touchEXPERT BRIEFING

Updates and comparisons in lipid guidelines – statin therapy and titrating according to risk

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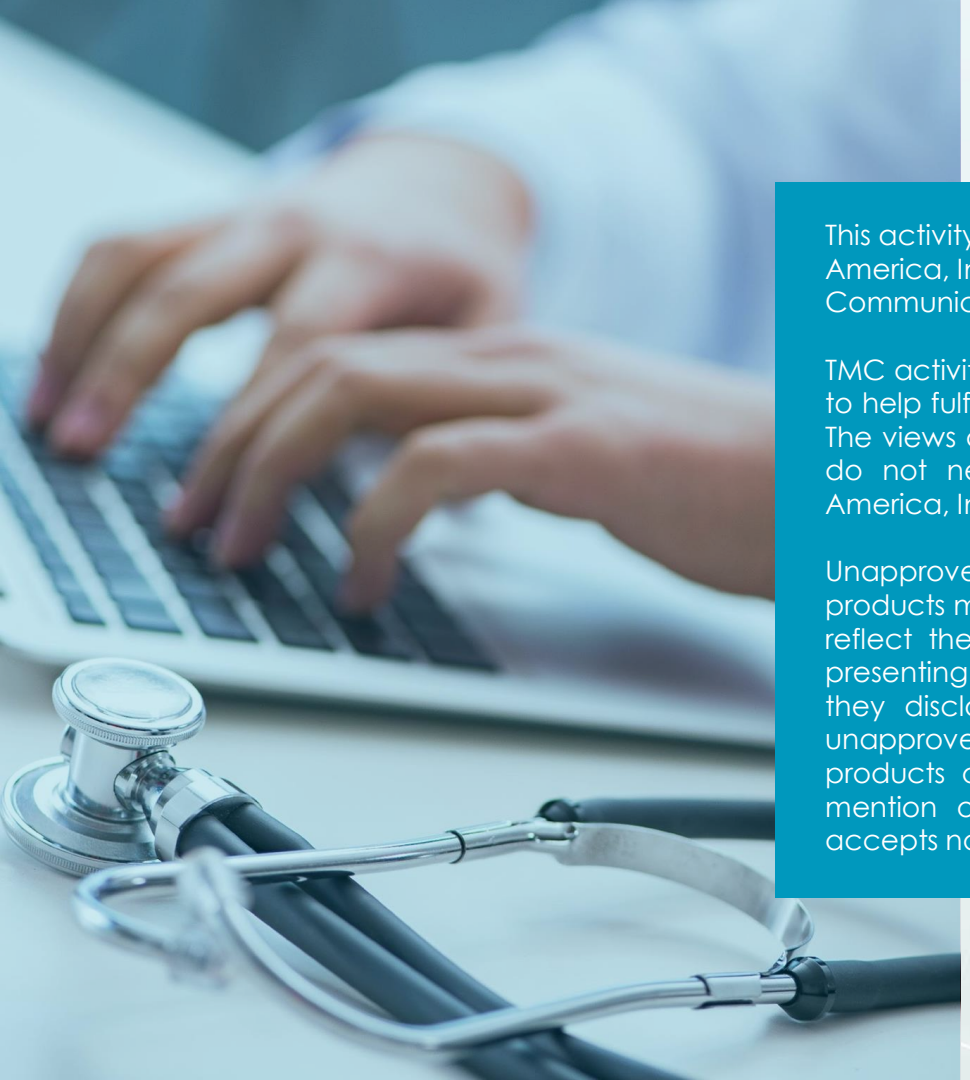

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Expert faculty

ALBERICO CATAPANO

University of Milan, Milan, Italy

ALAN BROWN

Lutheran General Hospital, Chicago, USA

KAUSIK RAY

Imperial College, London, London, UK

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Introduction

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Introduction

- Guidelines are valuable to assist physicians in the decision of the optimum treatment/dose for patients
  - The American College of Cardiology/American Heart Association (2018) and European Society of Cardiology guidelines give similar advice [1,2]

- Treatment of metabolic syndrome patients requires specific treatment requirements

- Overwhelming data exist for benefit of lowering cholesterol

1. Grundy SM, et al. Circulation 2018;139:e1082-e1143. 2. Mach F, et al. Eur Heart J 2020;41:111-88.

Guidelines update – where are we now?

Professor Catapano

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Guidelines update – where are we now?

- The American (2018) and European (2019) guidelines recommend low density lipoprotein cholesterol (LDL-C) as the target for therapy but have some differences:[1,2]
  - European guidelines include more demanding goals since more intensive therapy available and recommends cholesterol reduction especially in very high-risk patients and those with recurrent events
  - Further reduction in LDL-C proposed in these patients (40 mg/dL, 1.03 mmol/L) and 55 mg/dL (1.42 mmol/L) in patients without recurrent events
  - European guidelines consider other factors e.g. triglycerides, apoliprotein B (apo B), non-high density lipoprotein cholesterol (HDL-C)– these are also important

1. Grundy SM, et al. Circulation 2018;139:e1082-e1143. 2. Mach F, et al. Eur Heart J 2020;41:111-88.

Usefulness of guidelines published before 2018

- Every new guideline is important[1,2]
- New guidelines provide latest advice based on most recent data to give best possible clinical practice
  - Confirmed usefulness of LDL-C and safety profile of the recommended goals

1. Stone NJ, et al. J Amer Coll Cardiol 2014;63:2889-934. 2. Catapano AL, et al. Eur Heart J 2016;37:2999-3058.

Role of guidelines in clinical practice

- Guidelines state best possible management[1,2]
  - Often difficult to follow due to local reimbursements*
  - Takes time to include new guidelines in clinical practice
  - Identify patients needing more intensive treatment – physicians can categorize according to risk and LDL-C level
  - Guidelines recommendations are for the average patient, but as each patient is unique the physician must use their clinical judgement when choosing the optimal treatment

1. Grundy SM, et al. Circulation 2018;139:e1082-e1143. 2. Mach F, et al. Eur Heart J 2020;41:111-88.
*Based on clinical experience

How do the guidelines assist the decision for the optimal treatment?

- Some guidelines provide a threshold for treatment effectiveness*
- Physicians should aim for these thresholds
- Setting goals helps the physician but also the patient to understand the aim of treatment, helping to increase adherence

*Based on clinical experience

Metabolic syndrome – specific considerations for lipid-lowering therapies

Dr Brown, Professor Ray

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Metabolic syndrome – specific considerations for lipid-lowering therapies

- There are specific considerations for lipid-lowering therapies for metabolic syndrome (MS) patients[1,2]
- The vast majority of MS patients develop type 2 diabetes mellitus (T2D) [3,4]
- Patients should initially embrace lifestyle modification – to improve HDL, triglycerides etc.[5]
- Next intervention includes blood pressure control, therapy for LDL-C reduction[5]
- Important to achieve appropriate level of LDL-C with tolerable side effects[5]
- These patients have very high risk for cardiovascular disease (CVD) – often develops before DM[5]

1. Haffner SM, et al. Diabetes 1992;41:715-22. 2. Haffner SM, et al. JAMA 1990;263: 2893-8. 3. Sattar N, et al. Circulation 2003;108:414-9. 4. Feeman WE. Circulation 2004;109:e23. 5. Grundy SM, et al. Circulation 2018;139:e1082-e1143.

Metabolic syndrome – treatment with statins

- Statins give slight risk for T2D – those at risk predominantly have MS. Treat to minimize risk [1,2]
- If 255 patients are treated there will be one case of diabetes over 4 years of statin treatment [1]
  - First described in Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial[3]
  - Combine all data (~90,000 patients) risk increased by 9%, but is dose dependent
  - Patients may develop T2D slightly sooner but benefit from LDL and CVD reduction especially in very high-risk patients – outweighs T2D risk*
  - Statins generally glucose gentle / glucose neutral
  - Pitavastatin calcium does not increase parameters of glucose metabolism or risk of T2D in metanalyses[4]

1. Sattar N, et al. Lancet 2010;375:735-42. 2. Preiss D, et al. JAMA 2011;305:2556-64. 3. Ridker PM, et al. Lancet 2012;380:565-71 4. Vallejo-Vaz AJ, Atherosclerosis 2015;241:409-18.
*Based on clinical experience

Metabolic syndrome – treatment issues

- In clinical practice start patient on lipid-lowering therapy but be mindful that may subsequently be prescribed therapies for other disorders[1,2]
  - MS patients often suffer from hypertension and take therapy to reduce blood pressure
  - Use of LDL-C lowering therapy with minimal drug interactions is beneficial especially in MS patients

1. Grundy SM, et al. Circulation 2018;139:e1082-e1143. 2. Mach F, et al. Eur Heart J 2020;41:111-88.
*Based on clinical experience and personal opinion

Metabolic syndrome – treatments: Need for minimal drug interactions

- Most statins are principally metabolised via cytochrome P450 pathway[1,2]
  - Advantageous to prescribe therapies not metabolised in this way
  - Pitavastatin calcium not dependent on CYP450

- Many patients are older and prescribed lifelong treatments – potential for drug-drug interactions
  - Beneficial if do not need to change dose or statin in these patients as often resistance to changes

1. Rowan CG, et al. Pharmacoepidemiol Drug Saf 2012;21:494-506. 2. Pitavastatin prescribing information. https://www.kowapharma.com/documents/LIVALO_PI_CURRENT.pdf

Metabolic syndrome – treatments: Hepatic considerations

- Patients with MS often have abnormal liver function – can cause physician to delay LDL-C lowering therapy[1*]
- Such patients achieve larger absolute benefit from LDL-C lowering and hepatic fat may improve over time
- At high risk and should be treated promptly
- Hepatic fat predicts diabetes mellitus (DM) and CVD risk – development of fibrosis and more serious liver disease under recognized
- Important to treat patients with MS and hepatic fat early with statins – often most important group for treatment given additional risk of MS

1. Athyros VG, at al. Lancet 2010;376:1916-22.
*Based on clinical experience and personal opinion

High versus moderate intensity statins in atherosclerotic CVD – from PROVE IT to REAL-CAD*

Dr Brown, Professor Ray

PROVE IT: Pravastatin Or Atorvastatin Evaluation and Infection Therapy; REAL-CAD: High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease

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High versus moderate intensity statins in atherosclerotic CVD – from PROVE IT to REAL-CAD

- Initially prescribed lipid-lowering therapies for established heart disease as caused by cholesterol/ high LDL
- Now realise that dose and intensity of statin therapy should be titrated at level of risk[1,2]
- PROVE IT trial first to show high intensity statin therapy reduced risk of CVD versus moderate intensity[1,3]
- REAL-CAD showed 4 mg pitavastatin calcium superior to 1 mg in Japanese patients[2,4]

1. CTT collaborators. Lancet 2012;280:581-90. 2. Mach F, et al. Eur Heart J 2020;41:111-88.
3. Cannon CP, et al. NEJM 2004;350:1495-504. 4. Taguchi I, et al. Circulation 2018;137:1997-2009.

PROVE IT to REAL-CAD: Factors limiting high intensity statins in atherosclerotic CVD and guidelines

- Overwhelming data for benefit of lowering cholesterol but not always followed by physician. Why?
  - Fear of high dose statins from early trials
  - Many physicians have misguided concerns about safety of high dose statins – but high dose always better e.g. REAL-CAD data[1]

- Recent guidelines give a % reduction in LDL-C which is a threshold to indicate when additional therapy is needed[2,3]
  - Especially in patient at high or very high risk
  - Add-on treatment for LDL-C lowering correlates with the best outcomes emphasizing the need to use more aggressive therapies

1. Taguchi I, et al. Circulation 2018;137:1997-2009. 2. Grundy SM, et al. Circulation 2018;139(25):e1082-e1143. 3. Mach F, et al. Eur Heart J 2019;00:178.

PROVE IT to REAL-CAD: Goals and benefits of high intensity statins in atherosclerotic CVD

- A normal level of LDL-C is impossible to define – it is a continuous relationship[1,2,3]
- A lower LDL-C is the best goal
- No proven added risk for a lower LDL-C with high dose statins except may be increased risk of biochemical abnormalities (i.e. liver enzymes, muscle-related events)
- No relationship between achieved LDL-C level and harm
- Some patients may need high-intensity statin therapy, others combination therapy

1. Giugliano RP, et al. Circulation 2018;137:1571-82. 2. Giugliano RP, et al. Lancet 2017;390:1962-71.
3. Boekholdt SM, et al. J Am Coll Cardiol 2014;64:485-94.

PROVE IT to REAL-CAD: Effects of high intensity statins in atherosclerotic CVD

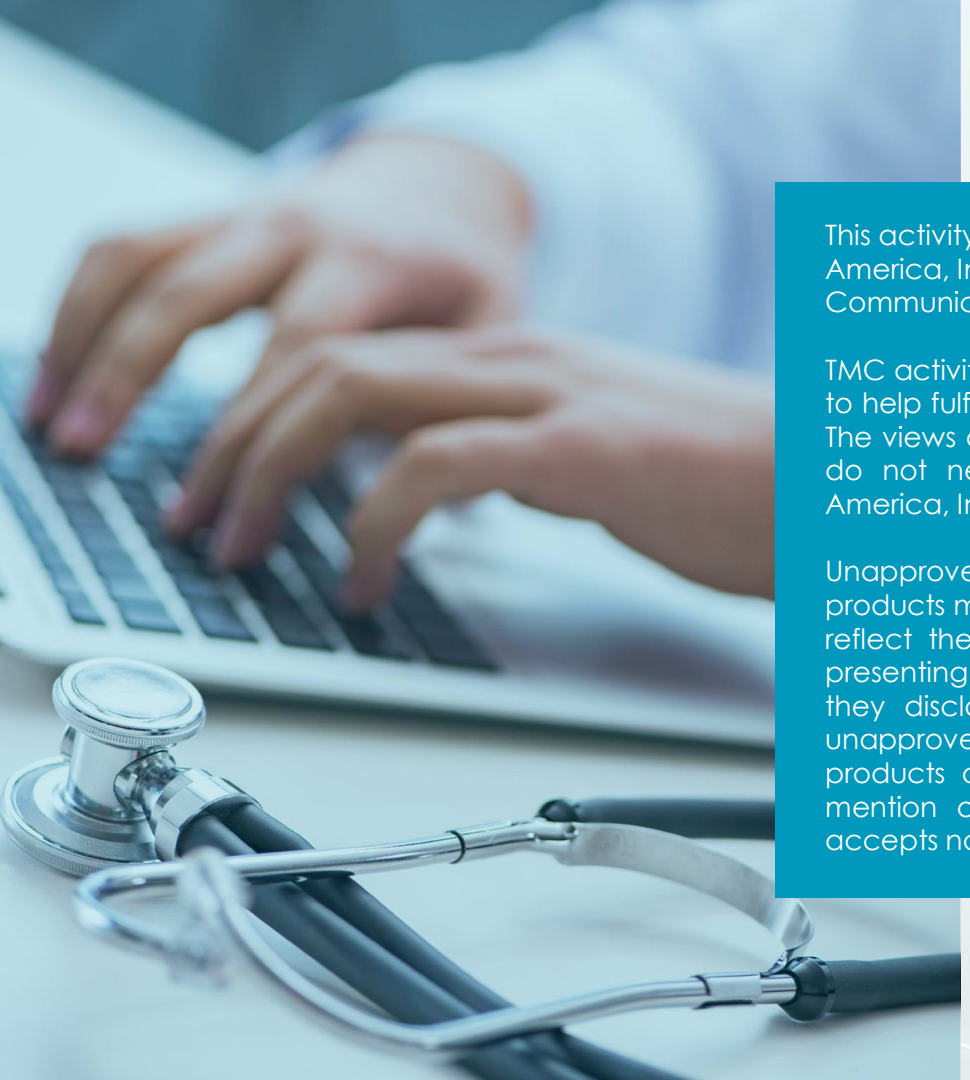
- Combination therapy is useful to give additional reduction in LDL-C level
  - Data from PROVE IT show the benefit of adding ezetimibe – additional 7.7% reduction in LDL-C[1]
  - Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors added to maximum tolerated statin gives additional benefit[2,3]
  - Combination beneficial especially in older patients where increasing statin dose may lead to potential drug interactions
  - Should aim for % reduction rather than an absolute target for LDL-C[4]
  - Important to achieve the appropriate % reduction in all patients[4]
  - Doubling statin dose generally results in a further reduction of LDL-C by 6%[4]
  - REAL-CAD shows high dose pitavastatin calcium has minimal additional side effects[45]

1. Cannon CP, et al. NEJM 2015;372:2387-97. 2. Sabatine MS, et al. NEJM 2017;376:1713-22. 3. Schwartz GC, et al. NEJM 2018;379:2097-2107. 4. Mach F, et al. Eur Heart J 2020;41:111-88 5. Taguchi I, et al. Circulation 2018;137:1997-2009.

PROVE IT to REAL-CAD: Lessons learned for high intensity statins in atherosclerotic CVD

- REAL-CAD demonstrated more intensive statin therapy is better with good safety profile in Asian patients[1,2]
- All patients at high risk or with CVD should be treated with more potent LDL-C lowering therapy[3,4]
- Statin dose should be titrated to risk[5]
- High-risk patients reduce LDL-C initially with statin therapy to achieve at least 50% reduction[5]
  - Use non-statin add on therapy if needed
  - Generally more aggressive therapy should be used
  - High-dose statin therapy is superior to low-dose in high-risk patients

1. Taguchi I, et al. Circulation 2018;137:1997-2009. 2. Cannon CP, et al. NEJM 2004;350:1493-504. 3. Sabatine MS, et al. NEJM 2017;376:1713-22. 4. Schwartz GC, et al. NEJM 2018;379:2097-2107. 5. Mach F, et al. Eur Heart J 2020;41:111-88.



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