Application of PCSK9 Inhibitors in Practice

Challenges and Opportunities

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Although the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) and development of therapeutic antagonists represent a major triumph of modern clinical medicine, efforts to implement PCSK9 inhibitors (PCSK9i) in patient care have been sobering. This practical guide examines the barriers and opportunities for the successful application of pharmacological inhibition of PCSK9 in clinical practice through introduction of a new model of care delivery—the PCSK9i clinic.

A New Era in Lipid-Lowering Therapy

Historically, the foundation of primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) has consisted of therapeutic lifestyle changes in combination with pharmacological therapy focused on lipid modulation, specifically low-density lipoprotein cholesterol (LDL-C) lowering.[1] In 2015, the Food and Drug Administration (FDA) approved a new class of cholesterol-lowering medications, PCSK9i, to great anticipation. The seminal discovery in 2003 by Abifadel et al[2] linked gain-of-function mutations in the PCSK9 gene with autosomal dominant hypercholesterolemia. This finding uncovered PCSK9 as a key player in cholesterol homeostasis, a circulating protein with the strongest influence on plasma LDL-C concentration.[3] PCSK9 directly interacts with the low-density lipoprotein receptor and enhances its degradation by targeting it for destruction by the lysosome and halting its efficient recycling. Because PCSK9 causes degradation of the low-density lipoprotein receptor, inhibiting its action prolongs the lifespan of the low-density lipoprotein receptor and leads to profound reductions in plasma LDL-C levels. The ultimate culmination of this work was the regulatory approval of 2 monoclonal antibody inhibitors of PCSK9 (alirocumab and evolocumab). More recently, the randomized, placebo-controlled trial, FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), demonstrated improved ASCVD outcomes when evolocumab was added to background treatment with a statin. The combination of statin plus evolocumab resulted in a significant absolute and relative risk reduction in both the primary composite end point (cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina or coronary revascularization) and the secondary end point (cardiovascular death, myocardial infarction, or stroke).[4]

Alirocumab and evolocumab are FDA approved as adjuncts to diet and maximally tolerated statin therapy in (1) adult patients with heterozygous familial hypercholesterolemia (FH) and (2) patients with clinical ASCVD who require additional LDL-C lowering.[5] Evolocumab has additional FDA approval for treatment of homozygous FH. Although statin intolerance is not an official indication for PCSK9i therapy, patients who are unable to take statins may meet criteria for PCSK9 inhibition because their maximally tolerated statin dose is zero (Online Table I). This latter scenario requires detailed and specific documentation of the adverse events associated with statin administration.

The indications for PCSK9 inhibition must be balanced with cost. Presently, the expenditure for 1 year of PCSK9i therapy is ≈US $14 600 although pharmacy benefit managers, intermediaries between the payer and the rest of the healthcare system, pay substantially below retail price, as much as 50% less. Clearly, these medications will only be cost effective when allocated to those who are at highest risk. In our center, a prescription for a PCSK9i is considered only as the necessary last resort for a patient who squarely qualifies for it. A critical element of our approach is to scrutinize all the cases that can be treated with less expensive therapies and only proceed with PCSK9i in cases falling within the core of each FDA indication for use. Less than 2% of all patients that we have seen in the last 2 years have been prescribed a PCSK9i, and our practice is made up predominantly of patients with ASCVD and FH-type hypercholesterolemia.

Despite the unmet need for additional LDL-C–lowering therapies in these high-risk populations, and initial expectations for widespread use of alirocumab and evolocumab, practice utilization for these agents has been low. There are myriad possible explanations for this observation; however, the single most important deterrent to prescription of these effective new therapies is the difficulty in obtaining coverage by health insurance payers because they face the immense challenge of rationally and intelligently allocating approval of these expensive drugs.

According to Symphony Health Solution's Integrated Dataverse, new claims for PCSK9i have a final approval rate of only 25% from commercial payers and ≈50% for Medicare.[6] The results from other studies have shown similar results, with a 79% to 83% rate of initial medication denials

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in 2 large cohorts of 44 000 and 45 000 new PCSK9 monoclonal antibody prescriptions and ultimate approval rates of only 43% and 47%.[7,8] Other recent data demonstrate that high-risk patients with FH and ASCVD are denied PCSK9i despite evidence that LDL-C lowering is inadequate on optimal statin and additional lipid-lowering therapy.[9]

Initial experience with the prior authorization process has proven to be formidable. More than 50% to 80% of all initial prior authorization requests are denied even when patients meet the FDA-approved indications for therapy and the standard preauthorization form is appropriately completed with all details. On appeal, however, about half of prior authorization requests are subsequently approved. This process, perhaps by design, is laborious, time consuming, and inefficient. The cynic may suggest that payers rely on the fact that providers lack the time or resources to navigate the approval process although the other side of the coin is that payers must devise filtering processes to avoid frivolous or unwarranted use of these expensive agents. A recent summary report provided theoretical suggestions for overcoming barriers to access to PCSK9i therapy,[9] but failure to achieve insurance approval is still a prevalent problem. We and others have learned that access to PCSK9i requires a dedicated team to traverse the complicated labyrinth of prior authorizations, appeals, reappeals, and peer-to-peer reviews. In this context, the proverb "necessity is the mother of invention" rings true. In this report, we describe real-world strategies that have allowed us to provide PCSK9i to most of our qualified patients in need.

Birth of the PCSK9i Clinic

Given the challenges in gaining approval for PCSK9i from payers, we have developed and implemented a specialized PCSK9i clinic to improve appropriate access to this therapy. Our PCSK9i clinic team is composed of physicians, a nurse, a medical assistant, a clinical pharmacist, and a physician assistant who coordinates the whole operation. Given our 92% success rate (n=142/153) for ultimately securing approvals for PCSK9i, we offer our PCSK9i clinic experience as a guide and model for all cardiology practices.

When a provider in our Center for Preventive Cardiology identifies a PCSK9i-eligible patient, an internal referral to the PCSK9i clinic is made. In addition, we do receive external referrals directly to our PCSK9i clinic, which serves as another source of patients into our Center. The coordinator for the PCSK9i clinic oversees the approval process, provides injection training, and arranges longitudinal management and surveillance while on PCSK9i medications. The initial visit to the PCSK9i clinic is organized into 3 parts, (1) meticulous documentation of all data required for prior authorization submission, (2) general education about PCSK9i, and (3) injection teaching. Some of the more common sources of insurance denial for PCSK9i therapy are presented in Online Table II. We have developed a template for the initial encounter with a patient in the PCSK9i clinic to address these important issues prospectively. The importance of a proper initial encounter note to improve the prospects of approval cannot be overstated.

The structure of this initial PCSK9i clinic encounter note includes the following key elements (see also Online Table I):

–Detailed medication history: This medication review must include all current and prior lipid-modulating therapies with doses, reasons for discontinuation, dates or length of time when taken, and whether symptoms resolved on discontinuation and returned on rechallenge. Note that most insurance companies require patients to have tried atorvastatin and rosuvastatin at the maximally tolerated doses and ezetimibe before approval of a PCSK9i, a strategy much in line with the 2016 American College of Cardiology Expert Consensus Decision Pathway recommendations.[10]

–Family history: This assessment includes family history of hypercholesterolemia, ASCVD, and tendon xanthomas.

–Dutch Lipid Clinic Network Score: If FH is the indication for the PCSK9i, many insurance companies will require a Dutch Lipid Clinic Network score of >8 as evidence for definite FH.

–Physical examination: The targeted examination must evaluate for the presence of cutaneous and tendon xanthomas and corneal arcus. Even mild findings should be recorded.

–Laboratory evaluation: Laboratory testing must include a recent lipid panel (typically within the last 30 days) with a request for documentation of the highest known (usually off treatment) LDL-C concentration if available.

–Indication for PCSK9i therapy: The provider must specify one of the following diagnoses: heterozygous FH, homozygous familial hypercholesterolemia, or ASCVD with inadequate LDL-C lowering despite maximally tolerated lipid-lowering therapy.

–The patient's LDL-C goal or target: Use a set of guidelines from a national agency to justify the goal.

–Documenting therapeutic lifestyle changes: Coverage for PCSK9i is frequently denied when this documentation is not included. Current smokers will likely be denied by some insurance plans.

–Additional factors to support necessity for aggressive LDL-C reduction with PCSK9i: In patients with elevated lipoprotein (a) or a diagnosis of ASCVD based on atherosclerosis imaging (eg, coronary artery calcium), it is useful to include excerpts from the primary scientific literature and national guidelines to support the contention that the patient is at high risk for ASCVD events and requires aggressive LDL-C lowering.

A lipid panel is ordered at the first visit in the PCSK9i clinic because most insurance companies will require laboratories within 30 days of the initial request. The patient is asked to sign a letter of consent granting permission to the coordinator to act as their representative to file future appeals and communications on approval or denial of requested medications. Although seemingly a small detail, this step is of utmost importance because significant delays can ensue when this provision is not in place as some insurance companies require patients to file appeals themselves or have signed written permission for others to do so on their behalf.

Practicalities of the PCSK9i Approval Process

The process of identifying potential patients who may benefit from PCSK9i therapy and providing general education, injection teaching, and documentation is straightforward. The real challenge with PCSK9i is navigating the prior authorization process. Our approach to the PCSK9i approval process is delineated in Online Figure I.

Even with ultimate approval of PCSK9i therapy from the payer, the financial burden imposed on the patient with high

copays and out-of-pocket maximums (or the "doughnut hole" of Medicare) is frequently another serious barrier to treatment (Online Table III). Fortunately, there are several viable options to defray patient liability, including institution-specific medication assistance programs, the Patient Access Network, Amgen Safety Net Foundation, and commercially sponsored discount and copay cards.

Within our practice, this model has significantly enhanced and streamlined the prescribing process for providers. Any potential obstacles are identified within the context of a PCSK9i clinic visit with the coordinator and addressed before submission of the prior authorization request. This model has quickly evolved into an effective platform that can be generalized to essentially any other specialty medication. Implementation of this practice has enhanced medication approval rates, provider efficiency and productivity, and the satisfaction of both patient and referring physician. The creation and implementation of a PCSK9i clinic have transformed a formidable challenge into an opportunity for process and quality improvement and added value to our program.

Compared with the specialty pharmacy-based model, the PCSK9i clinic model keeps the approval process in the hands of the clinical specialists, who are better equipped to address the nuances of lipid management, to act as patient advocates, and to maximize scholarly opportunities. Appealing inappropriate denials is an important part of the process of accessing PCSK9i. In taking the steps that we outline in this practical guide, providers can expect to have a high level of success in accessing PCSK9i for their patients without having to remove current lipid-lowering therapies.

Conclusions

Clinical trials of monoclonal antibodies targeting PCSK9 have demonstrated remarkable efficacy in LDL-C reduction with an excellent short-term safety and tolerability profile. More recently, the results of a large randomized placebo-controlled outcomes trial demonstrated the superiority of adding a PCSK9i to a statin versus statin monotherapy in patients with stable ASCVD. The ability to substantially lower LDL-C is an unmet clinical need in several patient populations, including those with FH, statin intolerance, and in those with established ASCVD with inadequate LDL-C lowering on conventional lipid-lowering therapy. The FDA approval of this novel class of LDL-C–lowering agents generated enthusiasm and angst. Perhaps surprising to many were the unanticipated barriers to PCSK9i access. Out of necessity, a new model for patient evaluation and management for this novel therapeutic class arose, the PCSK9i clinic. We propose a framework for the PCSK9i clinic as an efficient means to evaluate, manage, and gain access to an important therapeutic that has the potential to provide significant additional LDL-C lowering in a substantial proportion of patients at risk for ASCVD events.

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Supplemental Table I. Required documentation required for prior authorization

- Detailed medical history including prior and current medications, doses, dates of administration, reasons for discontinuation
- Family history of hypercholesterolemia and/or coronary artery disease
- Physical exam for xanthomas (for patients with FH)
- Dutch Lipid Clinic Network Score (for patients with FH)
- American Heart Association criteria for diagnosis of FH
- Most recent lab results (within the past 30 days) - including lipid panel and lipoprotein (a)
- Highest documented LDL-C concentration (ideally off treatment)
- Evidence of subclinical atherosclerosis (coronary artery calcium, carotid intima media thickness, ankle brachial index) or clinical ASCVD (myocardial infarction, stroke, arterial revascularization, angina, angiographic evidence, ischemia testing)
- Clear specification of diagnosis for which PCSK9 inhibitor therapy is being prescribed

FH = familial hypercholesterolemia; ASCVD = atherosclerotic cardiovascular disease

Table II. Common reasons for denial of PCSK9 inhibitor applications

- Patient has not tried ezetimibe
- Ezetimibe intolerance not acceptable unless labeled as “hypersensitivity”
- Statin intolerance other than “myalgia”
- Patient has not tried a bile acid sequestrant
- Labeled contraindication to all statins not documented
- No documented intolerance or contraindication to high dose atorvastatin and rosuvastatin
- LDL <100 mg/dL with ASCVD or <130 mg/dL without ASCVD
- Requires 80% compliance in fill history from pharmacy for statin and ezetimibe over 12-month period
- Requires 3-12-month trial of statin and/or ezetimibe
- LDL-C levels not documented
- Re-challenge with statin not documented in statin-intolerant patient
- Nutrition intervention not documented (specifically reduced intake of saturated fats and cholesterol; increased fruits and vegetables)
- Triglycerides >400 mg/dL
- Exercise regimen not documented
- Weight management regimen not documented
- Requires confirmation of FH with genetic testing
- Criteria for “definite” FH not documented (requires DLN Score >8)
- Current and target LDL –C levels not documented
- Indication for PCSK9 inhibitor not clearly documented
- Concurrent use of maximally tolerated statin therapy not documented
- Failure to submit office notes or labs with prior authorization request
- Missing statement that patient will continue to receive a maximally tolerated statin (or ezetimibe) while on PCSK9i
- ASCVD criteria not met (ACS, Angina, MI, PCI, CABG, Abnormal Stress Testing, Stroke/TIA/CEA, PVD)

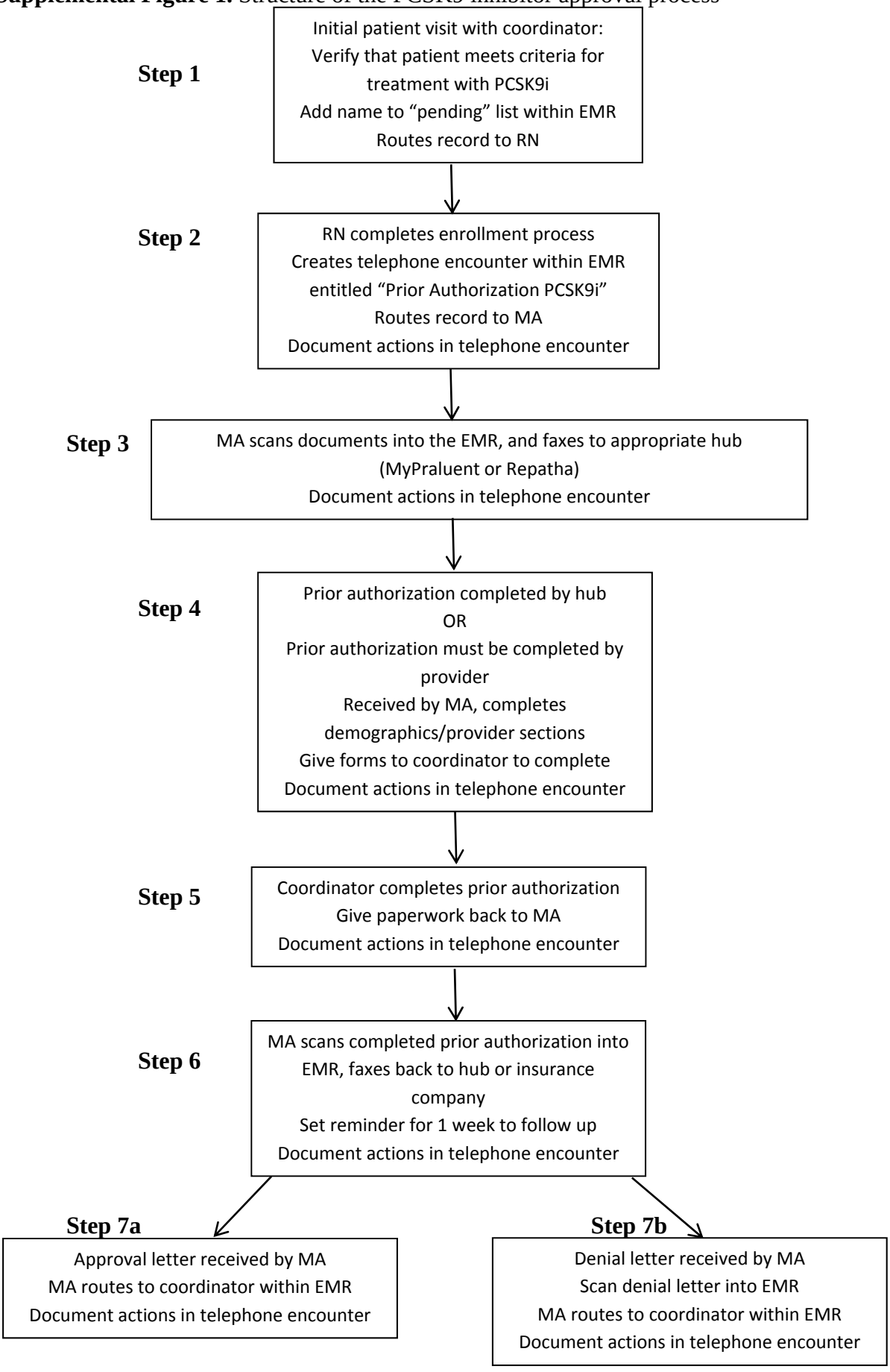
ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; DLCNS, Dutch Lipid Clinic Network Score; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor PVD, peripheral vascular disease; and TIA/CEA, transient ischemic attack/carotid endarterectomy.

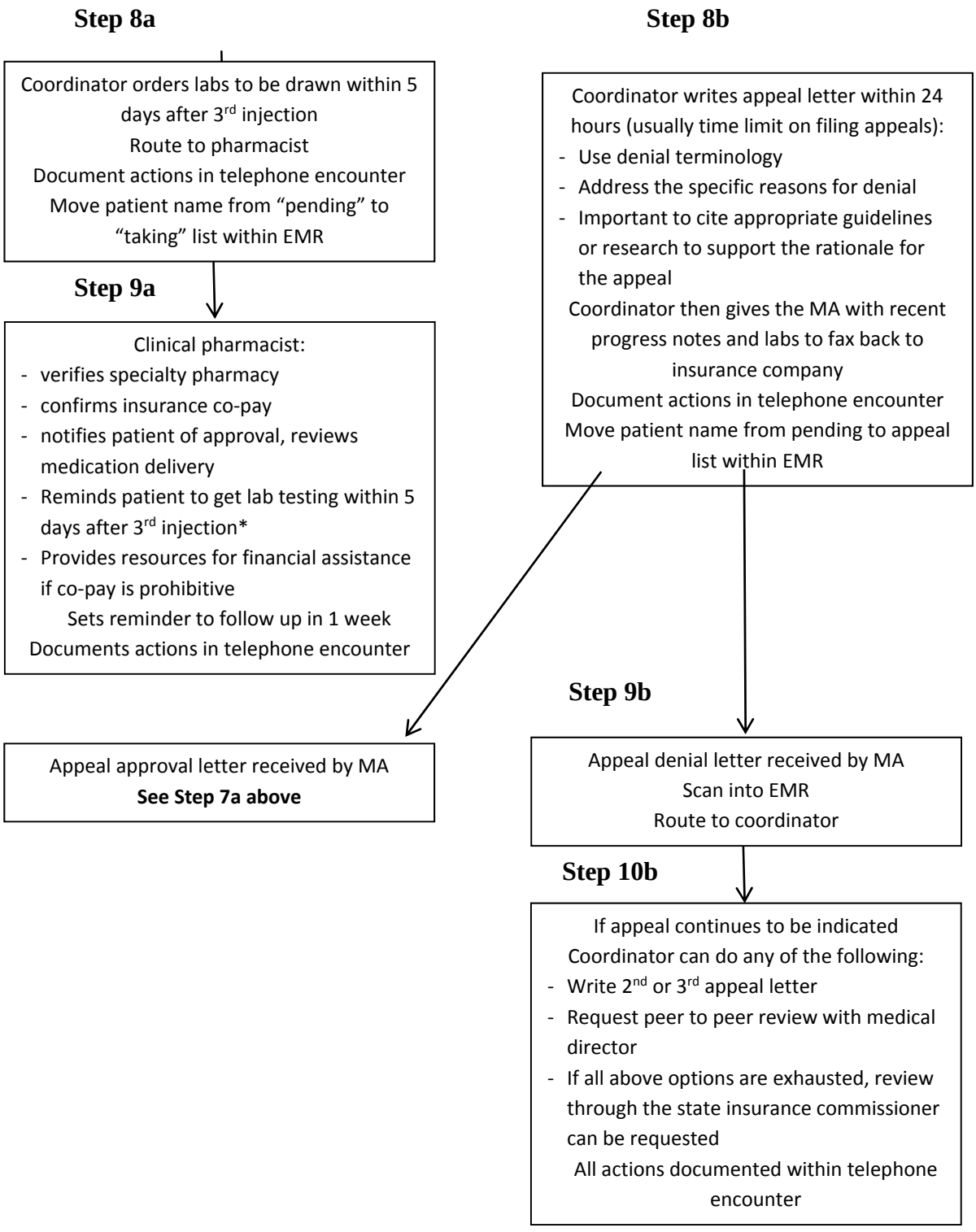
Supplemental Table III. Indications and reasons for discontinuation of PCSK9 inhibitor therapy for patients in our PCSK9 inhibitor clinic

Indication for therapy	**N**	
FH	46	36.8%
ASCVD	34	27.2%
ASCVD defined solely by CACS	5	14.7%
Average CACS		841 Agatston
FH with ASCVD	44	35.2%
Statin Intolerance	49	39.2%
Discontinuation of therapy		
Cost	5	4%
Side effects	5	4%
Personal choice	6	5%

FH = familial hypercholesterolemia; ASCVD = atherosclerotic cardiovascular disease; CACS = coronary artery calcium score

Supplemental Figure 1. Structure of the PCSK9 inhibitor approval process




Step 8a
Coordinator orders labs to be drawn within 5 days after 3rd injection
Route to pharmacist
Document actions in telephone encounter
Move patient name from "pending" to "taking" list within EMR
Step 9a
Clinical pharmacist:
- verifies specialty pharmacy
- confirms insurance co-pay
- notifies patient of approval, reviews medication delivery
- Reminds patient to get lab testing within 5 days after 3rd injection*
- Provides resources for financial assistance if co-pay is prohibitive
Sets reminder to follow up in 1 week
Documents actions in telephone encounter
Appeal approval letter received by MA
See Step 7a above
Step 8b
Coordinator writes appeal letter within 24 hours (usually time limit on filing appeals):
- Use denial terminology
- Address the specific reasons for denial
- Important to cite appropriate guidelines or research to support the rationale for the appeal
Coordinator then gives the MA with recent progress notes and labs to fax back to insurance company
Document actions in telephone encounter
Move patient name from pending to appeal list within EMR
Step 9b
Appeal denial letter received by MA
Scan into EMR
Route to coordinator
Step 10b
If appeal continues to be indicated
Coordinator can do any of the following:
- Write 2nd or 3rd appeal letter
- Request peer to peer review with medical director
- If all above options are exhausted, review through the state insurance commissioner can be requested
All actions documented within telephone encounter