Hong Kong College of Cardiology

28th Annual Scientific Congress

Session:

Common Cardiology Challenges in Primary Care

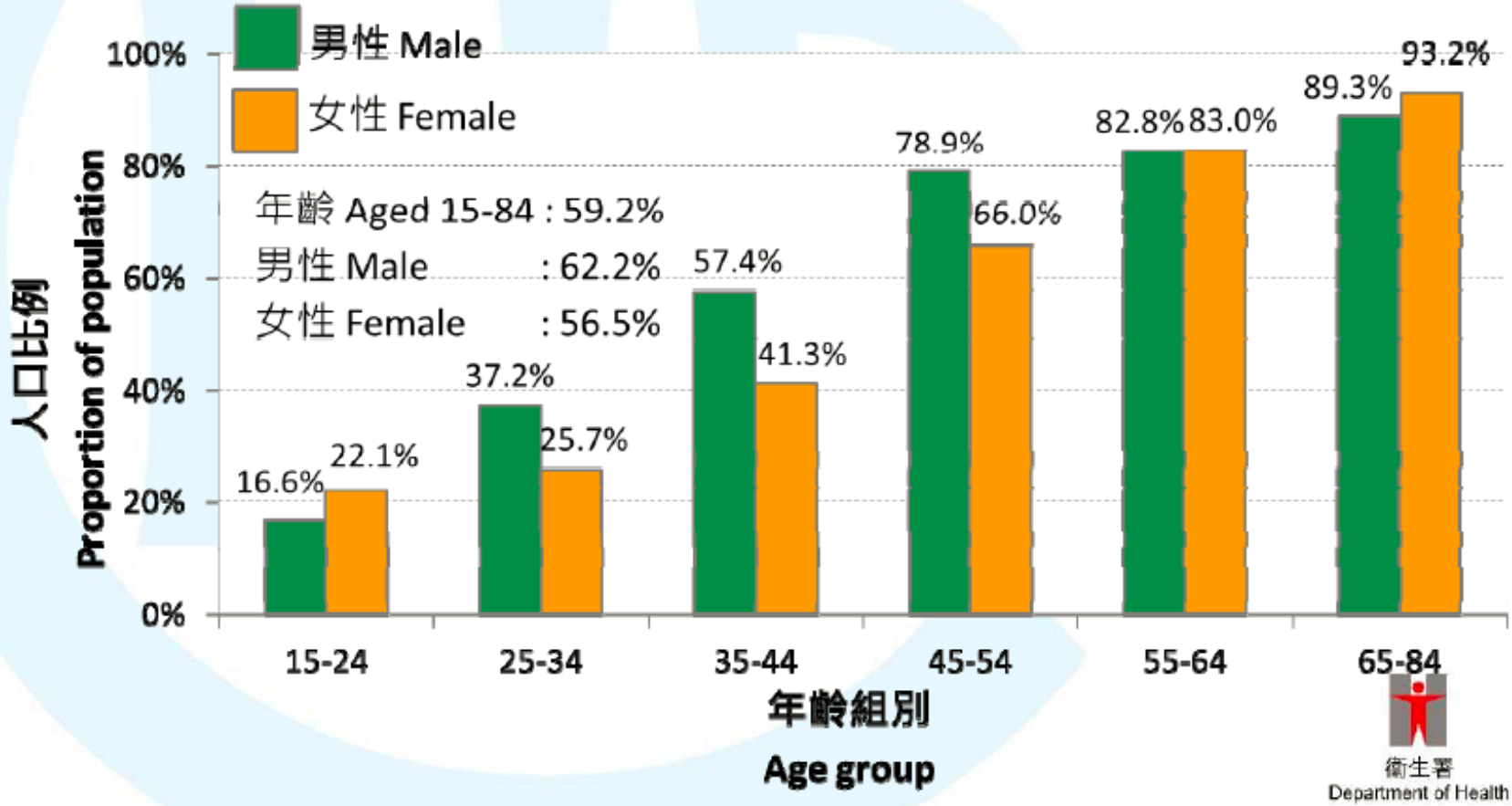
Topic:

How to Achieve maximally tolerated statin therapy for maximum protection

Dr. Wong Bun Lap Bernard

患上高血壓、糖尿病和高膽固醇血症其中一種或以上的比率

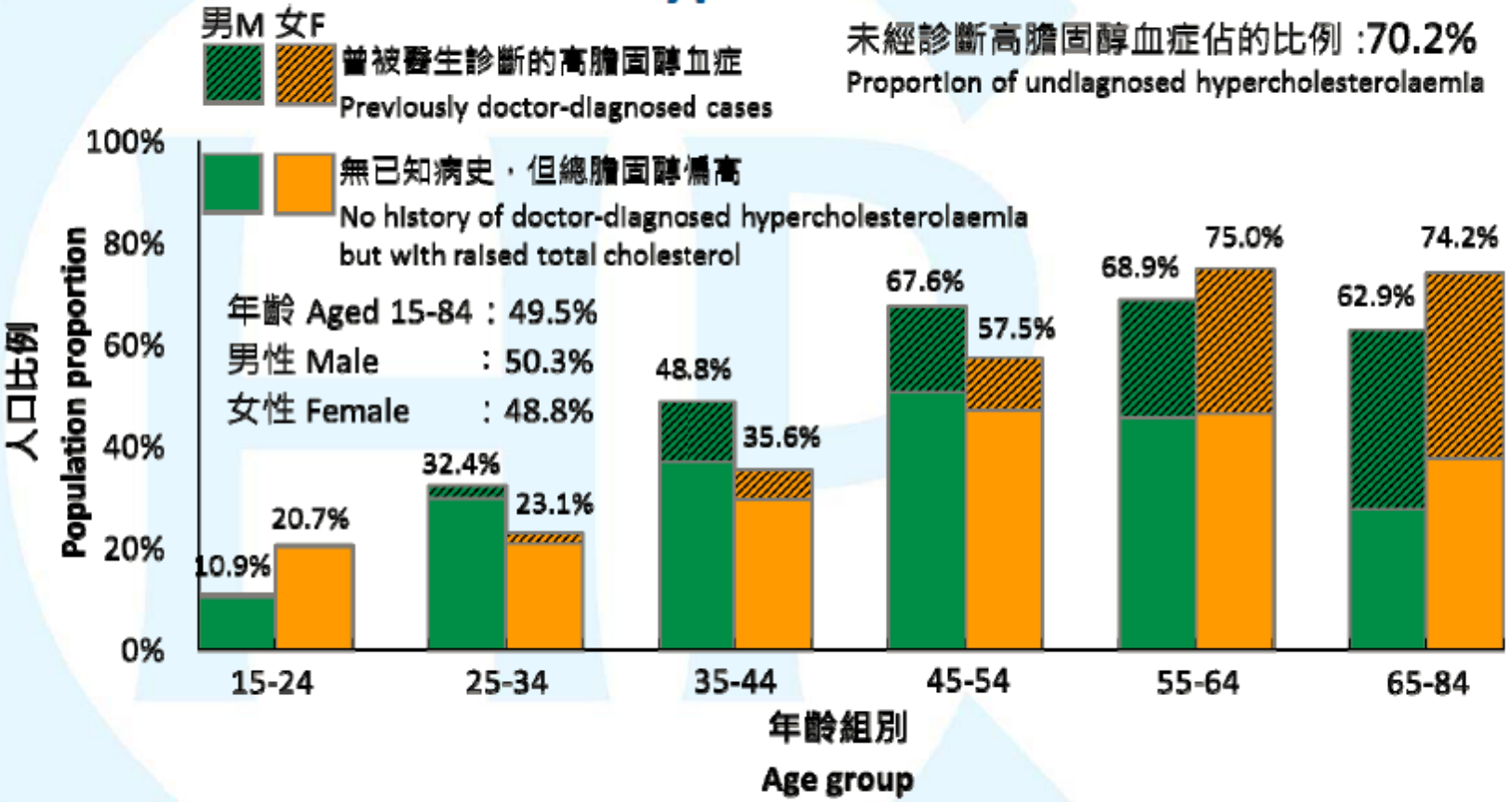
Prevalence of one or more of hypertension, diabetes mellitus and hypercholesterolaemia



Adapted from Report of Population Health Survey 2014/15
Available at: http://gia.info.gov.hk/general/201711/27/P2017112700588_272856_1_1511779180739.pdf

高膽固醇血症患病率

Prevalence of hypercholesterolaemia



註釋：高膽固醇血症的患病人士包括 (i) 曾被醫生診斷的高膽固醇血症與 (ii) 無已知病史，但總膽固醇濃度 ≥ 5.2 mmol/L。

Note : Prevalence of hypercholesterolaemia included (i) persons with previously doctor-diagnosed hypercholesterolaemia and (ii) persons with no history of doctor-diagnosed hyper-cholesterolaemia but with raised total blood cholesterol ≥ 5.2 mmol/L.

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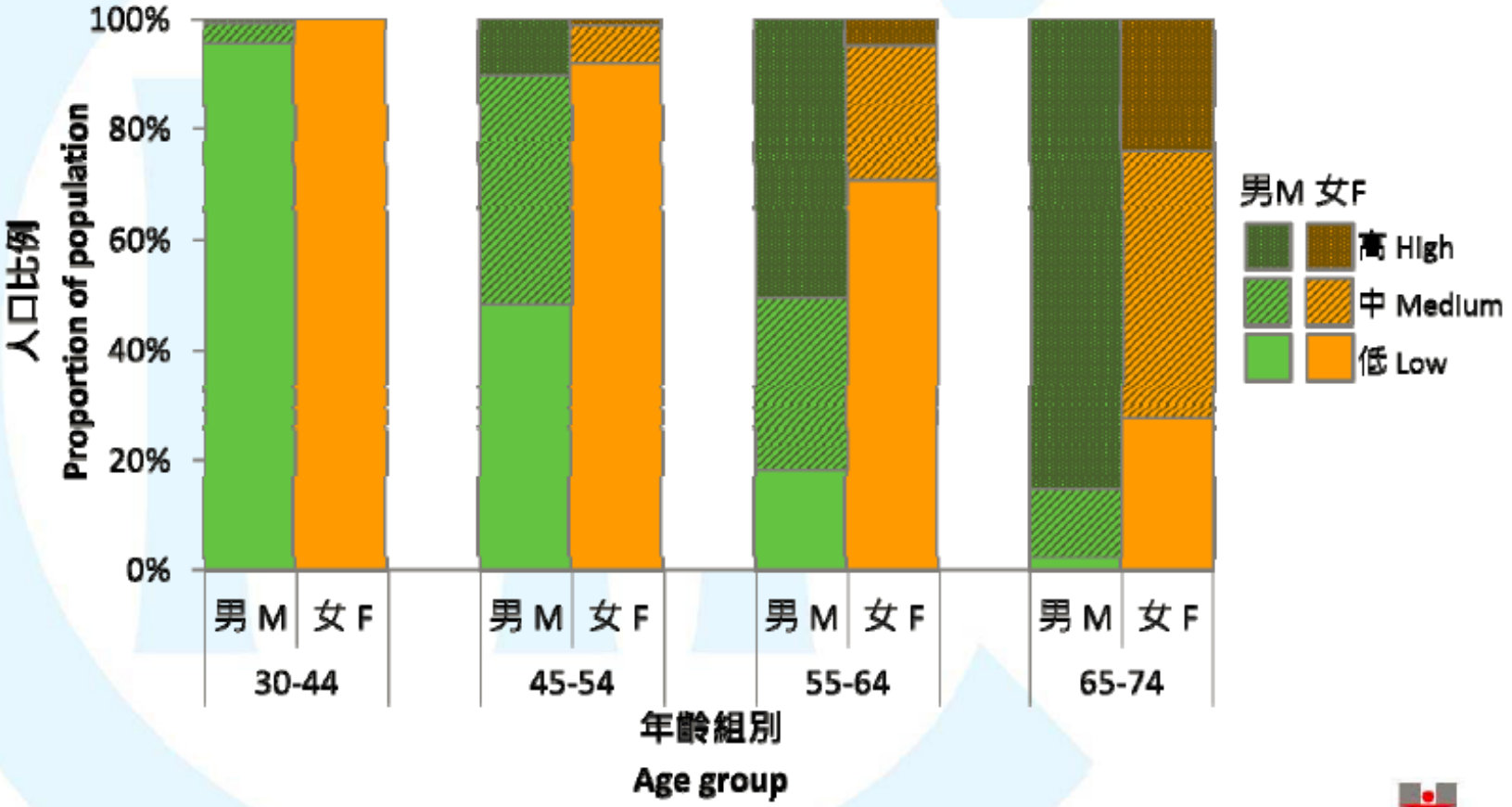
Adapted from Report of Population Health Survey 2014/15
Available at: http://gia.info.gov.hk/general/201711/27/P2017112700588_272856_1_1511779180739.pdf

未來 10 年心血管疾病風險

Cardiovascular disease (CVD) risk in next 10 years



註釋：高：心血管疾病風險≥20%；中：心血管疾病風險≥10% 及 <20%；低：心血管疾病風險<10%

Note : High: CVD risk ≥ 20%, Medium: CVD risk ≥ 10 and <20%, Low: CVD risk < 10%

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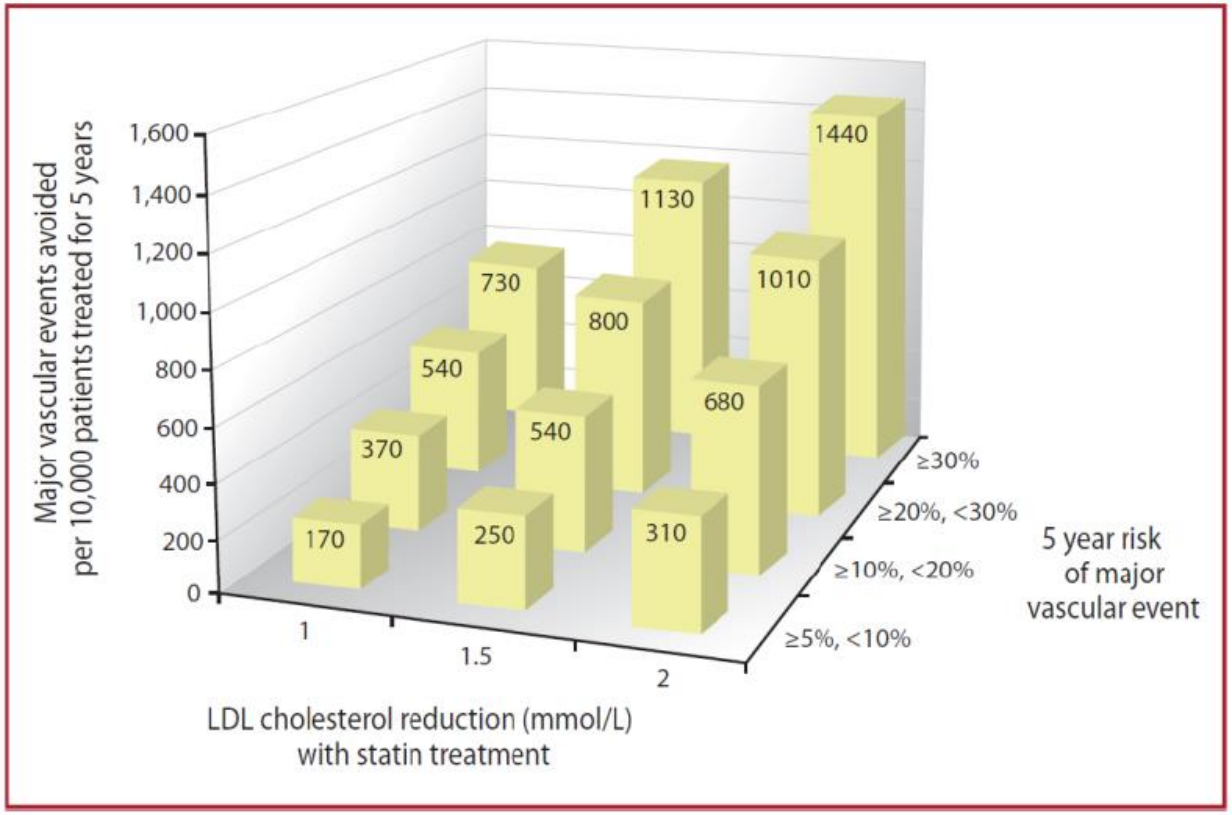
Adapted from Report of Population Health Survey 2014/15

Available at: http://gia.info.gov.hk/general/201711/27/P2017112700588_272856_1_1511779180739.pdf

Absolute reductions in major vascular events with statin therapy

EAS ESC
European Society of Cardiology



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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Evidence for efficacy of LDL-lowering therapies down to below 1.4 mmol/L (55 mg/dL)

EAS ESC European Society of Cardiology

Source of evidence	Mean reduction in LDL cholesterol; mmol/L [mg/dL]	Outcome	RR (95% CI)
CTT meta-analysis[1] (high-intensity vs standard statin; subgroup <2.0 mmol/L)	1.71 [66] vs 1.32 [50]	MI, CHD death, stroke, coronary revasc.	0.71 (0.56-0.91) [per mmol/L]
IMPROVE-IT[2] (eze plus statin vs statin)	1.55 [70] vs 1.40 [54]	CV death, MI, stroke, UA, coronary revasc	0.94 (0.89-0.99)
FOURIER[3] (evolocumab plus high-dose statin ± eze vs high-dose statin ± eze)	2.37 [92] vs 0.78 [30]	CV death, MI, stroke, UA, coronary revasc	0.85 (0.79-0.92)
ODYSSEYOUTCOMES[4] (alirocumab plus high-dose statin ± eze vs high-dose statin ± eze)	2.37 [92] vs 1.37 [53]	MI, CHD death, stroke, UA	0.85 (0.78-0.93)

[1] Lancet 2010; 376: 1670-81; [2] NEJM 2015; 372: 2387-97; [3] NEJM 2017; 376: 1713-22; [4] NEJM 2018; 379: 2097-107

www.escardio.org/guidelines

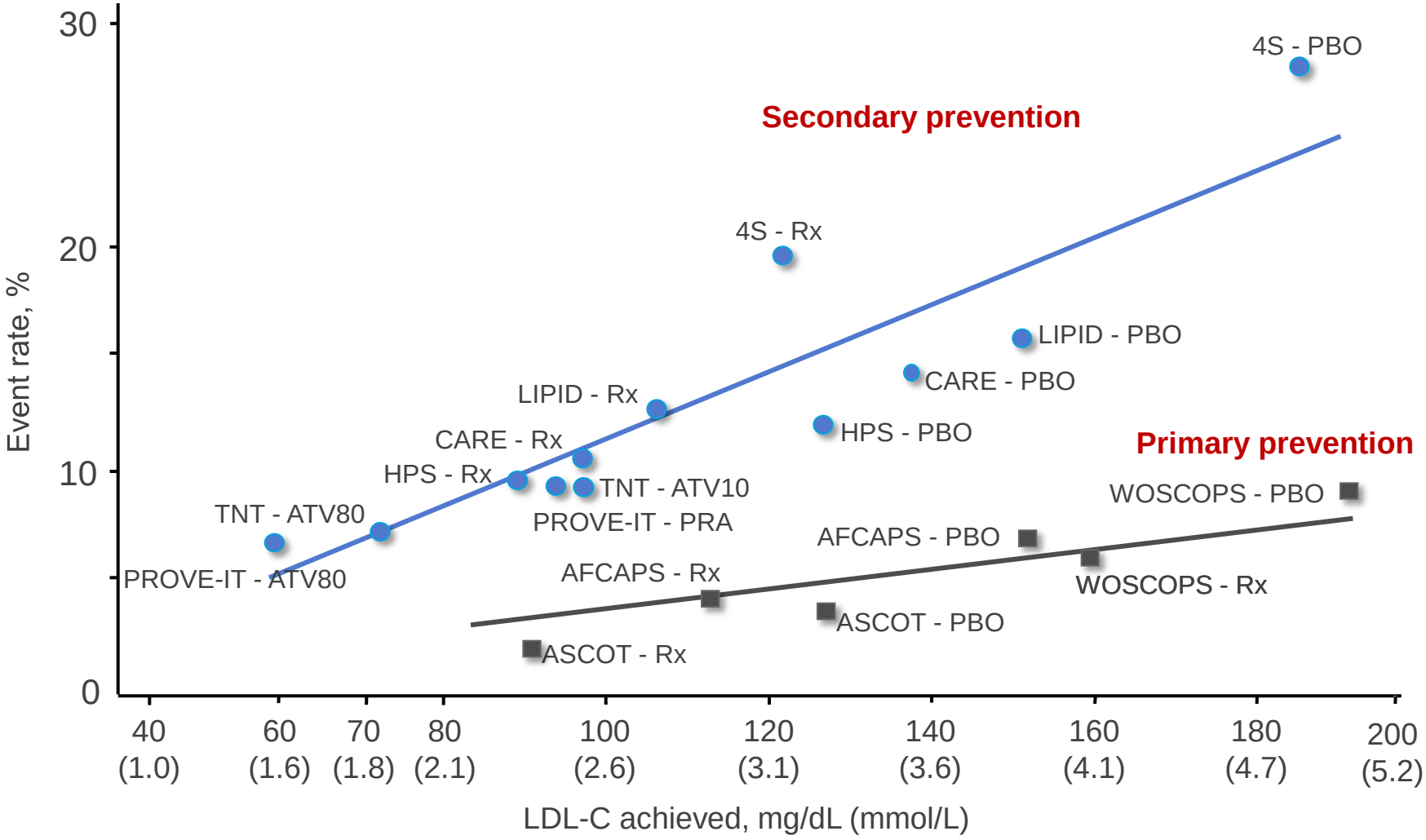
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Statin- Solid Hard Never-Failing Evidence

~ since 4S Study 1994’

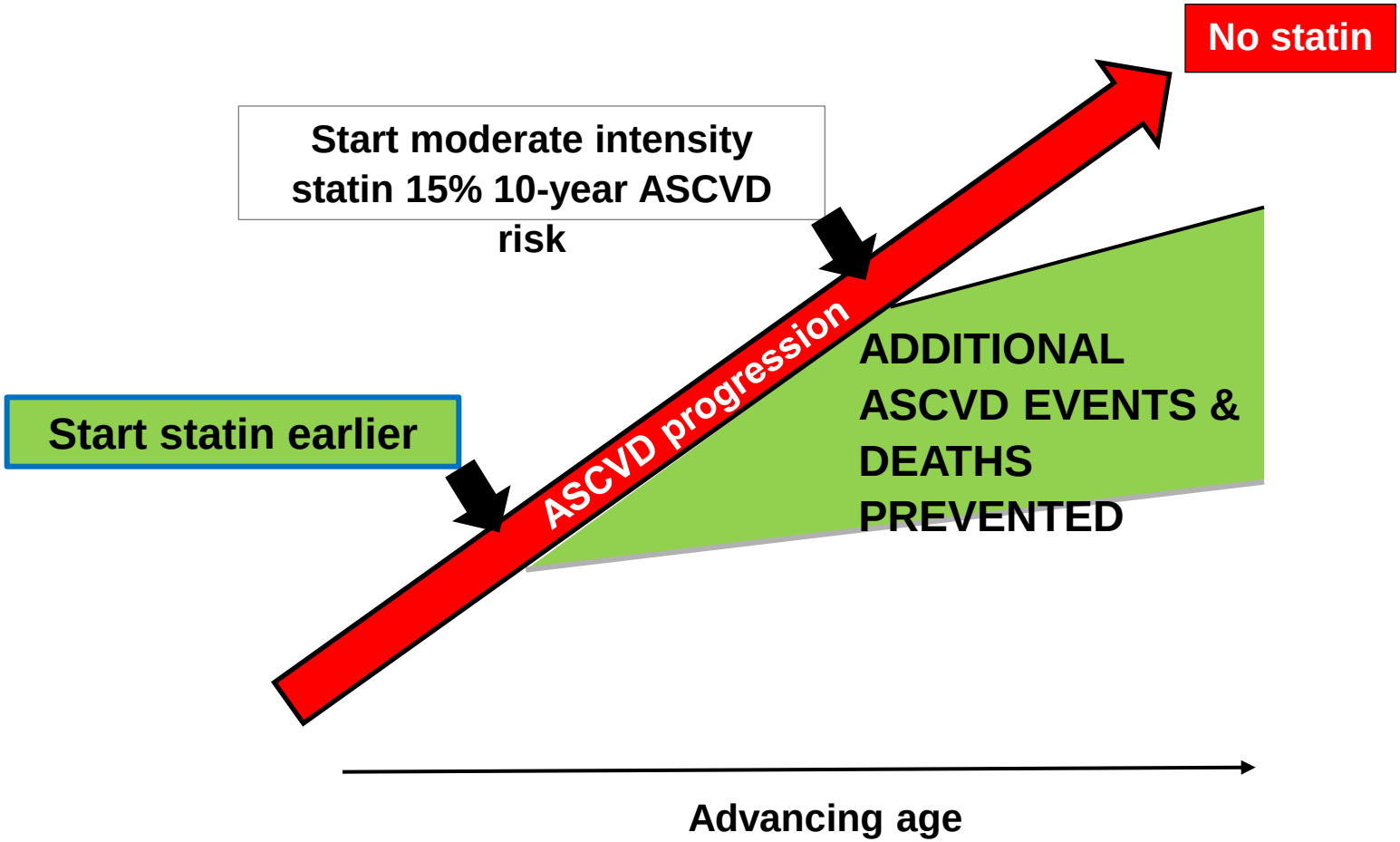
- ↓ LDL-C and other apoB-containing lipoproteins
- ↓ LDL-C depends on statin and dose
- ↓ CV mortality and morbidity
- ↓ All-cause mortality
- Benefits consistent across
  - Primary vs secondary prevention
  - Age
  - Sex
- Produce regression of atherosclerosis
  - Reduction of LDL-C <80 mg/dL (2.0 mmol/L) is needed
- Statins are among the most studied drugs in CV prevention

On-treatment LDL and CHD events in statin trials



Adapted from Rosenson RS. *Expert Opin Emerg Drugs* 2004;9:269-279;
LaRosa JC, et al. *N Engl J Med* 2005;352:1425-1435.

Start Statins Earlier to Prevent More Events



Guidelines identify four statin benefit groups

Trials:
TNT
IDEAL
PROVE-IT
SPARCL

Group 1

Clinical ASCVD

CHD, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin

Group 2

LDL-C ≥190 mg/dL (~5 mmol/L)

Trials:
N/A

Trials:
CARDS
ASCOT-LLA*
TNT*
HPS*

Group 3

Diabetes mellitus

+ age of 40-75 years
+ LDL-C 70-189 mg/dL (~1.8-5 mmol/L)

Group 4

ASCVD risk ≥7.5%

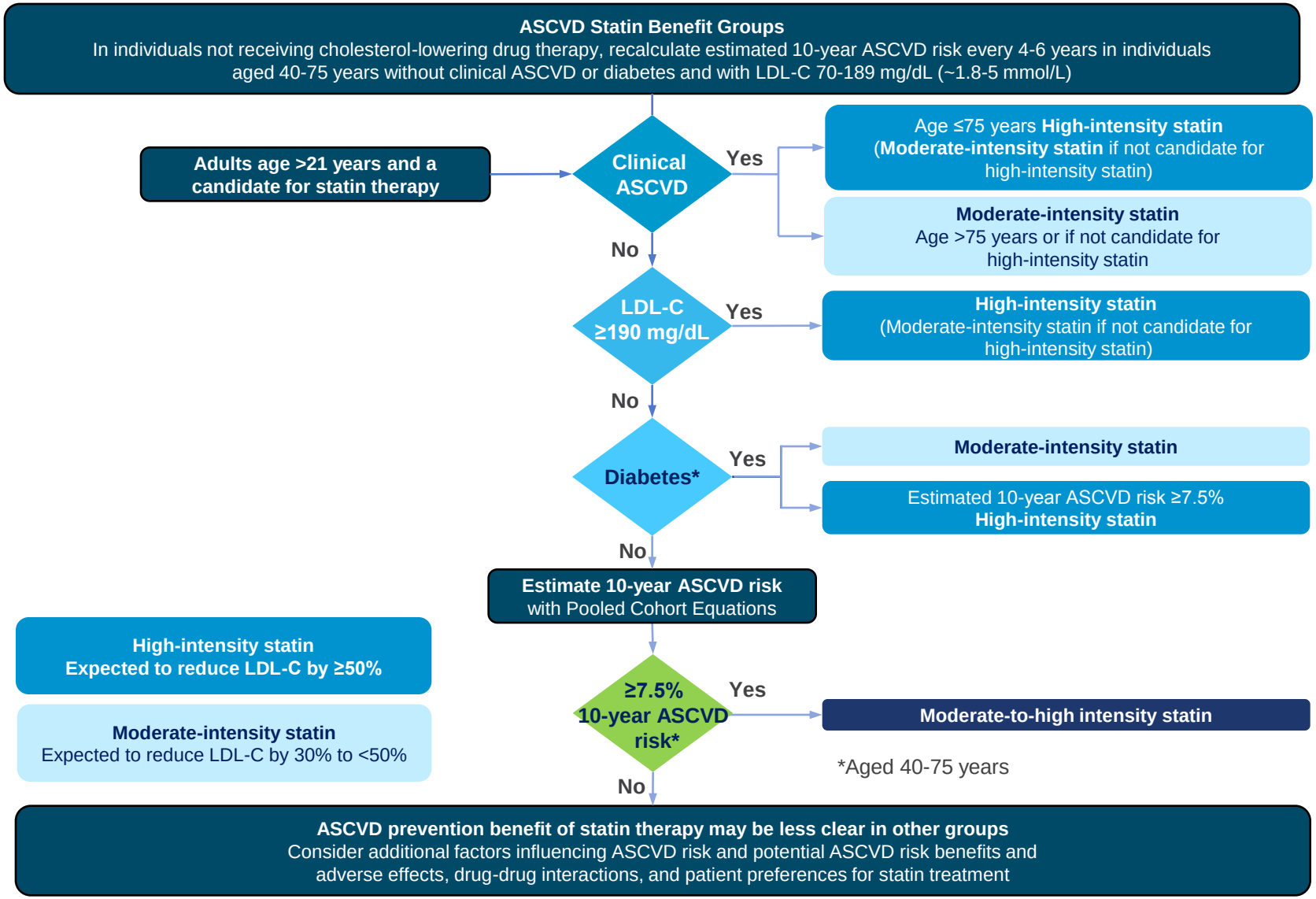
No diabetes
+ age of 40-75 years
+ LDL-C 70-189 mg/dL (~1.8-5 mmol/L)

Trials:
ASCOT-LLA
HPS
JUPITER

*Subgroup analysis

Stone NJ, et al. *J Am Coll Cardiol* 2014;63:2889-2934.

Treatment decision flow for four statin benefit groups



Stone NJ, et al. *J Am Coll Cardiol* 2014;63:2889-2934. Reproduced with

Guidelines specify statin doses

	High-intensity ↓ *LDL-C by ≥50%*	Moderate-intensity ↓ *LDL-C by 30-50%*	Low-intensity ↓ *LDL-C by <30%**
Atorvastatin	**(40)-80 mg**	**10**-*20* **mg**	–
Rosuvastatin	**20**-*40* **mg**	*5*-**10 mg**	–
Simvastatin	–	**20-40 mg**	*10 mg*
Pravastatin	–	**40**-*80* **mg**	**10-20 mg**
Lovastatin	–	**40 mg**	**20 mg**
Fluvastatin XL	–	*80 mg*	–
Fluvastatin	–	**40 mg bid**	*20-40 mg*
Pitvastatin	–	*2-4 mg*	*1 mg*

Bold: Statins and doses evaluated in RCTs
Italics: Statins and doses approved by US FDA but not tested in RCTs reviewed
*Should be used in patients unable to tolerate moderate-to high-intensity therapy
Asian ancestry may modify the statin dose prescribed

Stone NJ, et al. *J Am Coll Cardiol* 2014;63:2889-2934.
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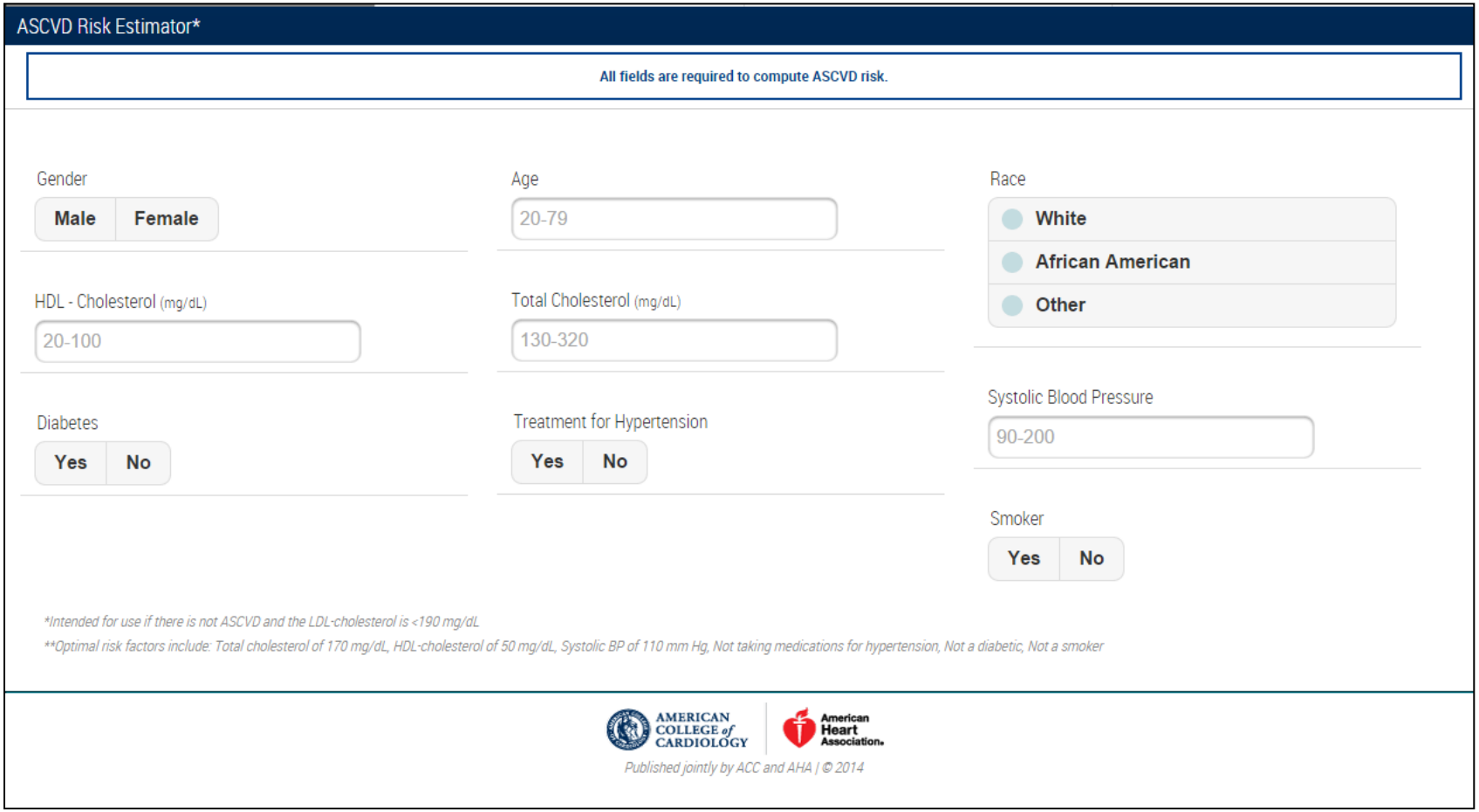
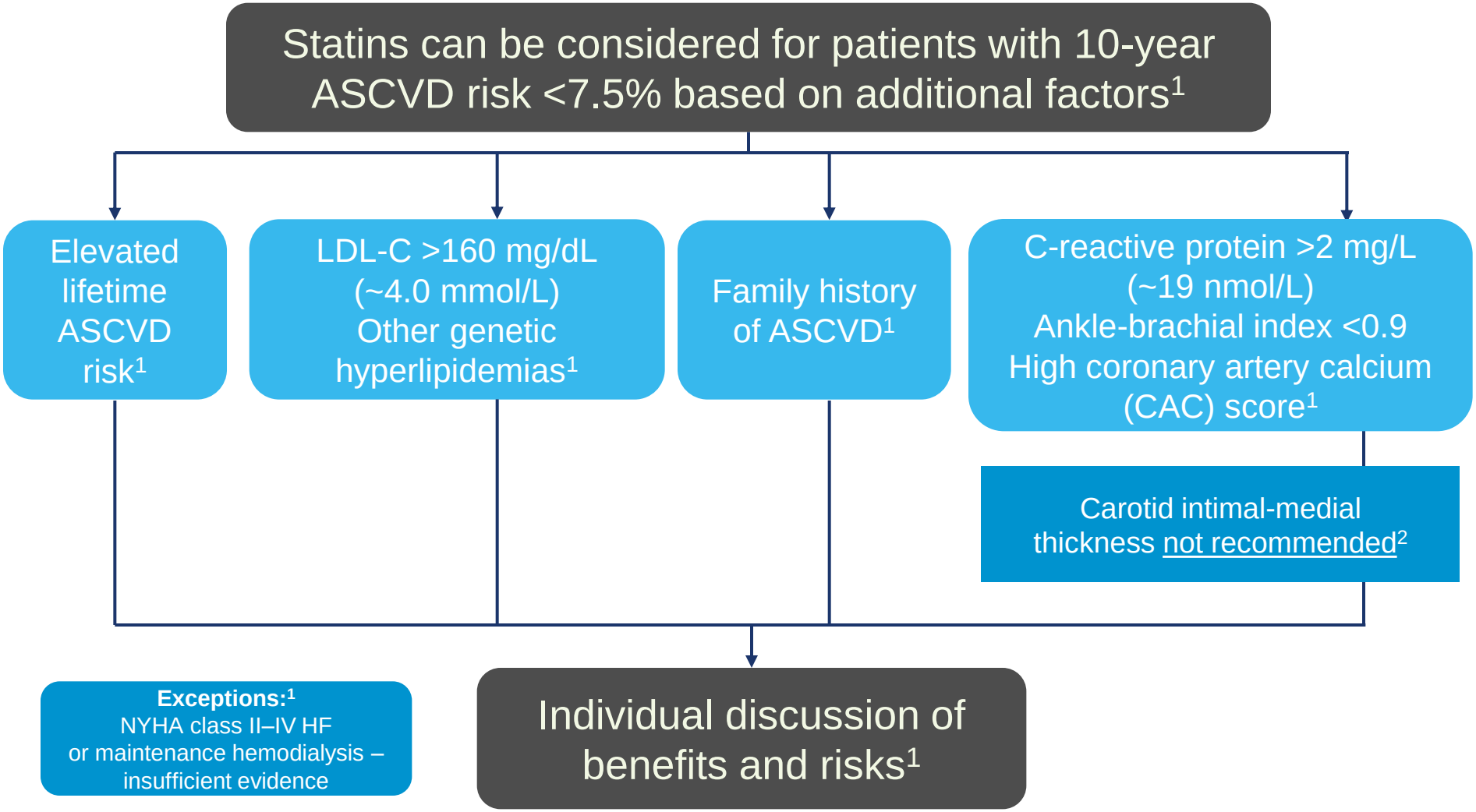
Pooled cohort equations: Estimating 10-year risk



http://tools.cardiosource.org/ASCVD-Risk-Estimator/

Patients outside the four benefit groups: Consider statin therapy individually



1. Stone NJ, et al. *J Am Coll Cardiol* 2014;63:2889-2934. 2. Goff DC Jr, et al. *J Am Coll Cardiol* 2014;63:2935-2959.

Adverse Effect – Myopathy ?

A Famous and Worldwide Nocebo Effect

- The most clinically relevant AE of statins
- Rhabdomyolysis: 1-3 cases/100,000 patient-years
- Statin-associated muscle symptoms (SAMS)
  - ✓ with muscular pain and tenderness (myalgia) without CK elevation or major functional loss
  - ✓ reported frequency vary between 10-15% in *non-randomized, observational studies*
    - In blinded randomized trials of statins vs placebo, there is no, or only slight increase in frequency of muscle symptoms in statin-allocated groups - Nocebo effect

Adverse Effect - Myopathy

A Famous and Worldwide Nocebo Effect

- ASCOT-LLA Study
- 1998-2002
- 10,180 patiets
- Age 40-79
- HT + 3 or more CV Risk factors
- UK, Ireland, Scandinavia
- Zocor (simavastatin)10mg vs Placebo

1. *Gupta A, Thompson D, Whitehouse A, et al. on behalf of the ASCOT investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase [published online May 2, 2017]. Lancet. 2017; http://dx.doi.org/10.1016/ S0140-6736(17)31075-9.*
2. *Statin-associated muscle symptoms: beware of the nocebo effect [published online May 2, 2017]. Lancet. 2017; http://dx.doi.org/10.1016/ S0140-6736(17)31163-7.*

Adverse Effect - Myopathy

A Famous and Worldwide Nocebo Effect

- 1st 3 years double blinded
- Then unblinded, open-labelled follow - up for 2 years, 9,899 patients, 65% on statin.
- Muscle –related symptoms

	Statin	Placebo
Blinded phase	2.03%	2% (nearly identical)
Open-labelled phase	1.26% (41% more likely)	1%

1. *Gupta A, Thompson D, Whitehouse A, et al. on behalf of the ASCOT investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase [published online May 2, 2017]. Lancet. 2017; http://dx.doi.org/10.1016/ S0140-6736(17)31075-9.*
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Adverse Effect - Myopathy

A Famous and Worldwide Nocebo Effect

- Examining data on 26 side effects from 10,000 patients
- “Patients were more likely to report side effects when they knew they were taking statins.”
- “When they has no idea, there was no increase in muscle – related effects”

1. *Gupta A, Thompson D, Whitehouse A, et al. on behalf of the ASCOT investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase [published online May 2, 2017]. Lancet. 2017; http://dx.doi.org/10.1016/ S0140-6736(17)31075-9.*
2. *Statin-associated muscle symptoms: beware of the nocebo effect [published online May 2, 2017]. Lancet. 2017; http://dx.doi.org/10.1016/ S0140-6736(17)31163-7.*

In a Nutshell

- Hypercholesterolaemia is a very important cause of CHD and CVA, the top killers in Hong Kong.
- Hypercholesterolaemia is a disease for all ages, including the very young and very old.
- Treatment that lowers cholesterol by 10% reduces the risk of CHD death by 15 %.
- Treatment for more than 5 years yields a 25% reduction in CHD events.
- The 2013 ACC/AHA Guideline is up-to-date, easy to use and good for patient education.
- Patients with clinical ASCVD, LDL ≥4.9 mmol/L and NIDDM can start with moderate to high intensity statin immediately.
- For other patients, we can use the friendly and free of charge ASCVD risk estimation software to estimate the risk and the required statin indication/intensity accordingly.

In a Nutshell

- Statins are a near perfect drug for hypercholesterolaemia. They are simple to use (once daily), efficient, effective, life-saving, with few side-effects, meticulously studied by numerous mega-trials, virtually without fatal adverse events and with a very reasonable price.
- No matter which trial you are referring to, whether it is primary or secondary prevention, reduction in morbidity or mortality, statins can give your patient a 20–30% improvement.
- At present, the long-debated safety issues with regard to statins, suicidal and homicidal inclination, psychosis, carcinogenesis, rhabdomyolysis and liver damage, have been clarified.
- The high potency rosuvastatin, ezetimibe + statin combination therapy and PCSK9 inhibitory monoclonal antibody + statin therapy may help us to achieve the LDL, and HDL goals with minimal side effects.
- Since most patients do not have a single symptom when you start medication that has non-negligible side effects, good communication is the core of successful lipid management

To face the powerful “Dark side”:

“Alternatives”,“Medias”, “Cult and Cultures”.

“Widespread claims of high rates of statin intolerance still prevent too many people from taking an affordable, safe and life-saving medication.”

~ Professor Peter Sever, National Heart and Lung Institute, Imperial College London, Editoral, Lancet 2017’

Statin-associated muscle symptoms: beware of the nocebo effect [published online May 2, 2017]. Lancet. 2017; http://dx.doi.org/10.1016/ S0140-6736(17)31163-7.

To face the powerful “Dark side” “alternatives”,“medias”, “Cult and cultures”.

- *“Begin with praise and honest appreciation.”*
- *“Call attention to people’s mistake indirectly.”*
- *“Let the other person save face.”*
- *“Praise the slightest improvement and praise every improvement. Be “hearty in your approbation and lavish in your praise.””*
- *“Give the other person a fine reputation to live up to.”*
- *“Use encouragement. Make the fault seem easy to correct.”*
- *“Make the other person happy about doing the thing you suggest.”*

~ Dale Carnegie 1888-1955