Atherosclerosis 263 (2017) 112–118

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Detection of atherosclerotic cardiovascular disease influences the perceived need for aggressive lipid management

G.B.John Mancini [a, *], Milan Gupta [b, c], Michelle Tsigoulis [c], Christopher P. Cannon [d], Jacques Genest [e], Kausik K. Ray [f], Raul D. Santos [g], Gerald F. Watts [h], Paolo Raggi [i]

[a] University of British Columbia, Vancouver, British Columbia, Canada
[b] McMaster University, Hamilton, Ontario, Canada
[c] Canadian Collaborative Research Network, Brampton, Ontario, Canada
[d] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
[e] McGill, Montreal, Quebec, Canada
[f] Imperial Centre for Cardiovascular Disease Prevention, Department of Public Health and Primary Care at Imperial College London and Imperial College NHS Trust, London, England, United Kingdom
[g] Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil
[h] Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Western Australia, Australia
[i] Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada

ARTICLE INFO

Article history:
Received 28 April 2017
Received in revised form
21 May 2017
Accepted 2 June 2017
Available online 3 June 2017

Keywords:
Atherosclerotic cardiovascular disease
Angina pectoris
Cardiovascular risk
Low density lipoprotein-cholesterol
Proprotein convertase subtilisin/kexin type 9 inhibitors
Primary prevention

ABSTRACT

Background and aims: Overt atherosclerotic cardiovascular disease (ASCVD) warrants aggressive lipid lowering. Imaging for ambiguous symptoms suggesting ischemia or for clarification of CV risk in asymptomatic individuals often uncovers previously unknown ASCVD. Guidelines do not provide clear recommendations for aggressive lipid lowering in such cases. We explored physicians' perception, as influenced by tests that detect ASCVD, regarding appropriateness of getting to lipid goals and for theoretically accessing proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i).

Methods: A questionnaire was developed including cases of low to high CV risk, chronic kidney disease (CKD) or type 2 diabetes mellitus (T2DM). Each case was considered with or without angina symptoms and, in turn, whether testing identified previously unknown advanced, early/subclinical or no ASCVD. Synthesis of responses was facilitated by using a scale for perceived appropriateness from 1 (lowest) to 9 (highest).

Results: Getting to goal and, if not achieved by statins and/or ezetimibe, accessing PCSK9i was considered appropriate in patients with T2DM with preclinical or advanced ASCVD, patients with moderate or high CV risk and advanced ASCVD, patients with CKD or low CV risk with angina symptoms and advanced ASCVD. For most of the remaining cases adding PCSK9i was considered only possibly appropriate.

Conclusions: Physicians' perception of appropriateness for achieving lipid goals, including access to PCSK9i, is markedly influenced by detection of previously unknown ASCVD. Since these commonly encountered scenarios do not clearly meet current indications for PCSK9i, our data identify pressing areas requiring further research.

1. Introduction

Several organizations have released guidelines for the management of dyslipidemia in a variety of clinical settings, including therapy of patients with atherosclerotic cardiovascular disease (ASCVD) [1–7]. ASCVD is readily diagnosed when there is a history of CV events or procedures, obvious symptoms or the presence of physical findings (e.g. vascular bruit). Guidelines are clear in recommending preventive therapies, particularly use of statins, and the goal to achieve (e.g. a 50% reduction of low density lipoprotein cholesterol [LDL-C], an LDL-C < 1.8 mmol/L, a non-HDL-C < 2.6 mmol/L, etc.). However, there remain numerous scenarios

* Corresponding author. Room 9111, Diamond Centre, Vancouver General Hospital, 2775 Laurel Street, Vancouver, British Columbia Canada, V5Z 1M9.
E-mail address: mancini@mail.ubc.ca (G.B.John Mancini).

http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.006

where patient management is still unclear. These may include discovery of previously unknown ASCVD, ranging from early/preclinical and asymptomatic ASCVD to more advanced ASCVD that could plausibly explain ischemic symptoms. When symptoms suggestive of angina pectoris are present, guidelines advocate methods that can be used to exclude or establish ASCVD not previously known [8–15]. Similarly, the process of CV risk assessment in asymptomatic patients often identifies ambiguous situations in which the patient or physician may not be convinced of the need for lipid lowering therapy. When this occurs, most guidelines support methods to help clarify the level of risk to facilitate a joint decision whether to treat or not [1,3,4,6,7]. This process often relies upon detection of ischemia or early/subclinical anatomical disease, essentially utilizing many of the same methods used to evaluate patients with symptoms suggestive of angina pectoris. As a result, ASCVD is uncovered in numerous, clinically routine circumstances in asymptomatic or minimally symptomatic individuals who have never had a CV event or procedure.

The recently approved proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), capable of inducing large reductions in LDL-cholesterol, are more costly compared with other agents, resulting in a very high threshold for payers to support this add-on therapy. Physicians also recognize the need to target more expensive therapies to those where the benefit will be greatest [16]. Thus, use is currently largely limited to patients with familial hypercholesterolemia or to patients with established and obvious ASCVD who are not achieving goals with statins and/or ezetimibe [1,17–20]. However, management of patients in whom ASCVD is discovered either when evaluating ambiguous risk in asymptomatic patients, or ambiguous symptoms suspected to be angina pectoris is unclear and is not covered in current guidelines. Hence there may be great dissonance between a desire to achieve a guideline-endorsed lipid goal and the lack of access to effective therapies, such as PCSK9i, even though the latter may facilitate optimal risk reduction when ASCVD is detected. The purpose of this project was to determine physicians' perceptions and practices in common, and ambiguous clinical circumstances toward the requirement of achieving a guideline-supported lipid goal and, when not achieved with statins and/or ezetimibe, the perceived appropriateness of adding PCSK9i.

2. Materials and methods

Questionnaires were developed by authors GBJM, MG and PR by consensus (see Supplement). General questions were developed to ascertain the ancillary test/s used most often to identify underlying ASCVD in asymptomatic patients with an ambiguous situation for implementation of statin therapy or for investigating symptoms possibly representing angina pectoris. Additional questions were designed to cover scenarios for which there are guideline recommendations for CV risk management using statin-based lipid lowering but not for use of PCSK9i: adult patients without overt or known ASCVD and type 2 diabetes mellitus (T2DM), patients with chronic kidney disease (CKD) (either pre-dialysis or on dialysis), high-risk primary prevention patients, moderate risk primary prevention patients (including those fulfilling the inclusion criteria of the Heart Outcomes Prevention Evaluation 3 [HOPE 3] trial, i.e. male 55 years of age or older, female 65 years of age or older with at least one of: elevated waist-to-hip ratio, history of a low HDL-C, current or recent smoking, dysglycemia, family history of premature coronary disease, mild renal dysfunction), and low risk primary prevention patients. Thus, patients with familial hypercholesterolemia or obvious ASCVD, who already meet indications for access to PCSK9i when needed, were excluded from consideration. Because the questionnaire was distributed by email internationally, low, moderate and high-risk were defined by the national guidelines applicable to or used by the individual respondent. These scenarios were crafted to represent either a totally asymptomatic patient, where large heterogeneity in the use of ancillary testing is expected, or one with symptoms suggestive of ischemia but not yet evaluated or diagnosed. These cases were further developed with respect to whether testing for ASCVD was undertaken or not, and when undertaken, whether the test result was negative, positive but not necessarily suggestive of ischemia or hemodynamically significant stenosis (early/subclinical ASCVD), or positive and suggestive of ischemia or hemodynamically significant stenosis (advanced ASCVD). Finally, respondents were asked to consider use of PCSK9i with respect to the gap between achieved and desired lipid goal and whether statins had already been supplemented with ezetimibe or not. Respondents were asked to identify their country, their practice type (i.e. clinics with university/academic affiliations and involved in training medical students, residents or fellows were considered “academic/training” and clinics without such affiliations or teaching roles were considered “non-academic/non-training” sites; trainees were not included in this survey) and their specialty (general practice, cardiology, endocrinology, internal medicine or other). For each case scenario there were two questions:

1) How appropriate is it to treat this patient to achieve a lipid goal according to your national guidelines (or those observed by the respondent)?
2) How appropriate is it to consider use of a PCSK9i if goal is not achieved with maximally tolerated statin therapy with or without ezetimibe?

The concept of appropriateness was chosen to facilitate synthesis of practitioner perceptions in a quantitative fashion and beyond mere majority consensus. Accordingly, level of appropriateness was graded numerically from 1 (lowest) to 9 (highest). Scores were interpreted as follows: scores of 1, 2, 3 (rarely appropriate), scores of 4, 5, 6 (“may be appropriate”) and scores of 7, 8, 9 (appropriate). A score of 5 implied complete neutrality. The median, mean and modal appropriateness scores were tabulated. The final appropriateness level was determined on the basis of the median score as long as confirmed by either the mean or the mode and, in general, all 3 parameters were concordant. When the median was discordant with both the mean and mode, concordance between the latter two determined the final appropriateness level. Final results were conveyed as either appropriate, “may be appropriate”, or rarely appropriate as per the numerical ranges defined above.

Analyses were planned to assess results overall and according to country, specialty and practice type. Based on initial responses, a second brief survey was distributed to help clarify initial responses about asymptomatic patients. The survey results were completed and compiled by February 2017 and well in advance of publication of the first PCSK9i outcome trial [16]. The surveys are provided in the Supplementary Materials.

3. Results

There were 212 physicians who completed the survey with 96% from North America, 2% from Europe, and 2% from other countries; 42% were Cardiologists and 51% practiced in an academic or training setting. Of these, 102 also helped clarify initial survey results by responding to the second, shorter survey regarding asymptomatic patients.

Table 1 shows the appropriateness levels for the use of diverse, ancillary tests to either clarify risk in asymptomatic patients or to

evaluate symptoms suggestive of ischemia. In asymptomatic patients cardiac computed tomographic angiography (CCTA) and invasive angiography (IA) were considered rarely appropriate whereas all other tests were deemed "may be appropriate". In contrast, in the evaluation of symptoms suggestive of ischemia, the use of a baseline electrocardiogram (EKG), a stress EKG and an exercise or pharmacologic imaging stress test were all considered appropriate; carotid ultrasound, ankle brachial index, coronary artery calcium scoring, CCTA and IA were deemed "may be appropriate".

Appropriateness results for the case scenarios were amalgamated when no differences were found. This was the case for patients on dialysis or with pre-dialysis CKD (the combined group is referred to as CKD hereafter); and for primary prevention patients at high or moderate risk, including those meeting criteria for the HOPE-3 study (the moderate risk and HOPE-3 profile group is referred to simply as having moderate risk hereafter), and irrespective of symptom status. Finally, physician preferences were not different in the absence of testing for ASCVD or testing that yielded a negative result. Thus, Table 2 summarizes the main results showing the perceived appropriateness to get to a guideline-supported LDL-C goal with statins and ezetimibe and the perceived appropriateness for considering access to PCSK9i. Getting to a guideline-supported goal was considered appropriate in all scenarios except in low risk, asymptomatic patients. In the presence of early/subclinical ASCVD or advanced ASCVD the use of PCSK9i was always considered to be appropriate or at least "may be appropriate" but never "rarely appropriate." In patients with T2DM without evidence of early or advanced ASCVD access to PCSK9i was considered "may be appropriate" while it was considered appropriate with early or advanced ASCVD and in the presence or absence of symptoms. In patients with moderate or high risk, access to PCSK9i was considered appropriate only if advanced ASCVD was detected, irrespective of symptoms.

Table 3 shows the physicians' inclination to consider PCSK9i as an add-on to either maximally tolerated statins or maximally tolerated statins plus ezetimibe as a function of the LDL-C gap between achieved and desired goal. In either case, it was considered appropriate to use a PCSK9i if the gap was $\geq$35%, even when ezetimibe was not being used with a statin. Practically, if the goal were, for example, <1.8 mmol/L, use of PCSK9i would be considered appropriate if the LDL-C on statins with/without ezetimibe were approximately 2.8 mmol/L or higher but only "may be appropriate" if below that threshold.

3.1. Differences according to specialty and practice settings

Only a few differences were found according to specialty and practice settings and owing to the resulting distribution of respondents, we show only results for the largest group, cardiologists (42% of respondents) as compared to non-cardiologists (58%) and responses from Academic/Training Settings (51%) as compared to those from Non-academic/Non-training Settings (49%). Responses from cardiologists were mostly similar to those from Academic/Training Settings; responses from non-cardiologists were commonly the same as responses from Non-academic/Non-Training Settings. These aggregated results are shown in Table 4. In general, the appropriateness expressed by cardiologists or practitioners in Academic/Training Settings was more conservative in all case scenarios but one. In the latter exception, cardiologists or physicians working in Academic/Training Settings indicated that, to address ambiguous risk assessment and treatment decisions in asymptomatic patients, CCTA "may be appropriate". In contrast, this was considered rarely appropriate by non-cardiologists or practitioners in a Non-academic/Non-training setting. Scenarios showing differences either between cardiologists and non-cardiologists, or between Academic/Training Settings and Non-academic/Non-training Settings are summarized in Table 5 and show again a more conservative attitude among cardiologists and physicians in Academic/Training Settings.

4. Discussion

This analysis is a theoretical exercise designed to assess the perceived appropriateness level ascribed by practitioners to many situations that may uncover previously unrecognized ASCVD through routine practice and for which there are no current indications for use of PCSK9i. The cases excluded primary prevention

Table 1
Summary of appropriateness for use of ancillary testing in a patient with no history of ASCVD for whom, after CV risk assessment according to national guidelines, it is unclear in the mind of the patient or the practitioner whether to pursue lipid lowering with a statin.

Diagnostic Test for Underlying ASCVD	Asymptomatic	Symptoms Suggesting Ischemia or Ischemic Equivalent
12 Lead EKG	M	A
Exercise EKG	M	A
Exercise/Pharmacologic Imaging Stress Test	M	A
Carotid Ultrasound	M	M
Ankle Brachial Index	M	M
Coronary Artery Calcium Score	M	M
Cardiac Computed Tomographic Angiography	R	M
Invasive Angiography	R	M

A, appropriate; M, "may be appropriate"; R, rarely appropriate; EKG, electrocardiogram; ASCVD, atherosclerotic cardiovascular disease.

Table 2
Perceived appropriateness for getting to a guideline-recommended lipid goal and, when failing to reach that goal with statin with/without ezetimibe, to have access to PCSK9i (proprotein convertase subtilisin/kexin 9 inhibitor).

Patient Characteristic	Clinical Presentation	ASCVD Absent/Not Known		Early/Subclinical ASCVD		Advanced ASCVD	
		Get to Goal	Consider PCSK9i	Get to Goal	Consider PCSK9i	Get to Goal	Consider PCSK9i
T2DM	Asymptomatic or Symptomatic	A	M	A	A	A	A
High/ moderate risk	Asymptomatic or Symptomatic	A	M	A	M	A	A
CKD/Low Risk	Symptomatic	A	M	A	M	A	A
CKD	Asymptomatic	A	M	A	M	A	M
Low Risk	Asymptomatic	M	R	A	M	A	M

Abbreviations as for Table 1; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease.

Table 3
Appropriateness for access to PCSK9i as a function of the size of gap between achieved and desired low density lipoprotein-C (LDL-C) goal.

PCSK9 Inhibitor Add on According to Residual LDL C Gap to Goal		
Gap	On Maximally Tolerated Statin	On Maximally Tolerated Statin + Ezetimibe
< 20%	M	M
21 – 34%	M	M
≥ 35%	A	A

in patients with familial hypercholesterolemia and excluded obvious or known ASCVD. The influence of imaging results was most apparent in the care of patients with T2DM without a history of ASCVD. In such patients, whether symptomatic or not, it was felt to be appropriate to consider PCSK9i if LDL-C goals were not met with statins and/or ezetimibe if there was evidence of either previously unrecognized, advanced ASCVD or even early/subclinical ASCVD. When advanced ASCVD was uncovered in patients with high or moderate risk, or in the course of evaluation of possible angina pectoris symptoms in patients with CKD or in patients with low CV risk, access to PCSK9i was also considered appropriate if LDL-C goals were not being met with statins and/or ezetimibe, irrespective of presence or absence of symptoms. The only situation considered in this survey to rarely warrant access to PCSK9i was that of low risk, asymptomatic patients with no known or a negative test for ASCVD. All other situations resulted in appropriateness scores suggesting that it "may be appropriate" to consider use of PCSK9i.

These results, summarized in Table 2, serve to highlight practice-relevant research priorities that must be addressed, ideally through randomized clinical trials. However, where there was strong uniformity of opinion regarding appropriateness of achieving aggressive LDL-C goals, including with the use of PCSK9i (e.g. patients with T2DM with any degree of underlying ASCVD), specific randomized clinical trials may be difficult to undertake because the perceptions suggest a lack of practice equipoise and, therefore, a potential unwillingness to allow randomization. Under these circumstances, guidelines may need to rely upon consensus statements or subset analyses of patients with T2DM enrolled in randomized clinical trials addressing broader populations. Similarly, achievement of lipid goals, including with the use of PCSK9i if necessary, was considered appropriate after detection of advanced ASCVD that could explain suspected angina pectoris symptoms or that could conceivably be associated with ischemia in patients with CKD or with moderate to high CV risk, possibly reflecting a desire to optimize medical therapy and to forestall possible intervention. Such patients would not normally be eligible for aggressive lipid lowering with PCSK9i until after a procedure or a CV event. Conversely, the results also highlight many situations in which there is a high variance, reflected in the "may be appropriate" categorization of practitioner attitudes as to whether PCSK9i should be used to reduce cholesterol-related residual risk. This may be interpreted as reflecting "clinical equipoise" which is an ideal situation for randomized clinical trials. Thus, excluding patients with T2DM and patients with advanced ASCVD, resolution of the debate regarding aggressive lipid lowering dependent upon presence or absence of early/subclinical ASCVD is a compelling research need in primary prevention [21].

Table 4
Summary of differences in appropriateness levels between cardiologist or practitioners in academic/training settings and non-cardiologists or practitioners in non-academic/non-training settings.

Differences in Practice Patterns Between Cardiologists or Academic/Training Setting versus Non-cardiologist/Non-academic or Non-training Setting					
Clinical Scenario	Testing for ASCVD	Asymptomatic		Symptomatic	
		Cardiologist or Academic/Training Setting	Non-cardiologist or Non-academic/Non-training Setting	Cardiologist or Academic/Training Setting	Non-cardiologist or Non-academic/Non-training Setting
Ambiguous Risk Assessment	CCTA	M	R		
Adult with T2DM, consider PCSK9i to achieve goal	Early/Subclinical ASCVD	M	A		
CKD (pre-dialysis or dialysis), treat to goal	Negative/not done	M	A	M	A
	Advanced ASCVD	M	A		
Moderate Risk, consider PCSK9i to achieve goal	Negative/not done	R	M		
	Advanced ASCVD	M	A		

Blank cells or scenarios shown in Table 2, but not listed here, indicate no differences of subgroup responses and no differences when compared to the overall responses in Table 2. Abbreviations as for Table 2.

Table 5
Summary of differences in appropriateness levels between cardiologists and non-cardiologists and between practitioners in Academic/Training settings and those in Non-academic/Non-training settings.

Differences in Practice Patterns Between Cardiologists versus Non-cardiologists and Academic or Training Setting versus Non-academic or Non-training Setting									
Clinical Scenario	Testing for ASCVD	Asymptomatic		Symptomatic		Asymptomatic		Symptomatic	
		Cardiologist	Non-cardiologist	Cardiologist	Non-cardiologist	Academic or Training Setting	Non-academic or Non-training Setting	Academic or Training Setting	Non-academic or Non-training Setting
Adult with T2DM, consider PCSK9i to achieve goal	Not done	M	A	M	A				
Adult with T2DM, consider PCSK9i to achieve goal	Advanced ASCVD	M	A						
High Risk, consider PCSK9i to achieve goal	Advanced ASCVD	M	A						
Moderate Risk, consider PCSK9i to achieve goal	Early/Subclinical ASCVD	M	A	M	A			M	A
Low Risk, consider PCSK9i to achieve goal	Advanced ASCVD	M	A						

Blank cells or scenarios shown in Table 2, but not listed here, indicate no differences of subgroup responses and no differences when compared to the overall responses in Table 2. Abbreviations as for Table 2.

The results of this survey further suggest that utilization of imaging methods to clarify CV risk in asymptomatic subjects is commonly considered appropriate and is therefore likely to identify patients with either early/subclinical or advanced ASCVD while also identifying those who have none. What is conjectural but worth considering is whether the highly constrained indications for and access to PCSK9i might augment utilization of imaging to identify patients with ASCVD to rationalize a request for PCSK9i.

This situation may, in the absence of outcome trials substantiating the benefit of such a practice, augment health care expenditures on imaging even while limiting expenditures on aggressive preventive treatment with the addition of PCSK9i or avoiding treatment where no ASCVD is discovered. The cost-effectiveness of this approach remains to be proven. Such analyses were beyond the scope of our survey, and would clearly be influenced by any changes in the current high cost of PCSK9i as well as any changes in the cost of advanced imaging.

An unexpected finding was that, in general, cardiologists and practitioners in Academic/Training Settings were more likely to be conservative toward use of PCSK9i. This was unexpected because it is often the case that such physicians are perceived to be early adopters of new therapies and inordinately influential in writing guideline recommendations. Accordingly, our findings may suggest the converse, perhaps explained by a greater reliance on randomized outcome trial results and evidence-based medicine. This is particularly evident from Tables 4 and 5 highlighting that even when obstructive ASCVD is detected, treatment to a guideline-defined lipid goal was considered only "may be appropriate" whereas the other specialities and practice settings indicated that goal achievement was appropriate. While this may be a partial explanation for this conservative attitude, the more aggressive views of the other practitioners cannot be discounted and warrant further understanding. For example, many of the case scenarios studied herein would have higher 10 year event rates when compared, for example, to primary prevention in patients with familial hypercholesterolemia, a situation for which access to PCSK9i is not questioned and for which a randomized clinical outcome trial is not ever expected.

It is apparent that although access to PCSK9i is often predicated by concomitant use of statins with ezetimibe, practitioners considered that if the gap to goal was large, it is appropriate to consider PCSK9i even if ezetimibe has not been used. This outcome may be explained by practitioners' desires for more efficient attainment of goals and minimization of polypharmacy. Such a practice would also avoid the commonplace situation during follow-up of patients on statins, ezetimibe and PCSK9i when the patient wishes to minimize or eliminate one of the three drugs and often focuses on a desire to eliminate or decrease the statin, a result contrary to the tenets of all guidelines.

This paper has limitations. We did not have equal participation from all international sites and we were unable to contrast different practice attitudes among all sub-specialities. Despite this, the results reflect the opinions of over 200 practitioners, which is markedly greater than many appropriateness statements that are often based on a very limited number of key opinion leaders. Moreover, although we did not incorporate a second phase of face-to-face discussion of interim results, a process not feasible for this type of survey, we believe that this is also a strength because it represents the aggregate of individual responses unaffected by responses of others or domineering views of only a small pool of opinion leaders. Because of the international scope, we did not formally assess the respondents' intimate knowledge of applicable guidelines in their jurisdiction of practice. However, support for the validity of the results is that utilization of ancillary testing (Table 1) was highly concordant with current guidelines [8–15].

This analysis provides a framework for areas needing attention and not fully addressed by existing guidelines and the current indications for use of PCSK9i. The results indicate that even recent guidance provided by several societies for the use of non-statin drugs for CV risk reduction does not pertain to these commonly encountered situations because the guidance is constrained largely to patients with familial hypercholesterolemia or those with obvious ASCVD based on prior events or prior procedures [17–20]. Residual LDL-C on statin and incremental, absolute risk reduction, both affecting numbers needed to treat, are key elements of this decision process for add-on medications [22,23]. However, fundamentally improved risk assessment, perhaps through imaging, appears to influence this decision-making process which underscores the need for further research to properly justify these strategies [21].

In summary, this analysis provides an assessment of physician attitudes with respect to aggressive management of commonly encountered patients who warrant CV risk reduction through lipid lowering. Despite the current expense of PCSK9i, their safety and efficacy promote numerous instances wherein access is considered appropriate or possibly appropriate care even though not currently indicated. The results provide strong insights into important research questions requiring resolution, hopefully through randomized clinical outcome trials whenever feasible.

Conflict of interest

Mancini: Advisory board/speaking fees: Amgen, Sanofi; Research grants: Merck Canada, Sanofi, Amgen, Aegerion. Gupta: Advisory board/speaking fees: Amgen, Sanofi; Research grants: Amgen, Sanofi. Tsigoulis: none. Cannon: Research grants from (all >$10 K) Amgen, Arisaph, Boehringer-Ingelheim (BI), Bristol-Myers Squibb (BMS), Daiichi Sankyo, Janssen, Merck, and Takeda; Consulting fees from Alnylam, Amgen, Arisaph, Astra Zeneca, BI, BMS, GlaxoSmithKline, Kowa, Lipimedix*, Merck, Pfizer, Regeneron*, Sanofi*, and Takeda (* denotes >$10 K). Genest: Advisory board/speaking fees: Amgen, Sanofi; Novartis, Cerenis, Lilly. Research grants: Lilly, Cerenis, Sanofi, Amgen, Aegerion. Ray: Advisory board/speaking fees: Amgen, Sanofi, Lilly, Esperion, Kowa. Research grants to institution: MSD, Sanofi, Amgen, Pfizer. Santos: Advisory board/speaking fees: Amgen, Astra Zeneca, Biolab, Boehringer-Ingleheim, Kowa, Eli-Lilly, Merck, Sanofi/Regeneron, Procaps. Watts: Advisory board/research grants/speaking fees: Sanofi, Amgen, Gemphire, Kowa. Raggi: Advisory board/speaking fees: Sanofi, Amgen.

Financial support

This project was supported by the Canadian Collaborative Research Network through an unrestricted grant from Amgen, Canada.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.006.

References

[1] T.J. Anderson, J. Gregoire, G.J. Pearson, et al., 2016 canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult, Can. J. Cardiol. 32 (2016) 1263–1282.
[2] A.L. Catapano, I. Graham, G. De Backer, et al., 2016 ESC/EAS guidelines for the management of dyslipidaemias, Eur. Heart J. 37 (2016) 2999–3058.
[3] T.A. Jacobson, M.K. Ito, K.C. Maki, et al., National lipid association recommendations for patient-centered management of dyslipidemia: part 1-executive summary, J. Clin. Lipidol. 8 (2014) 473–488.
[4] P.S. Jellinger, Y. Handelsman, P.D. Rosenblit, et al., American association of clinical endocrinologists and american college of endocrinology guidelines for management of dyslipidemia and prevention of atherosclerosis, Endocr. Pract. 23 (4) (2017) 479–497.
[5] National Vascular Disease Prevention Alliance, Guidelines for the management of absolute cardiovascular disease risk. https://www.heartfoundation.org.au/images/uploads/publications/Absolute-CVD-Risk-Full-Guidelines.pdf, 2012 (Accessed 1 March 2017).
[6] A.F. Simao, D.B. Precoma, J.P. Andrade, et al., I brazilian guidelines on cardiovascular prevention, Arq. Bras. Cardiol. 101 (2013) 1–63.

[7] N.J. Stone, J.G. Robinson, A.H. Lichtenstein, et al., 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, Circulation 129 (2014). S1–45.
[8] S.D. Fihn, J.C. Blankenship, K.P. Alexander, et al., 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, Circulation 130 (2014) 1749–1767.
[9] G.B. Mancini, G. Gosselin, B. Chow, et al., Canadian cardiovascular society guidelines for the diagnosis and management of stable ischemic heart disease, Can. J. Cardiol. 30 (2014) 837–849.
[10] National Institute for Health and Care Excellence, Stable angina: management (Accessed 1 March 2017), https://www.nice.org.uk/guidance/cg126/resources/stable-angina-management-35109453262021, 2011.
[11] Task Force Members G. Montalescot, U. Sechtem, et al., 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology, Eur. Heart J. 34 (2013) 2949–3003.
[12] M.J. Wolk, S.R. Bailey, J.U. Doherty, et al., ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation appropriate use criteria task force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons, J. Am. Coll. Cardiol. 63 (2014) 380–406.
[13] L.A. Cesar, J.F. Ferreira, D. Armaganijan, et al., Guideline for stable coronary artery disease, Arq. Bras. Cardiol. 103 (2014) 1–59.
[14] L. Erhardt, J. Herlitz, L. Bossaert, et al., Task force on the management of chest pain, Eur. Heart J. 23 (2002) 1153–1176.
[15] National Institute for Health and Care Excellence, Chest pain of recent onset: assessment and diagnosis (Accessed 2 March 2017), https://www.nice.org.uk/guidance/cg95/resources/chest-pain-of-recent-onset-assessment-and-diagnosis-975751036117, 2010.
[16] M.S. Sabatine, R.P. Giugliano, A.C. Keech, et al., Evolocumab and clinical outcomes in patients with cardiovascular disease, N. Engl. J. Med. 376 (18) (2017) 1713–1722.
[17] D.M. Lloyd-Jones, P.B. Morris, C.M. Ballantyne, et al., 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology task force on clinical expert consensus documents, J. Am. Coll. Cardiol. 68 (2016) 92–125.
[18] U. Landmesser, M. John Chapman, M. Farnier, et al., European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk, Eur. Heart J. (2016) published online ahead of print http://dx.doi.org/10.1093/eurheartj/ehw480.
[19] National institute for Health and Care Excellence, Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (Accessed 2 March 2017), https://www.nice.org.uk/guidance/ta393/resources/alirocumab-for-treating-primary-hypercholesterolaemia-and-mixed-dyslipidaemia-82602908493253, 2016.
[20] National institute for Health and Care Excellence, Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (Accessed 2 March 2017), https://www.nice.org.uk/guidance/ta394/resources/evolocumab-for-treating-primary-hypercholesterolaemia-and-mixed-dyslipidaemia-82602910172869, 2016.
[21] J.G. Robinson, Planning a research agenda to incorporate imaging into clinical practice, JACC Cardiovasc Imaging (2017) in press, available online http://dx.doi.org/10.1016/i.jcmg.2016.12.018.
[22] J.G. Robinson, K. Ray, Moving toward the next paradigm for cardiovascular prevention, Circulation 133 (2016) 1533–1536.
[23] J.G. Robinson, R. Huijgen, K. Ray, et al., Determining when to add nonstatin therapy: a quantitative approach, J. Am. Coll. Cardiol. 68 (2016) 2412–2421.