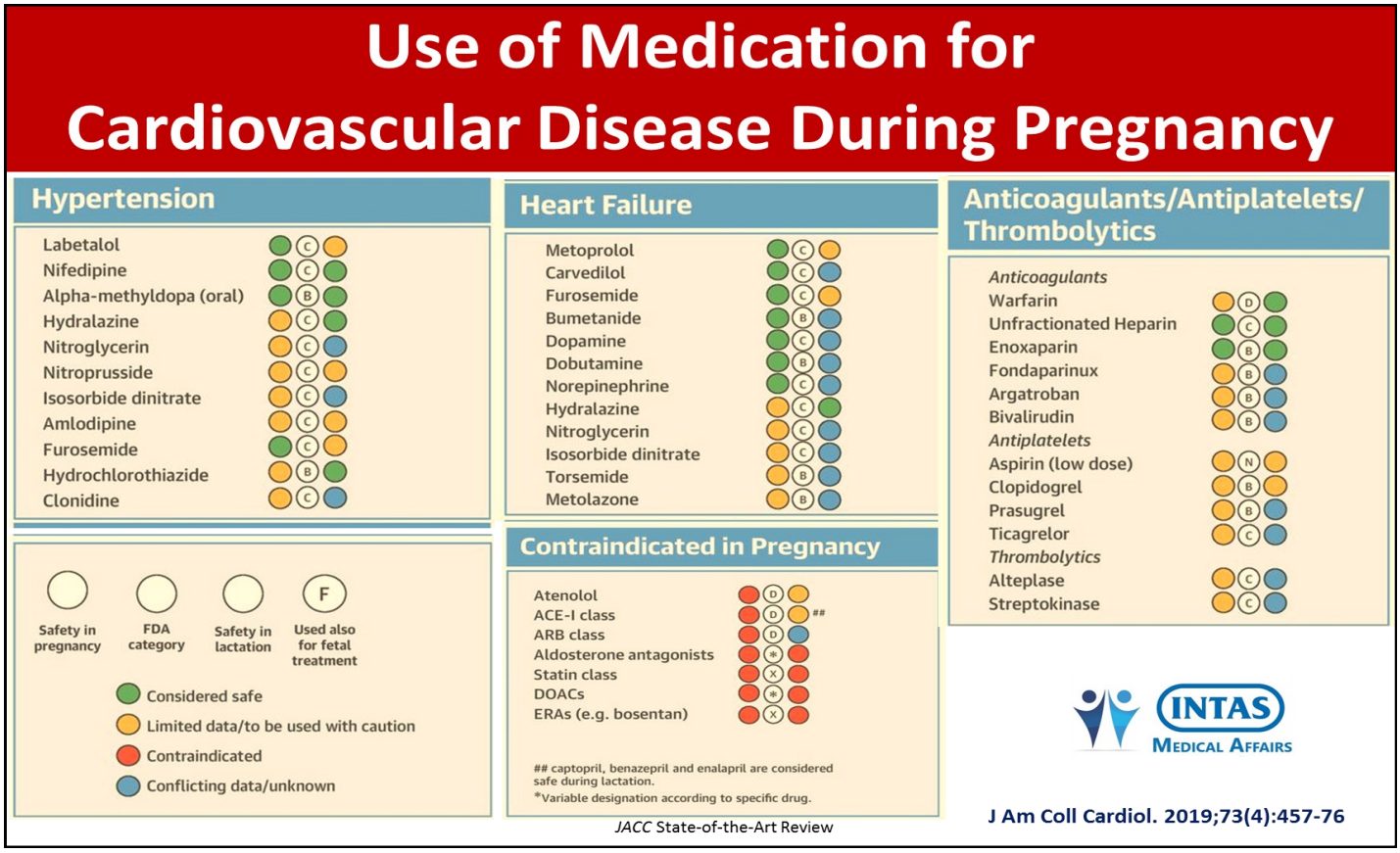
Patients are regarded as statin intolerance if they need to discontinue statin therapy due to these adverse effects. To date, there is no universal standard definition of statin intolerance. But a pragmatic definition of statin intolerance is essential and helpful for clinicians in daily practice.

Statin intolerance should fulfill the following four criteria:

- At least 2 statins are assessed for tolerability - one statin at the lowest starting daily dose and another statin at any daily dose;
- Development of either objectionable symptoms or abnormal results of laboratory testing after statins;
- The adverse effects are reversible upon statin discontinuation but reproducible by rechallenge;
- Exclude other possible etiology.

" Although a variety of side effects resulting from statin therapy have been reported, most of them are devoid of solid evidence supporting causal relationship with statin. Identifying patients with statin intolerance by the recommended criteria helps to avoid unnecessary discontinuation of statin."

3. Use of Medication for Cardiovascular Disease During Pregnancy



- Several hemodynamic and physiologic adaptations occur during pregnancy and the pharmacokinetics of cardiovascular medications can change throughout gestation .
- The Food and Drug Administration has replaced the ABCDX classification system for labeling the safety of medications during pregnancy with a narrative labeling system. The Pregnancy and Lactation Labeling Rule (PLLR) is intended to provide more information about available data, clinical considerations, and differences in degrees of fetal risk.
- Unstable arrhythmias should be treated with electrical cardioversion. Antiarrhythmic medications should be avoided in the first trimester if possible, and the lowest effective dose should be used. Amiodarone should be avoided due to the risk of fetal thyroid and neurodevelopmental complications.
- Beta-blockers are used frequently for the treatment of several cardiovascular conditions during pregnancy. Large, retrospective studies show no association between the use of beta-blockers and major congenital abnormalities. Atenolol is not recommended due to increased risk of fetal growth restriction.
- First-line agents for chronic or gestational hypertension include labetalol, nifedipine, and methyldopa. Dose reduction may be needed in the second trimester when a 5-10 mm Hg decrease in mean blood pressure is often observed due to the physiologic changes of pregnancy .
- Statins continue to be considered contraindicated during pregnancy, although no associations with birth defects were found in a multicenter, observational, prospective trial and a recent systematic review.
- Low-dose aspirin is considered safe during pregnancy and lactation, and is commonly used for the prevention of pre-eclampsia. Clopidogrel has been used in pregnancy but since there are limited data, it is recommended to use it for the shortest duration possible.

4. Presence And Severity Of Coronary Artery Calcium Identifies Patients Most Likely To Benefit From Statins

Presence And Severity Of Coronary Artery Calcium Identifies Patients Most Likely To Benefit From Statins

Methods

Study Population: Subjects without pre-existing ASCVD or malignancy who underwent CAC scoring from 2002 to 2009 **(n=13,644)**
Median follow up: 9.4 years
Primary outcome: first major adverse cardiovascular event (MACE). The effect of statin therapy on outcomes was analyzed stratified by CAC presence and severity.

Results

- Statin therapy was associated with **reduced risk of MACE in patients with CAC** [adjusted subhazard ratio: 0.76;p = 0.015).
- The **effect of statin** use on MACE was **significantly related to the severity of CAC** (p < 0.0001)

The presence and severity of CAC identifies patients most likely to benefit from statins for the primary prevention of cardiovascular diseases.

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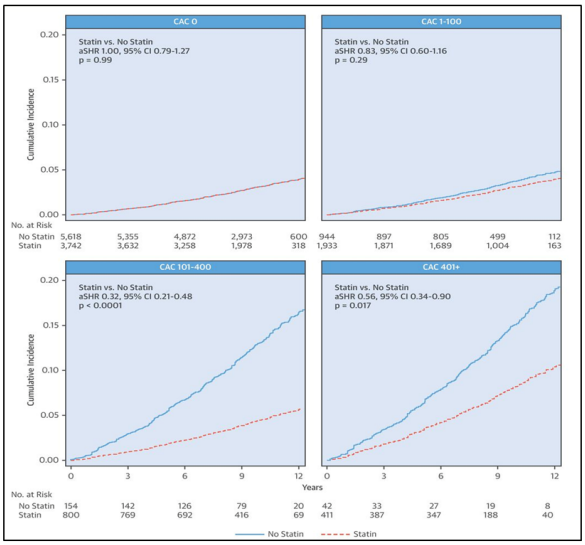
Cumulative Incidence Of MACE Stratified By Statin Treatment And CAC Severity



J Am Coll Cardiol. 2018; 72 (25): 3233-42

Background and Objective

Compared with traditional risk factors, coronary artery calcium (CAC) scores improve prognostic accuracy for atherosclerotic cardiovascular disease (ASCVD) outcomes. However, the relative impact of statins on ASCVD outcomes stratified by CAC scores is unknown. The authors sought to determine whether CAC can identify patients most likely to benefit from statin treatment.

Methods

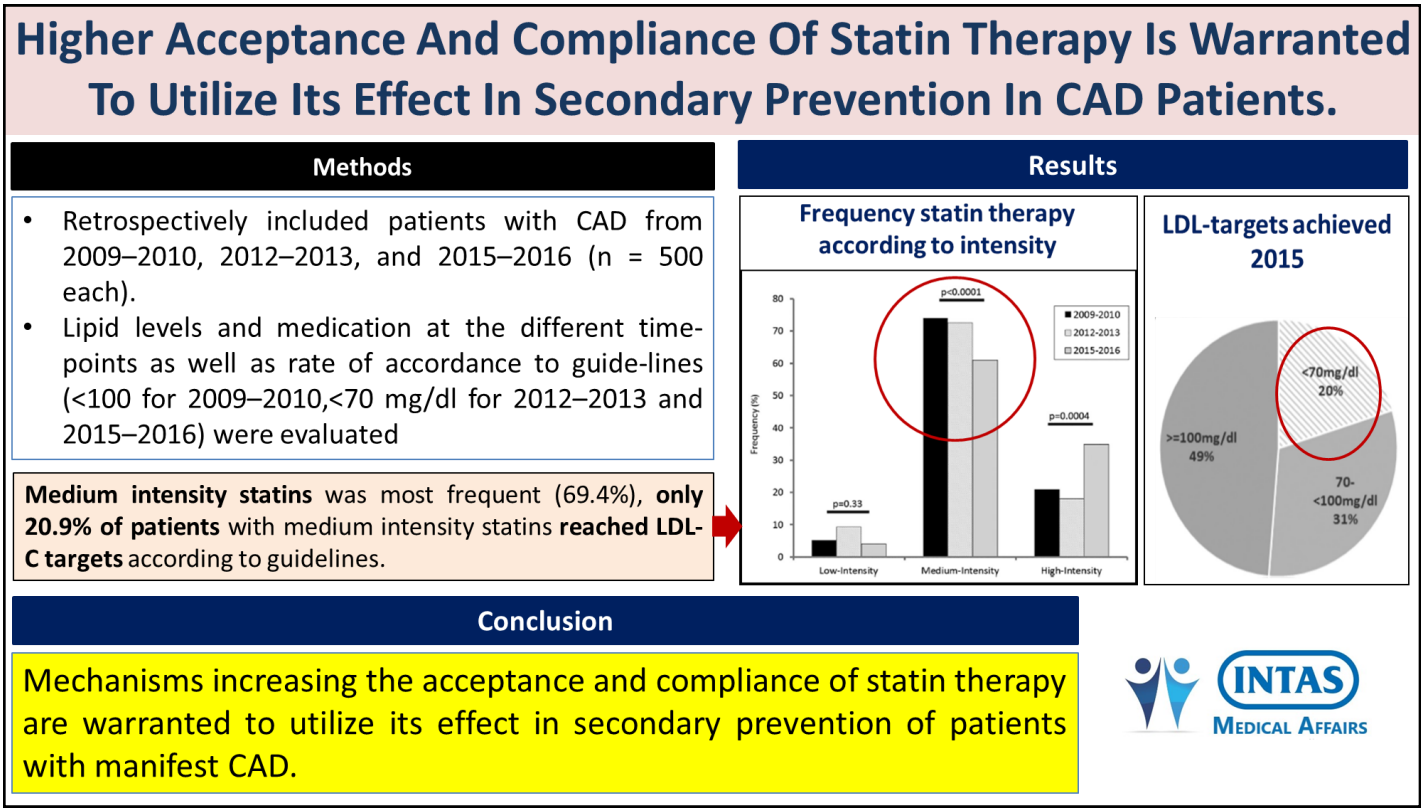
The authors identified consecutive subjects without pre-existing ASCVD or malignancy who underwent CAC scoring from 2002 to 2009 at Walter Reed Army Medical Center. The primary outcome was first major adverse cardiovascular event (MACE), a composite of acute myocardial infarction, stroke, and cardiovascular death. The effect of statin therapy on outcomes was analyzed stratified by CAC presence and severity, after adjusting for baseline comorbidities with inverse probability of treatment weights based on propensity scores.

Results

A total of 13,644 patients (mean age 50 years; 71% men) were followed for a median of 9.4 years. Comparing patients with and without statin exposure, statin therapy was associated with reduced risk of MACE in patients with CAC (adjusted subhazard ratio: 0.76; 95% confidence interval: 0.60 to 0.95; p = 0.015), but not in patients without CAC (adjusted subhazard ratio: 1.00; 95% confidence interval: 0.79 to 1.27; p = 0.99). The effect of statin use on MACE was significantly related to the severity of CAC (p < 0.0001 for interaction), with the number needed to treat to prevent 1 initial MACE outcome over 10 years ranging from 100 (CAC 1 to 100) to 12 (CAC >100).

"THE PRESENCE AND SEVERITY OF CAC IDENTIFIES PATIENTS MOST LIKELY TO BENEFIT FROM STATINS FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASES."

5. Higher Acceptance And Compliance Of Statin Therapy Is Warranted To Utilize Its Effect In Secondary Prevention In CAD Patients.



Aim

To describe whether updated low-density lipoprotein (LDL)-targets in patients with manifest coronary artery disease (CAD) led to a change in lipid profile over time.

Methods

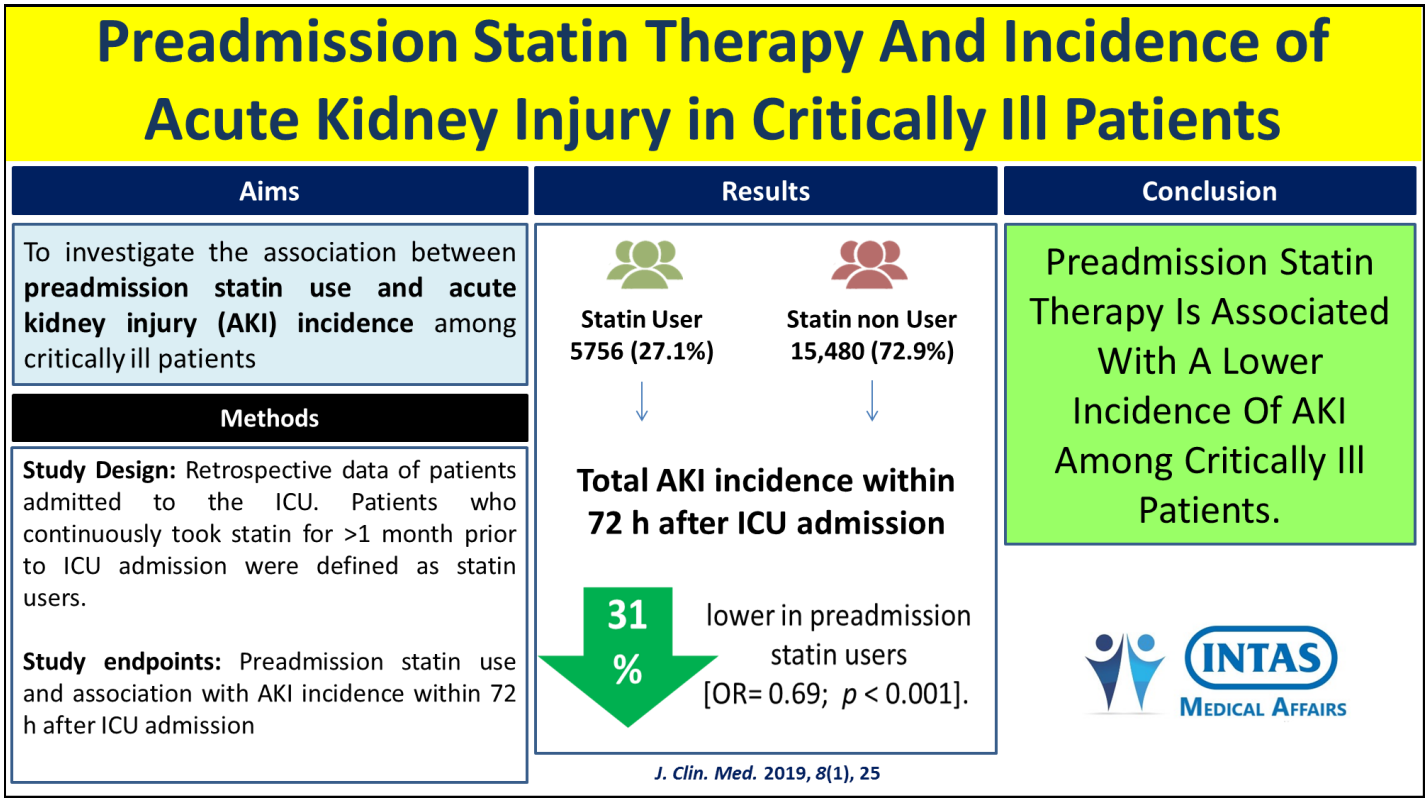
Retrospectively included patients with manifest CAD from 2009–2010, 2012–2013, and 2015–2016 (n = 500 each). Lipid levels and medication at the different time-points as well as rate of accordance to guidelines (<100 for 2009–2010, <70 mg/dl for 2012–2013 and 2015–2016) were evaluated.

Results

Overall, 1500 subjects (mean age: 68.4 ± 11.2 years, 75.8% male) from 813 attending primary care physicians were included. Mean LDL-level was 98.0 ± 35.7 mg/dl, whereas 34.1% reached LDL-targets according to guidelines as applied at each time-point. Reduction of LDL-goals in 2011 lead to an initial decrease in LDL from 98.3 ± 33.4 mg/dl in 2009–2010 to 93.9 ± 36.3 mg/dl in 2012–2013 ($p = 0.045$). This effect was no longer present in 2015–2016 (101.6 ± 36.6 mg/dl, $p = 0.17$). The rate of patients meeting recommended LDL-targets decreased over time (2009–2010: 56.6%, 2012–2013: 25.4%, 2015–2016: 20.2%, $p < 0.0001$ for trend). Likewise, the frequency of statin-intake decreased over time (93.6% in 2009–2010 to 83.7% in 2015-2016, $p < 0.0001$). While use of medium intensity statins was most frequent (69.4%), only 20.9% of patients with medium intensity statins reached LDL-targets according to guidelines.

"Mechanisms increasing the acceptance and compliance of statin therapy are warranted to utilize its effect in secondary prevention of patients with manifest CAD."

6. Preadmission Statin Therapy And Incidence of Acute Kidney Injury in Critically Ill Patients



Aim:
This study aimed to investigate the association between preadmission statin use and acute kidney injury (AKI) incidence among critically ill patients who needed admission to the intensive care unit (ICU) for medical care.

Methods:
Medical records of patients admitted to the ICU were reviewed. Patients who continuously took statin for >1 month prior to ICU admission were defined as statin users. Authors investigated whether preadmission statin use was associated with AKI incidence within 72 h after ICU admission and whether the association differs according to preadmission estimated glomerular filtration rate (eGFR; in mL min−1 1.73 m−2).

Results::
Among 21,236 patients examined, 5756 (27.1%) were preadmission statin users and 15,480 (72.9%) were non-statin users. Total AKI incidence within 72 h after ICU admission was 31% lower in preadmission statin users than in non-statin users [odds ratio (OR), 0.69; 95% confidence interval (CI), 0.61–0.79; p < 0.001]. This association was insignificant among individuals with eGFR <30 mL min−11.73 m−2 (p > 0.05).

"Preadmission statin therapy is associated with a lower incidence of AKI among critically ill patients."

Abbreviated Prescribing Information

Lipicure

Active Ingredient: Lipicure 10/20/40/80 tablet contains atorvastatin 10mg, 20mg 40mg or 80 mg respectively. **Indication:** To reduce elevated total cholesterol and triglyceride levels in patients with primary hypercholesterolemia and mixed dyslipidemia. **Dosage & Administration:** Once a day or as directed by physician. **Contraindications:** Active liver disease, women who are pregnant or may become pregnant. **Warnings & Precautions:** Skeletal muscle effects (e.g., myopathy and rhabdomyolysis), A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months atorvastatin 80 mg. **Pregnancy & Lactation:** Pregnancy Category X. It is contraindicated in women who are or may become pregnant. **Interactions:** It is metabolized by cytochrome P450 3A4. Concomitant administration with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. **Adverse reactions:** The most common adverse reaction in adults was nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection **Overdose:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance. **Updated on:** Feb 2015

Lipitas

Active ingredient: Lipitas 5/10/20/40 mg tablet contains rosuvastatin 5/10/20/ 40 mg respectively. **Indication:** As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non HDL-C, and TG levels to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and on familial) and mixed dyslipidaemia (Fredrickson Type IIa and IIb), elevated serum TG levels (Fredrickson type IV), slow the progression of atherosclerosis in adult patients as part of a treatments strategy to lower Total-C and LDL-C to target levels. **Dosage and administration**: Once a day or as directed by physician. **Contraindication:** Rosuvastatin is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminase. **Warning & precautions:** The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0 and 0.1% patients who received rosuvastatin 5, 10, 20 and 40 mg, respectively. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in the class. **Pregnancy & Lactation:** Category X. Rosuvastatin may cause fatal harm when administered to pregnant women. Rosuvastatin is contraindicated in who are may become pregnant. Safety in pregnant women has not been established. There are no adequate and well controlled studies of rosuvastatin in pregnant women. If this drug is administered to a woman with reproductive potential, the patient should be appraise of the potential hazard to a foetus. **Interactions:** Co-administration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600mg twice daily) resulted in 2.2 and 1.9 fold, respectively. Increase in mean Cmax and mean AUC of rosuvastatin. Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). **Adverse reactions:** Adverse experiences reported in 2% patients in placebo controlled clinical studies of rosuvastatin are as follows; pharyngitis, headache, diarrhea, dyspepsia, nausea, myalgia, asthenia, back pain, flu syndrome, urinary tract infection, rhinitis, sinusitis. **Overdose:** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin

SARTEL

Active ingredient: Sartel 20/40/80 tablet contains telmisartan 20/ 40/80 mg respectively. **Indication:** Treatment of hypertension to lower blood pressure. For the prevention of cardiovascular morbidity and mortality in patients 55 years older at high risk of CVD **Dosage and administration**: Once a day or as directed by physician. **Contraindication:** Telmisartan is contraindicated in patients with a known hypersensitivity to any component of this product. **Warning & precautions:** Avoid fetal or neonatal exposure. Correct any volume or salt depletion before initiating therapy and observe for signs and symptoms of hypotension. Monitor carefully in patients with impaired hepatic or renal function. Avoid concomitant use of ACE inhibitor and angiotensin receptor blocker **Pregnancy & Lactation:** Category D. When pregnancy is detected, discontinue telmisartan as soon as possible. Discontinue nursing or drug, taking into account the importance of the drug to the nursing mother **Interactions:** NSAIDs– increased risk of renal impairment and loss of antihypertensive effect. Do not co-administer aliskiren with telmisartan in patients with diabetes **Adverse reactions:** The most common adverse events (> 1%) reported in hypertension trials are back pain, sinusitis and diarrhea. **Overdose:** Hypotension, dizziness and tachycardia can occur. If symptomatic hypotension occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis. **Updated on:** Feb 2015

ARVAST

Active ingredient: Arvast 5/10/20/40 mg tablet contains rosuvastatin 5/10/20/ 40 mg respectively. **Indication:** As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non HDL-C, and TG levels to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and on familial) and mixed dyslipidaemia (Fredrickson Type IIa and IIb), elevated serum TG levels (Fredrickson type IV), slow the progression of atherosclerosis in adult patients as part of a treatments strategy to lower Total-C and LDL-C to target levels. **Dosage and administration**: Once a day or as directed by physician. **Contraindication:** Rosuvastatin is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminase. **Warning & precautions:** The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0 and 0.1% patients who received rosuvastatin 5, 10, 20 and 40 mg, respectively. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in the class. **Pregnancy & Lactation:** Category X. Rosuvastatin may cause fatal harm when administered to pregnant women. Rosuvastatin is contraindicated in who are may become pregnant. Safety in pregnant women has not been established. There are no adequate and well controlled studies of rosuvastatin in pregnant women. If this drug is administered to a woman with reproductive potential, the patient should be appraise of the potential hazard to a foetus. **Interactions:** Co-administration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600mg twice daily) resulted in 2.2 and 1.9 fold, respectively. Increase in mean Cmax and mean AUC of rosuvastatin. Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). **Adverse reactions:** Adverse experiences reported in 2% patients in placebo controlled clinical studies of rosuvastatin are as follows; pharyngitis, headache, diarrhea, dyspepsia, nausea, myalgia, asthenia, back pain, flu syndrome, urinary tract infection, rhinitis, sinusitis. **Overdose:** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin

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