Atherosclerosis stabilization with PCSK-9 inhibition: An evolving concept for cardiovascular prevention

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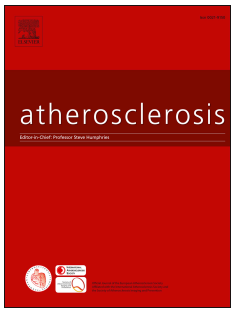

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Atherosclerosis stabilization with PCSK-9 inhibition: An evolving concept for cardiovascular prevention

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Relationships with industry:
Dr. Robinson serves as the Principal Investigator for clinical trials of PSCK-9 monoclonal antibodies and CETP inhibitors (Amgen, Merck, Pfizer, Regeneron/Sanofi). She serves as a consultant for manufacturers of PSCK-9 monoclonal antibodies and CETP inhibitors (Amgen, Eli Lilly, Merck, Pfizer, Regeneron/Sanofi).

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Dr. Fox serves as a consultant for manufacturers of PSCK-9 monoclonal antibodies (Regeneron/Sanofi and Eli Lilly), and Bayer/Janssen, Glaxo Smith-Kline.

Key words

PCSK-9 inhibitor

Plaque stabilization

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Abstract

Monoclonal antibodies (mAbs) to proprotein convertase subtilisin/kexin type 9 (PCSK-9) can further lower LDL-C by ≥60% in statin-treated patients. Preliminary data suggest they may reduce cardiovascular (CVD) events. Ongoing PCSK-9 mAb cardiovascular outcomes trials could provide the opportunity to determine whether a "legacy effect" similar to that observed for statins will occur over the post-trial observation period. We hypothesize these trials could demonstrate that (1) very aggressive LDL-C lowering with PCSK-9 mAbs added to background statin therapy will induce extensive atherosclerosis stabilization and regression in the large majority of treated patients, and (2) continued maintenance therapy with high intensity statin therapy (with or without ezetimibe) should then inhibit new plaque formation, with a long-term prevention of CVD events. The necessity of expensive lifetime treatment with PCSK-9 inhibitors could then be avoided in all but a small subset of patients who could benefit from longer treatment.

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Statins reduce the risk of cardiovascular events in patients with clinical atherosclerotic cardiovascular disease but many patients remain at increased risk of recurrent events.(1). Monoclonal antibodies (mAbs) to proprotein convertase subtilisin/kexin type 9 (PCSK-9 can further lower LDL-C by 60% or more when added to background statin therapy, and preliminary data from shorter-term follow-up of efficacy/safety trials suggest they further reduce recurrent CVD events in high risk patients by about 50% over a treatment period of 11-18 months.(2, 3) While PCSK-9 mAbs hold the promise of great clinical benefit for a significant number of patients, they are very expensive drugs (approximately US$14,000 per year)(4). We propose testing a new paradigm for cardiovascular prevention that moves away from lifetime preventive therapy and capitalizes on a substantial impact on a legacy effect cardiovascular events over the long-term, thereby minimizing the expenditures for these new drugs while capturing the benefit . Extended follow-up of the large ongoing cardiovascular outcomes trials of PCSK-9 mAbs provide just such an opportunity. (5-8) We hypothesize that (1) very aggressive LDL-C lowering with PCSK-9 mAbs added to background statin therapy during the trials will promote atherosclerosis stabilization and lesion regression in treated patients, and (2) continued maintenance therapy with high intensity statin therapy (with or without ezetimibe) should inhibit new plaque formation, with long-term prevention of CVD events. Therefore, it may be possible for shorter-term PCSK-9 inhibitor therapy could be sufficient for the large majority of patients, and the necessity of lifetime treatment with PCSK-9 inhibitors avoided in all but a small subset of patients.

Legacy effects

Meta-analysis of post-trial follow-up of the statin trials found long-term reductions in the relative risk of recurrent CVD events after discontinuation of statin therapy, with a magnitude of relative risk reduction similar to that observed in the active treatment period of the trial in primary and

secondary prevention trials.(9, 10) This may suggest persistent benefit from statin-induced plaque stabilization and reduction in plaque volume through regression, a phenomenon observed in the coronary intravascular ultrasound trials. This concept raises the possibility that more marked LDL-C reductions with PCSK-9 mAbs may have an even greater impact on plaque burden and disease stabilization and hence exhibit an even more profound "legacy effect". In support of this hypothesis, meta-analyses have found that statin therapy reduces fibrous plaque volume and improves vascular remodeling by virtual histology ultrasound, with plaque regression occurring after an average 19 months of treatment.(11, 12) Meta-analysis of high intensity statin coronary intravascular ultrasound trials has found that the lower the achieved LDL-C levels, the greater the magnitude of plaque regression down to an LDL-C level of 15 mg/dl (**Figure 1**). (13) Optical coherence tomography reveals more stable plaque features in patients with very low on-treatment LDL-C levels.(14) Other These vascular changes are consistent with the greater reduction in CVD events observed when progressively lower levels of LDL-C levels to <50 mg/dl were achieved in statin CVD outcomes trials of 2-6 years duration.(15)

PCSK-9 mAbs

Notably, when added to maximal statin or other lipid-lowering therapy in high risk patients, PCSK-9 mAbs lower LDL-C an additional 60-65% and result in achieved average LDL-C levels of 35-50 mg/dl.(2, 3, 16) Over 40% of patients on high intensity statins achieved persistent reductions in LDL-C <25 mg/dl with the addition of a PCSK-9 mAb.(16)

In preliminary analyses of Phase 3 efficacy/safety trials of the PCSK-9 mAbs, alirocumab and evolocumab, these remarkable reductions in LDL-C appear to have resulted in CVD event reductions of approximately 50% over a period of 11-18 months.(2, 3) Both drugs reduced LDL-C by an additional 60% when added to background therapy. An early separation of the event curves was observed in both studies. A meta-analysis of events reported in 24 phase 2 and 3 efficacy/safety trials of evolocumab and

alirocumab (n=10,159) found a preliminary suggestion that PCSK-9 mAbs may also reduce cardiovascular and total mortality.(17)

The further reduction in CVD events when PCSK-9 mAbs are added to statin therapy is at least the magnitude expected from the degree of LDL-C lowering when compared to the statin trials. The Cholesterol Treatment Trialists' meta-analysis of statin trials found that each 39 mg/dl (1 mmol/L) reduction in LDL-C was associated with a 21% reduction in major cardiovascular events.(18) The average 70 mg/dl reduction in LDL-C reduced cardiovascular events by 50% in the PCSK-9 trials. Thus, it appears the cardiovascular risk reduction from PCSK-9 inhibitors is at least as much as expected from a similar magnitude of LDL-C reduction from statins (eg, a 38% relative risk reduction in cardiovascular events expected for a 70 mg/dl reduction in LDL-C). Ezetimibe is another LDL-C lowering drug shown to modestly reduce cardiovascular events in relationship to the modest magnitude of LDL-C lowering.(19) Along with data from a trial of intestinal bypass surgery and diet, this suggests statin's pleiotropic effects are unlikely to be contributing additional risk reduction benefit(20), and that LDL-C lowering with PCSK-9 mAbs is likely to have analogous effects on plaque stabilization and regression as a function of the magnitude of LDL-C lowering. On the other hand, whether the anti-inflammatory effects of statins are mediated by LDL-C lowering, and if these same anti-inflammatory effects occur with PCSK-9 mAbs remains to be determined. (21) No cardiovascular imaging trials have yet been completed with PCSK-9 mAbs, although a coronary intravascular ultrasound trial is underway with evolocumab.(22) However, based on the reduction in cardiovascular outcomes observed to date, it appears that PCSK-9 mAbs are likely to result in further plaque regression and stabilization in statin-treated patients.

Further plaque stabilization and regression with the addition of a PCSK-9 inhibitor to statin therapy is supported by animal data that have found more plaque regression, along with a greater proportion of stable plaque, occurs from the addition reduction in LDL-C.(23) The PCSK-9 inhibitor alirocumab has been shown to reduce apolipoprotein B-containing lipoproteins, atherosclerotic lesion

size and severity, and to increase lesion stability in APOE*3Leiden.CETP mice fed a Western diet. (24) The distribution of plaque was reversed in alirocumab+atorvastatin treated animals, with about 75% of lesions in the undiseased state compared to about 75% in the severe state in untreated animals. Alirocumab improved plaque morphology by reducing monocyte recruitment and content of macrophages and necrotic core, and increasing smooth muscle and collagen content. These effects occurred after 18 weeks of alirocumab treatment and were enhanced when added to atorvastatin therapy, with an 89% reduction in lesion size in that group. Lesion area correlated well with cholesterol-lowering. These findings are consistent with animal models where atherosclerotic changes resulting from a high cholesterol diet regress when animals are returned to a standard diet.(23)

Proving the hypothesis

Continued follow-up of study participants once the ongoing PCSK-9 mAb cardiovascular outcomes trials end will provide a critical opportunity to test a new paradigm for cholesterol treatment: Is there a legacy effect after a period of profound LDL-C lowering? Planned post-trial follow-up can document whether shorter term therapy (2-4 years) with PCSK-9 mAbs will result in a long term reduction in cardiovascular events once treatment is stopped and patients are maintained long-term on maximal statin therapy. It is unlikely there will be large-scale cross-over to PCSK-9 mAbs after the end of the trial given the likelihood of high cost and restrictive access, at least over the nearer term, providing the opportunity for a natural experiment if post-trial follow-up is through a planned long-term observational program. Such follow-up would also provide the opportunity to collect biomarkers or perform imaging that could be used to identify patients at high risk of another cardiovascular event who could benefit from continued PCSK-9 treatment. In several countries, record linkage provides a cost-effective method of obtaining robust mortality data over the very long-term.(25) Other methods of regular follow-up have been successful for large epidemiologic studies and registries (26, 27). Planned

post-trial follow-up would also facilitate a randomized trial of biomarker or imaging-guided treatment to evaluate whether continued PCSK-9 mAb treatment will further reduce cardiovascular risk in study participants who are identified as being at persistently high risk of recurrent events at the end of the trial through clinical characteristics, biomarkers, or imaging evidence of unstable plaque. ^{18}F-NaF PET-CT has recently been identified as a particularly promising noninvasive measure of unstable plaque.(28)

After the end of the PCSK-9 outcomes trial treatment period, participants are very likely to continue maximal statin or statin/ezetimibe therapy as the standard of care therapy. Prevention of new plaque formation is the second important component of the new treatment paradigm. Epidemiologic evidence suggests atherosclerotic lesions are unlikely to form when non-HDL-C levels are <125 mg/dl (corresponding to LDL-C <95 mg/dl) through middle-adulthood.(29) Whether this same phenomenon occurs in those with an extensive burden of atherosclerosis such as those enrolled in the PCSK-9 mAb trials remains to be determined. In addition, longer-term follow-up will reveal whether there is an LDL-C level that results in prevention of new lesion formation.

Animal studies may be helpful in supporting the new paradigm of time-limited but very intensive LDL-C lowering. Studies evaluating plaque morphology after the discontinuation of aggressive lipid-lowering therapy while maintained on background statin therapy will be an important area for future investigation.(23) To our knowledge, such trials have not been performed to date.

Other drugs in development

This strategy could be investigated for other lipid-modifying agents under development, such as cholesteryl ester transfer protein (CETP) inhibitors which have been shown to have similar effects to PCSK-9 mAbs plaque regression in animal models which re mediated by non-HDL-C lowering. (30) In humans, a similar relationship with achieved non-HDL-C level and a reduction in cardiovascular events was observed in the statin trials.(15) If shown to reduce cardiovascular events in ongoing trials,(31, 32)

and with long-term follow-up, these drugs could be used in a similar fashion as proposed for PCSK-9 mAbs.

Clinical implications

We have proposed a new paradigm for cardiovascular prevention that could be supported by data from ongoing cardiovascular outcomes trials of PCSK-9 mAbs. After an initial period of atherosclerosis stabilization through shorter-term, very aggressive LDL reduction during the trial, long-term post-trial follow-up may document persistent risk reductions after the PCSK-9 mAb therapy has been discontinued(a "legacy effect"), while the patient remains maintenance statin therapy. These data may provide a potent, more cost-effective strategy for long-term cardiovascular risk reduction since the cost of 2-4 years of PCSK-9 inhibitor therapy (depending on the length of the randomized, controlled trial treatment period) could then amortized over periods of time as long as 10 years off the PCSK-9 mAb. For example, if the preliminary results of the PCSK-9 efficacy/safety trials are substantiated, and a 50% relative risk reduction during the trial is sustained off the PCSK-9 mAb over a period of up to 10 years, this could result in marked reductions in risk for patients across the spectrum of cardiovascular risk. As shown in **Table 1**, a consistent 50% reduction in the relative risk of a cardiovascular event would result in a number-needed-to-treat of 10 or less to prevent one event after 10 years for patients with 20% 10-year cardiovascular risk, such as those with clinical ASCVD on a statin.(33) This approach could also be evaluated in younger patients with heterozygous familial hypercholesterolemia, where a period of intensive plaque regression and stabilization might be followed by less intensive therapy to maintain LDL-C levels of approximately 100 mg/dl. Therefore, it is possible that the cost of expensive drugs used for a limited period (2-3 years) could be averaged over a longer period, and prove cost-effective.

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Figure 1. Change in percent (PAV) and total atheroma volume (TAV) by coronary intravascular ultrasound by achieved mean LDL-C level on treatment with 18-24 months of rosuvastatin 40 mg or atorvastatin 80 mg (n=1881). Adapted from Puri R, Nissen SE, et al. Am J Cardiol 2014; 114: 1465-1472.(13)

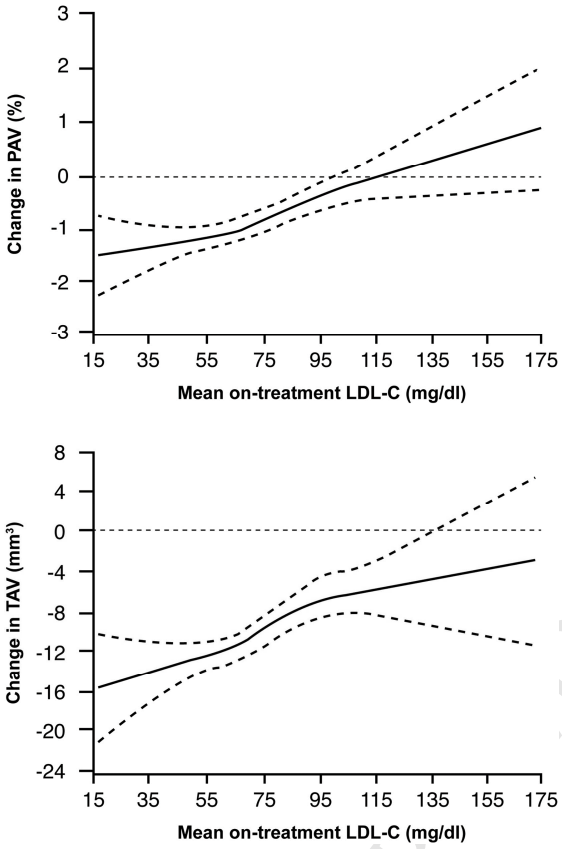

Table 1. Number-needed to treat to prevent 1 CVD event. As an example, patients with 20% 10-year hard cardiovascular risk would include those in the Treating-to-New-Targets trial, where the 5-year risk of patients with coronary heart disease were treated with atorvastatin 10 or 80 mg was 9-11%.(33) Adapted from Robinson J, Stone N. The 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardivoascular disease risk: A new paradigm supported by more evidence. From Robinson JG, Stone NJ. Eur Heart J 2015 Online ahead of print May 20, 2015:doi: 10.1093/eurheartj/ehv182.(34)

5-year CVD rate	5-year NNT: LDL-C reduction (mg/dl) 18	26	35	44	61
	Relative risk reduction 10%	15%	20%	25%	35%	50%
25%	40	27	20	16	11	**8**
20%	50	33	25	20	14	**10**
15%	67	44	33	27	19	**13**
10%	100	67	50	40	29	**20**
5%	200	133	100	80	57	**40**

10-year CVD rate	10-year NNT: LDL-C reduction (mg/dl) 18	26	35	44	61
	Relative risk reduction 10%	15%	20%	25%	35%	50%
50%	20	13	10	8	6	**4**
40%	25	17	13	10	7	**5**
30%	33	22	17	13	10	**7**
20%	50	33	25	20	14	**10**
10%	100	67	50	40	29	**20**