Pharmacy E-News

February 2019

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Aspirin for Primary Prevention in Patients with Diabetes

By Danielle Pringle, Pharmacist Intern; Edited by Sophia Lai, PharmD; Reviewed by Lindsey Helm, PharmD, BCACP, Melissa Hull, PharmD, CACP, CLS, Dan Kent, PharmD, CDE, Avantika Waring, MD

Key Points:

- The benefit of primary prevention with aspirin in patients with diabetes is unclear.
- Current guidelines may be promoting over-usage of low-dose aspirin for primary prevention in patients with diabetes mellitus.
- The ASCEND study is a randomized controlled trial that assesses the efficacy and safety of low-dose aspirin as primary prevention in diabetes mellitus patients with no known cardiovascular risk.

Background

- The role of daily low-dose aspirin (ASA) in patients with cardiovascular disease has been clearly established as beneficial to prevent additional cardiovascular (CV) events and reduce mortality.[1] Its role in primary prevention, however, is less clear.
- The American Diabetes Association (ADA)[2] and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)[3] have issued recommendations on ASA use for primary prevention based on existing literature (**Table 1**).
- However, primary literature addressing the use of ASA for primary prevention in diabetes mellitus (DM) patients did not conclude a clear benefit. These studies also did not adequately assess relevant bleeding risk data, resulting in an uncertain risk versus benefit profile.[4,5]
- The ASCEND trial was designed to evaluate the risk and benefit of low-dose ASA for primary prevention in patients with diabetes mellitus.

Table 1. ADA and AACE/ACE Recommendations on ASA use in Primary Prevention

ADA	AACE / ACE
ASA 75-162 mg may be considered for primary prevention in patients with diabetes and increased cardiovascular risk after discussion of benefit and increased risk of bleeding.[2]	ASA 75-162 mg for primary prevention in diabetic patients with very high cardiovascular risk, defined as 10-yr risk greater than 10%.[3]

Study Design

- The ASCEND study[6] is a 2x2 factorial design randomized study (N=15,480) that included patients who were at least 40 years-old with DM (type 1 or 2) and no known cardiovascular disease.
- Composite CV events primary outcomes and bleed-related safety outcomes (**Table 2**) were assessed in the two study arms (Placebo versus ASA 100 mg daily).

Table 2. ASCEND Efficacy and Safety Outcomes of Interest

Composite Primary Efficacy Outcome	Composite Safety Outcome
Nonfatal myocardial infarction, stroke, transient ischemic attack, and death from vascular cause. Intracranial hemorrhage was excluded.	Confirmed intracranial hemorrhage, gastrointestinal bleeding, sight-threatening bleeding event, or bleeding event that resulted in hospitalization, transfusion, or death.

Results

- Patients in the ASA treatment arm showed a statistically significant **relative risk reduction of 12%** compared to placebo, in the primary outcome (ASA vs Placebo: 8.5% vs 9.6%; Rate Ratio 0.88; 95% CI 0.79 – 0.97, P= 0.01). The **number needed to treat was 91 patients over 7.4 years**.
- Patients in the ASA treatment arm also demonstrated a significant **relative increase of 29% in major bleeding events**. (ASA vs Placebo: 4.1% vs. 3.2%; Rate Ratio 1.29; 95% CI 1.09 – 1.52, P=0.003). The **number needed to harm was 112 patients over 7.4 years**.
  - 41.3% of major bleeding events reported were gastrointestinal (GI).
  - There was no statistical difference between ASA and placebo for hemorrhagic stroke, sight-threatening bleeding of the eye, or fatal bleeding events.

Conclusion

- Results of ASCEND support the need for continued discussion on the use of low-dose ASA for primary prevention in DM patients.
- The majority of bleeding events in the ASA treatment group were gastrointestinal, further emphasizing the need to weigh individual patient CV risk against patient risk for GI bleed.
- Clear risk-benefit discussions with patients and assessment of patient specific factors (e.g., CV and bleeding risks) are recommended to determine appropriate use of ASA as primary prevention.
- Current evidence does not support a general recommendation for ASA in all DM patients beyond the U.S. Patient Safety Task Force recommendations for the **initiation** of low-dose ASA (81 mg) for patients **aged 50–59** at > 10% risk of ASCVD over 10 years.

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Important Updates to Hypertension Guideline

By Sophia Lai, PharmD; Reviewed by Angela Sparks, MD, FAAFP

Key points:

- In October 2018, Kaiser Permanente Washington adopted the KP National Guideline with its new blood pressure threshold for the diagnosis of hypertension and new blood pressure goals for specific patient populations.
- Findings of the SPRINT trial supported lower systolic blood pressure treatment goal to reduce cardiovascular-related events.

Background

- In 2017, the American College of Cardiology (ACC) and American Heart Association (AHA) released an update on the management of high blood pressure in adults, which revealed changes to the blood pressure threshold for hypertension diagnosis.
- Among the supporting literature for the changes, the SPRINT trial was one of the most important and controversial.

Hypertension Guideline Updates

- The 2018 KP National guideline, which KPWA has adopted, is mostly aligned with the 2017 ACC/AHA update with a few differences in the blood pressure goals for certain patient populations and blood pressure threshold for diagnosing high blood pressure.
  - **Diabetes Mellitus (DM) blood pressure goals**: ACC/AHA[7] recommends a systolic blood pressure (SBP) goal of < 130 mmHg. Whereas, KP National states that having DM alone does not qualify for SBP goal of < 130 mmHg. This change is also different from previous KPWA guidelines (**Table 1**). Ultimately, it depends on the level of cardiovascular risk in individual patients to determine the most appropriate blood pressure goal.

Table 1. Updates to Blood Pressure Goals in Patient Populations

	Previous guideline (mmHg)	KP National/KPWA guideline* (mmHg)
Age ≥ 75 years old	Age ≤ 79 years: < 140/90 Age >79 years: <150/90	SBP ≤ 130
ASCVD history or 10-year ASCVD risk ≥ 15%	BP < 140/90	SBP ≤ 130
Chronic kidney disease	CKD without albuminuria < 140/90 CKD with albuminuria < 130/80	SBP ≤ 130
Diabetes	BP < 140/90	DM alone does not qualify for SBP < 130

*KPWA updated guideline aligns with KP National

  - **Diagnosis threshold**: The ACC/AHA threshold changes in diagnosing high blood pressure was supported by scientific literature, particularly the SPRINT trial. KP is keeping the threshold for hypertension diagnosis as ≥ 140/90 (**Table 2**).

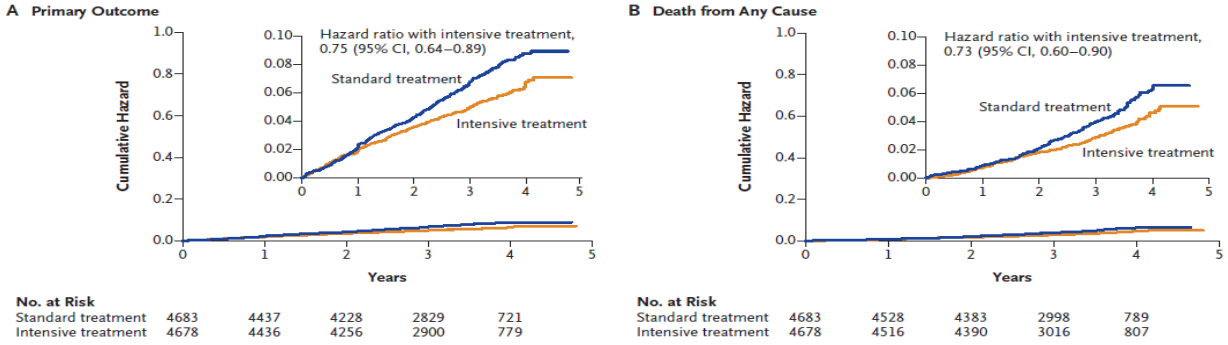
Table 2. KP vs. ACC/AHA on the Diagnosis of Hypertension

	ACC/AHA (mmHg)	KP National/KPWA (mmHg)
Normal	< 120/80	< 120/80
Prehypertension	120-129/80-89	120-139/80-89
Hypertension	**≥130/80**	**≥ 140/90**

The SPRINT Trial

- SPRINT[8] was a multicentered, open-label, randomized-controlled trial that included patients age 50 years or older with systolic blood pressure 130-180 mmHg and at least 1 cardiovascular risk factor. Patients were excluded if they had diabetes or prior stroke.
- Patients (N=9,361) were randomized to either a SBP goal of < 120 mmHg (intensive group) or SBP goal of < 140 mmHg (standard group).
- Results showed that the intensive treatment group reduced the primary outcome (first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) by 25% [Number needed to treat (NNT)=61] and all-cause mortality by 27% (NNT=90) (**Figure 1**).
- Results from the subgroup analysis also showed reductions in primary outcome (NNT=32) and all-cause mortality (NNT=41) in patients aged 75 years or older treated in the intensive group [Hazard ratio (HR) 0.67; 95% Confidence Interval, 0.51 to 0.86]
  - This result raised safety concerns as elderly patients in the intensive group also experienced significantly higher adverse effects such as hypotension, syncope, and electrolyte abnormality (HR 1.88; p<0.001).
- KP National and the ACC/AHA adopted a SBP goal of < 130 mmHg for the general population, including the elderly, and not the intensive goal of <120 mmHg as studied in SPRINT.
- A major limitation of this study was exclusion of patients with diabetes, history of stroke, and patients younger than 50 years old.
- There was also criticism on the generalizability of this study as only 7.6% of the U.S. adult or 16.7% of adults actually currently treated for hypertension would meet the SPRINT eligibility[9]. In addition, there was no guidance from either the SPRINT researchers or the ACC/AHA on how to treat newly diagnosed adults who are refractory to lifestyle modifications and considered low-risk.

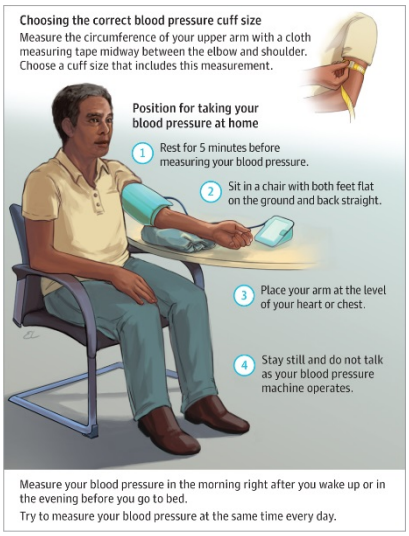
Figure 1. Primary Outcome and Death from Any Causes of the General Patient Population



Blood Pressure Monitoring

- Self-directed or ambulatory blood pressure measurement and lifestyle modifications are both areas of focus in the 2018 KP Update.
- The guideline gave more details on the proper measurement technique (**Figure 2**) and the importance of using validated measurement instruments. A patient handout developed by KP National is available.

Figure 2. Instructions on Home Blood Pressure Measurement[10]



Conclusion

- The SPRINT trial was an important trial that contributed to the updates in the blood pressure goals.
- New practice standards and clinical consideration should be used with patient-specific characteristics that may alter the goal.
- Proper self-directed blood pressure monitoring and lifestyle modifications should also be re-emphasized.
- KPWA continues to improve care for adult patients with hypertension by providing evidence-based care with adoption of KP National's guideline.

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Oral Anticoagulant Prescription Trends in Patients with Atrial Fibrillation

By Charlene Liu, PharmD; Reviewed by Melissa Hull, PharmD, CACP, CLS

Key Points:

- Warfarin had been the preferred oral anticoagulant for stroke prevention prior to the emergence of the direct oral anticoagulants (DOACs).
- In patients initiated on oral anticoagulants, utilization of DOACs has surpassed warfarin in patients with atrial fibrillation over the past few years.
- DOACs are becoming the preferred oral anticoagulant due to their efficacy, safety, decreased patient monitoring and decreased potential for drug interactions.
- Among the DOACs, dabigatran is the most affordable for KPWA members, and has been on the market the longest.

Background

- The anticoagulant of choice for stroke prevention in patients with atrial fibrillation has been warfarin for decades. However, warfarin dosing requires close monitoring due to its narrow therapeutic window and inter- and intra- patient variations in dose.
- Over the past few years, several direct oral anticoagulants (DOACs) have been approved by the U.S. Food and Drug Administration (FDA) for nonvalvular atrial fibrillation. Dabigatran was initially approved in 2010, followed by rivaroxaban, apixaban, and edoxaban.
- The 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/ Health Rhythm Society (HRS) Guideline for the Management of Patients with Atrial Fibrillation

recommends warfarin, dabigatran, rivaroxaban and apixaban as oral anticoagulant options for patients with nonvalvular atrial fibrillation. Choice of therapy varies by patient-specific factors and preferences. Edoxaban was not FDA approved at the time of guideline publication.[11]

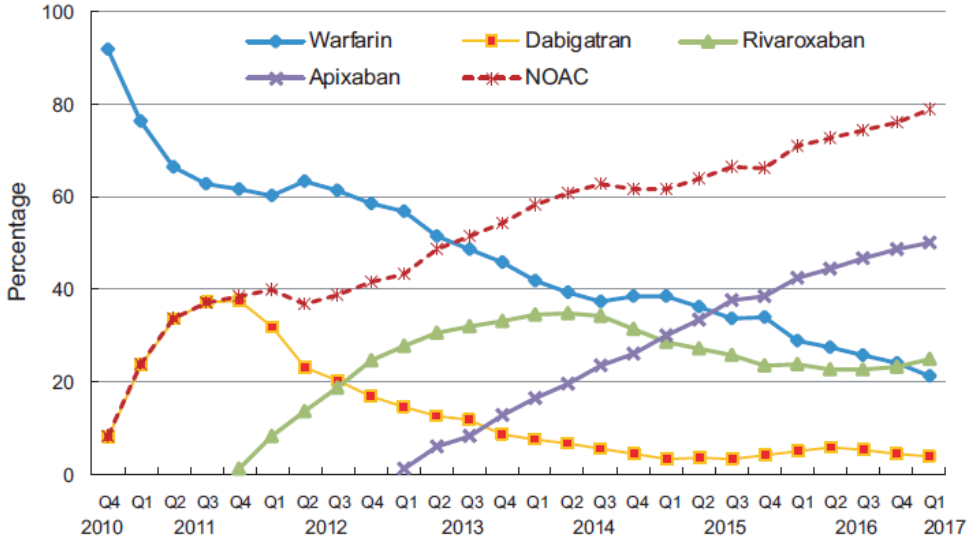
DOACs compared to Warfarin

- DOACs are similar in efficacy to well-controlled warfarin (time in therapeutic range [TTR]>65%) in preventing ischemic stroke but have a significantly reduced risk of intracranial hemorrhage.[12]
    - In the RE-LY study, dabigatran was superior to warfarin in preventing stroke or systemic embolic events in patients with nonvalvular atrial fibrillation. However, when warfarin patients had greater time in therapeutic range, dabigatran was similar in efficacy.[13]
- DOACs do not require frequent laboratory monitoring or dosage adjustments. They also have fewer drug and food interactions compared to warfarin.
- Despite the increased expenditure on DOACs, external analyses demonstrate that oral anticoagulants are still cost-effective compared to warfarin when considering laboratory monitoring, medication-related adverse events and incidence of stroke.[14,15]
- However, within Kaiser Permanente Washington (KPWA), warfarin remains the most cost-effective agent given the Anticoagulation Management Service's high quality TTR.
    - At KPWA, warfarin is preferred over DOACs in patients with the following characteristics:
        - TTR >70%
        - Renal disease: Creatinine clearance (CrCl) <30 mL/min
        - Concurrent p-gp and CYP 3A4 inhibitors
        - History of gastrointestinal resection or bariatric surgery
        - Weight >120 kg or <50 kg

Increased Uptake of DOACs[17]

- As new oral anticoagulants have been introduced to the market in recent years, prescriptions for the newer agents have increased.[14,16,17,18]
- National utilization of DOACs from 2009-2014 using data from IMS Health National Disease and Therapeutic Index found that, at the end of 2014, rivaroxaban (47.9%) was the most prescribed DOAC followed by apixaban (26.5%) and dabigatran (25.5%), respectively.[16]
- Within 5 years of the introduction of DOACs, the proportion of prescriptions for warfarin decreased by 24% in a Texas Medicaid population.[14] A similar shift in marketshare was also observed in a large, geographically diverse U.S. health plan.[17]
- A retrospective cohort study evaluated oral anticoagulant marketshare trends in 112,187 patients between October 2010 and March 2017 in commercial and Medicare Advantage members in a large, geographically diverse U.S. health plan (**Figure 1**).[17]
    - Dabigatran was the first FDA approved DOAC in 2010 and utilization peaked at the end of 2011 at 37.4%, prior to when other agents entered the market.
    - As other DOACs were approved, utilization of rivaroxaban and dabigatran plateaued over time.
    - Since 2013, apixaban has become the most prescribed oral anticoagulant for atrial fibrillation. At the first quarter of 2017, 50.1% of new oral anticoagulant prescriptions were for apixaban.

Figure 1. Trend in oral anticoagulant prescriptions from 2010 to 2017 for atrial fibrillation[7]



- DOAC prescriptions surpassed warfarin in 2013 and the proportion of incident users for DOACs was 78.9% in 2017 (**Table 1**).[17]

Table 1. Utilization of oral anticoagulants for atrial fibrillation in 2013 and 2017[17]

Year	Warfarin Utilization	DOAC Utilization
2013	91.9%	8.1%
2017	21.2%	78.9%

- At Kaiser Permanente Washington, dabigatran currently has the highest utilization compared to the other DOACs (**Table 2**).
    - Dabigatran is KPWA's preferred product placed at Tier 3 on the Medicare 2018 formulary compared to the other agents which are Tier 4.

Table 2. Kaiser Permanente Washington DOAC utilization from June 2018 to September 2018

	Apixaban (NF)[a]	Dabigatran (F)[a]	Edoxaban (NF)[a]	Rivaroxaban (F-PA)[a]
% of DOAC prescriptions	12%	59%	0%	29%

NF= non-formulary, F = formulary, F-PA = formulary with prior authorization
[a] Formulary status as of 11/14/2018

Patient-specific trends[17]

- Generally, patients prescribed warfarin are older with the highest Charlson comorbidity index, risk for ischemic stroke, and risk for bleeding.[17,18]
- For patients with a higher stroke risk (CHA_2DS_2-VASc score ≥4), uptake of DOACs was initially slower but apixaban became the most prescribed oral anticoagulant in this patient population in 2016.
- In 2010, women were more likely prescribed warfarin than men. However, with the increased uptake of DOAC prescriptions in women, more women were prescribed apixaban compared to men in 2017.

    - A meta-analysis demonstrated that women had a lower risk of major bleeding when treated with a DOAC compared to men.[19]
- In patients ≥75 years, prescriptions for warfarin remained higher than dabigatran or rivaroxaban from 2010 to 2017. Apixaban was generally preferred over the other DOACs (dabigatran and rivaroxaban) in elderly patients, women, and patients with higher risk for stroke, higher risk for bleeding or more comorbidities.
    - Meta-analyses have shown that there is no significant difference between DOACs and warfarin for ischemic stroke prevention. In randomized controlled trials, dabigatran was more effective compared to warfarin in RE-LY and apixaban was more effective in ARISTOTLE studies.[20,21] However, the risk of any bleeding, major bleeding or death is lower for apixaban and dabigatran compared to warfarin.[12]
    - Gastrointestinal bleeding was higher compared to warfarin for dabigatran 150mg twice daily dosing and rivaroxaban 20mg daily dosing.
- Dabigatran was mostly prescribed in younger patients with the lowest Charlson comorbidity index, risk for ischemic stroke and risk for bleeding.[17]

Conclusion

- Since the introduction of dabigatran in 2010, there has been an increased uptake of DOACs compared to warfarin in patients with atrial fibrillation.
- If patients received warfarin, they were more likely elderly and had a higher bleeding risk, stroke risk and more comorbidities.
- DOACs are increasingly becoming the oral anticoagulant of choice.
- Dabigatran is KPWA's preferred DOAC. Warfarin is still considered cost-effective and may be preferred in certain patients monitored by AMS.

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New Requirements in Opioid Prescribing

By Mena Raouf, PharmD, BCPS; Reviewed by Melissa Sturgis, PharmD, BCACP

Key points:

- In July 2018, opioid prescription quantity limits were placed for opioid naïve KPWA commercial patients for acute pain.
- As of October 1, 2018, KPWA commercial patients require an annual attestation if they are on chronic high dose opioid therapy.
- As of January 1, 2019, opioid naïve KPWA Medicare patients who require opioid prescriptions for acute pain will be limited to a 7-day supply.

Background

- In response to the National Opioid Crisis and the 2016 CDC Opioid Prescribing Guidelines, Washington state, Centers for Medicare & Medicaid Services (CMS), and many health plans including Kaiser Permanente Washington are implementing new prescribing requirements to improve opioid safety. **Tables 1 and 2** summarize some of the more significant changes.

Changes at Kaiser Permanente Washington

- Quantity limits for new opioid prescriptions in patients who are opioid naïve on pharmacy claims review were implemented for commercial patients in July 2018, and will start January 2019 for Medicare patients (**Table 1**).

- Pharmacy claims where opioid dose is > 90 morphine milligram equivalent (MME) require prior authorization for commercial members and will prompt a pharmacy review in 2019 for Medicare members (**Table 2**).
- General questions related to opioid prescribing limits may be directed to the Kaiser Permanente Washington Pharmacy Drug Benefit Help Desk.
    - **Hours:** Monday through Friday 8 a.m. to 6 p.m.
    - **Phone:** (206) 901-4411, option 1, or toll-free (800) 729-1174, option 1

Table 1. Quantity Limits in Acute Pain Prescribing in Opioid naïve patients

	KPWA Commercial	KPWA Medicare
Quantity Limit	**Age ≥ 21:** Max 42 doses or 210 mL of short-acting opioid **Age <21:** 18 doses or 90 mL of short-acting opioid	***Beginning January 1, 2019*** A 7 days' supply quantity limit
Definition of Opioid Naïve	<7 day supply within last 180 days	***Beginning January 1, 2019***, no opioids in 120-day look-back period.
Is a Point-of-Service (pharmacy) Override Available?	No, requires pharmacies to adjust dispensed quantity to quantity limit or call the Kaiser Permanente Washington Help Desk to request an override.	No, requires pharmacies to adjust dispensed quantity to the 7 day quantity limit or call the KPWA Help Desk to request an override.
Exceptions	Cancer, Hospice, Palliative Care	Cancer, Hospice, Palliative care

Table 2. Monitoring Requirements for Chronic High Dose Therapy (> 90 MME)

	KPWA Commercial	KPWA Medicare
Requirement	Annual Prior Authorization/Provider Attestation required for Chronic Opioid Therapy (COT). WPMG providers documenting in the EPIC EMR, completing COT standard work utilizing COT tools fulfills this requirement.	**New in 2019**: Pharmacy staff will be required to use override codes that identify that prescriber was consulted and will need to document the encounter with provider.
Is a Point-of-Service (pharmacy) Override Available?	No. This notice requires pharmacies to call the KPWA Help Desk to request an override.	Yes, but in 2019, the override will require that the pharmacist have a discussion with the provider.
Exceptions	Cancer, Hospice, Palliative Care	Cancer, Hospice, Palliative care

Additional Medicare POS pharmacy messaging required by CMS beginning January 1, 2019, include drug-drug interaction screening for opioid claims filled after buprenorphine medication assisted treatment (MAT) and combinations of opioid and benzodiazepines. For a complete list of changes, see the CMS 2019 Call Letter.

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FDA Medication Alert

Drug	Safety Alert	Link
Fluoroquinolones	**Increased Risk of Aorta Dissection or Aneurysm** The use of systemic fluoroquinolone antibiotics (both oral and injections) may increase the occurrence of aortic dissections or ruptures. Providers should avoid prescribing fluoroquinolones to patients with history or at high risk of aortic aneurysm unless no other treatment options available. Educate patients on symptoms suggestive of aortic aneurysm or dissection.	Link
Fingolimod (Gilenya®)	**Severe Worsening of Multiple Sclerosis After Stopping Gilenya®** When Gilenya® (fingolimod) is stopped for the treatment of multiple sclerosis (MS), the disease can become much worse than before the medicine was started or while it was being taken. This MS worsening is rare but can result in permanent disability. Providers should remind patients to not self-discontinue fingolimod prior to speaking with their healthcare team.	Link

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