



**Indian Health Service
National Pharmacy and Therapeutics Committee**



**Antiplatelet Agents: Clopidogrel and Prasugrel
March 2011**

Introduction:

Coronary artery disease (CAD) is a frequently encountered disease seen in the United States. It is a major contributor to morbidity, mortality and healthcare costs. An estimated 2200 Americans die of cardiovascular disease (CVD) each day and just over 1 in 3 American adults have 1 or more types of CVD. There are approximately 470,000 recurrent myocardial infarctions each year.¹

For American Indian/Alaska Natives (AI/AN), CVD is frequently encountered. According to the IHS Fact Sheets, “Diseases of the heart, malignant neoplasm, unintentional injuries, diabetes mellitus, and cerebrovascular disease are the five leading causes of Indian deaths (2004-2006).”² This contributes to a life expectancy that is 5.2 years less than the all race population in the US. The mortality rate for AI/AN for cerebrovascular death is 46.6, while heart disease is 206.2 (age-adjusted mortality rates per 100,000 population).³ In some of the geographic regions, the CVD mortality rate was similar to the US averages, but it was two times higher in the Dakotas.⁴ Stroke rates for AI/AN have not declined as quickly as with those of Caucasian and African American descent.⁵ Overall prevalence numbers for stroke are currently not reported.¹

Risk factors for CVD are well documented and include hypertension, cigarette smoking, elevated LDL cholesterol, obesity, sedentary lifestyle and eating an atherogenic diet.⁶ Many AI/AN patients have risk factors that are commonly associated with CVD. For instance, cigarette smoking is common within AI/AN communities, at rates of approximately 42.2% for men and 36.7% for women.⁷ The rate of these important CVD risk factors is highest for any race or ethnicity in the US.⁷⁻⁸ While AI/ANs have similar cardiovascular risks as other populations, they have a higher propensity for the development of diabetes, an important risk factor in the development of CVD.⁸ Those of AI/AN descent also have a high frequency of having two or more risk factors (46.7%).⁴

These numbers show the importance of primary prevention measures, targeting the risk factors listed above. Secondary prevention measures should not be overlooked. One such secondary prevention measure is the use of dual antiplatelet agents for patients after experiencing an acute coronary event. The ACC/AHA guidelines for the treatment of UA/NSTEMI recommend the use of clopidogrel (75mg/day) and aspirin (75-162mg/day) indefinitely for patients treated medically without stenting. They also recommend dual therapy for patients treated with stent placement, ideally for one year.⁹⁻¹⁰ It should be noted that prasugrel was not approved for use in the United States when these guidelines were written.

This monograph provides an overview of two antiplatelet agents used in the United States, Plavix® (clopidogrel) and Effient® (prasugrel).

Pharmacology/Pharmacokinetics:¹¹⁻¹³

Clopidogrel:

Mechanism of Action: irreversible binding to P2Y₁₂ class of ADP receptors on platelets by its active metabolite. This prevents activation of the GPIIb/IIIa receptor complex, thus reducing platelet aggregation. This reduction is seen for the lifespan of the platelet, approximately 7-10 days.

Prasugrel:

Mechanism of Action: irreversible binding to P2Y₁₂ class of ADP receptors on platelets to inhibit platelet activation and aggregation. This reduction is seen for the lifespan of the platelet, approximately 7-10 days.

Table 1. Pharmacokinetic Properties¹¹⁻¹⁴

Drug	Absorption	Distribution	Metabolism	Excretion
Clopidogrel	Rapidly absorbed Bioavailability: ~50% Food: no effect	Cmax ~30-60 minutes after dosing T1/2=6 hours (clopidogrel) T1/2=0.5-0.7 hours (active metabolite)	CYP2C19 is the primary (CYP3A, CYP 2B6 and CYP 1A2 also involved)	~50% in urine and ~46% in feces
Prasugrel	Rapidly absorbed Bioavailability: ~79% Food: delayed absorption, but no effect on extent.	Cmax ~30 minutes after dosing T1/2=7 hours Vd=44-68 L	Via hydrolysis in intestine and to active metabolites via CYP3A4 and CYP2B6 as primary (CYP2C9 and CYP2C19 also involved)	~68% in urine and ~27% in feces

Pharmacodynamic/Pharmacokinetic Studies:

Mega and colleagues conducted a pharmacogenetic analysis of 2932 patients from the TRITON-TIMI 38 study.¹⁵ These patients had ABCB1 genotype. It is thought that ABCB1 polymorphisms (especially 3435C→T) may affect drug transport and therapeutic efficacy. This analysis evaluated the effect of an ABCB1 3435C→T genotype, variants of CYP2C19 and the rates of the primary endpoint (cardiovascular death, MI or stroke) for patients taking either clopidogrel (n=1471) or prasugrel (n=1461). The findings from this analysis suggest patients with ABCB1 3435C→T genotype and treated with clopidogrel, have a statistically significant risk of the primary endpoint (p=0.0064). Additionally, patients with reduced CYP2C19 function were at increased risk for the primary end-point. There were limitations to this study that should be taken into consideration.

SWAP Study: A pharmacodynamic study was conducted by Angiolillo and colleagues from multiple sites in the United States.¹⁶ This randomized, double-blind, double-dummy, active-control study assessed the pharmacodynamic effects of switching post ACS patients from maintenance clopidogrel to either placebo loading dose (LD)/clopidogrel 75mg maintenance dose (MD), placebo (LD)/prasugrel 10mg MD or prasugrel 60mg LD/10mg MD. Platelet function was measured at 2 hours, 24 hours, 7 days and 14 days. The prasugrel patients had a greater reductions in platelet function with the LD at 2 hours and with the MD by day 7. Of note, this was a pharmacodynamic study and did not analyze hard clinical end-points.

ACAPULCO: Montalescot et.al conducted a randomized, double-blind, cross-over pharmacodynamic study of patients with ACS.¹⁷ All patients received a 900mg clopidogrel LD with aspirin, then a 14-day MD of prasugrel 10mg daily or clopidogrel 150mg daily. Patients then switched to the alternate therapy for 14 days. Platelet function was measured after the LD, at cross-over and at study completion. The data revealed:

- Further reduction with prasugrel MD (day 15) versus clopidogrel 900mg LD (p=0.011)
- Greater reduction with prasugrel MD (day 15) versus clopidogrel 150mg MD (p=0.008)

- Greater reduction with prasugrel MD (day 29) versus clopidogrel 150mg MD (p<0.001)

Similar to previously discussed studies, this was a pharmacodynamic study and did not include hard clinical outcomes. It was based on surrogate end-points of platelet inhibition and had a small number of subjects (n=43). It used clopidogrel dosing that was higher than frequently utilized in the United States (900mg LD, 150 MD), yet the prasugrel group yielded greater platelet inhibition. This study size was not large enough to assess safety, but reported no serious bleeding risks. Additionally, this study was of short duration.

An additional pharmacokinetic/pharmacodynamic study of prasugrel versus clopidogrel was published by Varenhorst and colleagues.¹⁸ This study compared the effect of genetic variations of CYP2C19 (extensive metabolizer, EM; reduced metabolizer, RM) in patients with stable CAD. It was a randomized, double-blind, double-dummy, two-arm parallel-group study that included 98 patients and compared platelet inhibition of prasugrel 60mg LD/10mg MD to clopidogrel 600mg LD/75mg MD. With prasugrel, no difference was seen with the pharmacokinetics in those with reduced CYP2C19 metabolism (p=0.6361). Lower total plasma exposure was noted with the RM clopidogrel group versus EM clopidogrel group (p=0.0015). Prasugrel LD active metabolite exposure was higher in the EM group versus the clopidogrel LD (p=0.000). Clopidogrel treated patients with RM revealed a reduced pharmacodynamic response as compared to the prasugrel RM group. Limitations to this study are similar to others listed as these were surrogate endpoints versus clinical outcomes and included a small number of subjects. Additionally, the sample size did not include a sufficient number of subjects with decreased CYP3A4 as this pathway is involved in metabolizing both drugs.

FDA Approved Indications:¹¹⁻¹²

Clopidogrel:

- Non-ST segment elevation acute coronary syndrome (ACS) [Unstable angina (UA) / (Non-ST-elevation myocardial infarction (NSTEMI)
- ST-elevation myocardial infarction (STEMI)
- Recent MI, recent stroke, or established peripheral arterial disease (PAD)

Prasugrel:

- ACS patients who are to be managed with PCI (percutaneous coronary intervention) (including stent thrombosis)
- UA/NSTEMI
- STEMI when managed with either primary or delayed PCI

Current National Core Formulary Alternatives:¹⁹

Clopidogrel bisulfate is currently on the IHS National Core Formulary (NCF).

Table 2. Dosage and Administration:¹¹⁻¹²

Agent	Indication	Dosage	Special Considerations
Clopidogrel	ACS/NSTEMI	300mg oral loading dose, then 75mg once daily; use in combination with aspirin 75-325mg once daily.	Pregnancy Cat. B
	STEMI	75mg once daily orally, in combination with aspirin 75-525mg once daily	No dosage adjustment for hepatic impairment
	Recent MI, stroke or PAD	75mg once daily orally	Limited experience with severe and moderate renal impairment
Prasugrel	ACS with PCI	60mg oral loading dose, then 10mg once daily; use in combination with aspirin 75-325mg daily	Pregnancy Cat. B
	UA/NSTEMI	Note: for patients <60kg, consider maintenance dose of 5mg (effectiveness/safety of 5mg dose have not been prospectively studied)	No dosage adjustment for mild/moderate hepatic impairment
	STEMI with PCI		No renal dosing needed

Guidelines/Systematic Reviews:**NICE²⁰**

In September, 2010, the National Institute for Health and Clinical Excellence (NICE) completed a review of the use of prasugrel for the treatment of ACS with PCI. This group provides systematic reviews for the United Kingdom National Health System. They noted that much of the review was based on the TRITON-TIMI 38 trial, a comparison of prasugrel and clopidogrel. It pointed out that, while there were statistically significant reductions in the composite end-point, non-fatal MI and stent thrombosis, it was associated with an increased rate of major bleeds. This document pointed out some areas of limitation within the study that may have contributed to the findings seen in TRITON-TIMI 38. These include:

- Study used clopidogrel 300mg loading dose instead of the frequently used 600mg loading dose

- Study findings based on composite endpoints
- Study was limited to 15 months for follow-up
- Dosing with 300mg versus 600mg may have contributed to the greater reductions seen with the prasugrel group in the diabetic population

It was noted that the delayed onset by clopidogrel as compared to that of prasugrel may be an important advantage when immediate PCI is needed.

Because of this information, the use of prasugrel was seen as an optional agent and may be used with aspirin for:

- patients with ACS and PCI when immediate PCI for STEMI is necessary
- patients with stent thrombosis with clopidogrel treatment
- diabetes mellitus patients with ACS and PCI

ACC/AHA 2007 UA/NSTEMI Guidelines¹⁰

The 2007 ACC/AHA guidelines for the management of UA/NSTEMI provided recommendations for both the diagnosis and the treatment of patients with known or suspected CVD. This guidance was developed using a compilation of published studies since 2002. In this guideline, aspirin should be given to patients as soon as possible and continued indefinitely. If they have contraindications for use, clopidogrel* should be used. If an invasive approach will be utilized (PCI), clopidogrel* (loading dose then maintenance dose) or an IV GPIIb/IIIa inhibitor (abciximab, eptifibatide, tirofiban) should be added to aspirin and used before the procedure. For noninvasive strategies, clopidogrel should be added to aspirin for at least one month, preferably up to one year.

ACC/AHA/SCAI 2007 PCI Guideline Update⁹

Similar to the ACC/AHA UA/NSTEMI guidelines, the 2007 guideline update for PCI was compiled from updated published studies to provide guidance on the use of PCI. Aspirin is again a mainstay in therapy with PCI. A 600mg loading dose of clopidogrel* should be given before or when PCI is performed. When drug-eluting stents (DES) are used, clopidogrel* therapy should be continued for at least 12 months (†class I recommendation) and continuation may be considered (††class IIb recommendation). If a bare metal stent (BMS) is placed, clopidogrel* should be given for at least 1 month, preferably up to 12 months.

ACC/AHA 2007 STEMI Guideline Update²¹

The 2007 ACC/AHA guideline update provided guidance on acceptable approaches to the diagnosis and management of STEMI based upon available data from publications since the last guidance document. Clopidogrel* is recommended to be added to aspirin in all patients with STEMI regardless of whether they received reperfusion therapy with a fibrinolytic. Clopidogrel* should be continued for at least 14 days with STEMI. Clopidogrel* should be held for at least 5 days, with a preference to 7 days, for patients with planned CABG. With STEMI treatment, long-term clopidogrel* therapy should be considered (††class IIa recommendation). Of note, this guidance does not recommend a loading dose in patients older than 75 years of age and receiving fibrinolytic therapy.

(*prasugrel unavailable at time of publication; † benefit much greater than risk; procedure/treatment **should** be performed/administered; †† benefit greater than or equal to risk; procedure/treatment **may be considered**)

Efficacy:

TRITON-TIMI 38

Wiviott and colleagues published the results from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 in 2007.²² This pivotal trial included 13,608 patients with moderate-to-high-risk ACS (10,074 with UA/NSTEMI, 3534 with STEMI) and with scheduled PCI. Patients were randomized to receive aspirin (75-162mg) plus clopidogrel (300mg LD/75mg MD) or prasugrel (60mg LD/10mg MD) for 6 to 15 months. Prasugrel was associated with a reduction in the composite primary endpoint (9.9% vs. 12.1%; HR 0.81; 95% CI 0.73-0.9; p<0.001). That cohort of patients with UA/NSTEMI saw a more favorable benefit with prasugrel (HR, 0.82; 95% CI, 0.73-0.93; p=0.002). Within the STEMI cohort, a significant benefit in favor of prasugrel was observed (HR, 0.79; 95% CI, 0.65-0.97; p=0.02).

Overall, patients with diabetes tended to derive a greater benefit from prasugrel (17% vs. 12.2%; HR 0.70; 95% CI 0.58-0.85; p<0.001). However, patients with a history of TIA/stroke (HR 1.54; 95% CI, 1.02-2.32; p=0.04) had a net harm from prasugrel, while patients age ≥ 75 years (HR 0.99; 95% CI, 0.81-1.21; p=0.92) or with a body weight of less than 60kg had no net benefit with prasugrel (HR 1.03; 95% CI, 0.69-1.53; p=0.89).

It must be noted that there are potential limitations that must be considered when reviewing these data. The study utilized a 300mg LD, while a 600mg dose is generally recommended in clinical practice.⁹ Additionally, the timing of the LD, with 75% of patients receiving the drug during PCI may have contributed to the findings, as there is a slightly delayed antiplatelet effect with clopidogrel.

Table 3. Efficacy Outcomes from TRITON-TIMI 38²²

Endpoint	Prasugrel (n=6813)	Clopidogrel (n=6795)	HR (95% CI)	P Value	ARR	NNT
*Composite of CV death, nonfatal MI, nonfatal stroke	9.9%	12.1%	0.81 (0.73-0.9)	<0.001	2.2%	46
CV Death	2.1%	2.4%	0.89 (0.7-1.12)	0.31	0.3%	-
Nonfatal MI	7.3%	9.5%	0.76 (0.67-0.85)	<0.001	2.2%	46
Nonfatal Stroke	1%	1%	1.02 (0.71-1.45)	0.93	-	-
Stent Thrombosis	1.1%	2.4%	0.48 (0.36-0.64)	<0.001	1.3%	77

*primary end-point

TRITON-TIMI 38 Subgroup Analyses:

A subgroup analysis of the TRITON-TIMI 38 trial was published by O'Donoghue and colleagues that analyzed the efficacy and safety of prasugrel and clopidogrel with patients who received a GP IIb/IIIa inhibitor.²³ This study had 7414 patients who received a GP IIb/IIIa inhibitor. The authors note a consistent benefit of prasugrel over clopidogrel for reducing the primary end-point (composite of CV death, nonfatal MI or nonfatal stroke; follow-up 15 months; with GP IIb/IIIa HR: 0.76; 95% CI: 0.64-0.90; without GP IIb/IIIa, HR: 0.78; 95% CI: 0.63-0.97). Major and minor bleeding at 30 days yielded a significant increase in non-CABG-related bleeding with prasugrel compared to clopidogrel (HR: 1.26; 95% CI: 1.01-1.75, p=0.04), but was similar regardless of whether a GP IIb/IIIa inhibitor was used (with: HR: 1.16; 95% CI: 0.89-1.50; without: HR: 1.62, 95% CI: 1.05-2.52). Limitations were noted as this was a subgroup analysis with the use of GP IIa/IIIa inhibitor non-randomized. Specific safety and efficacy outcomes in the GP IIb/IIIa inhibitor group were not compared. As noted elsewhere, this study compared clopidogrel 300mg LD/75mg MD versus the commonly prescribed 600mg LD/75mg MD.

A subgroup analysis of the TRITON-TIMI 38 was conducted by Montalescot et.al.²⁴ This analysis focused on a cohort of patients with STEMI requiring PCI. It included 3534 participants randomized to

receive prasugrel 60mg LD/10mg MD or clopidogrel 300mg LD/75mg MD with a composite primary endpoint (CV death, non-fatal MI or non-fatal stroke). Patients were followed at 30 days and 15 months. At 30 days, the data favored prasugrel (6.5% vs. 9.5%; HR; 0.68; CI 0.54-0.87; p=0.0017) and continued to 15 months (10% vs. 12.4%; HR 0.79; CI 0.65-0.97; p=0.025). These data were similar to that of the UA/NSTEMI group. TIMI major bleeding after CABG was significantly increased with prasugrel (p=0.0033). It should be noted that there were slight differences in patient characteristics that may have accounted for these results.

Adverse Events:¹¹⁻¹⁴

Clopidogrel:

- Bleeding: most commonly reported and may be life-threatening or fatal. (4% major; 5% minor)
- Hematologic: <1% agranulocytosis, aplastic anemia, TTP (<0.4%)
- Colitis (<1%)
- Respiratory: Bronchospasm, interstitial pneumonitis

Prasugrel:

- Bleeding: most commonly encountered
- Hypertension (7.5%), hyperlipidemia (7%), headache (5.5%)
- Neoplasm of colon noted
- TTP

Precautions/Contraindications:¹¹⁻¹⁴

Clopidogrel:

Boxed Warning

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.**
- **Poor CYP2C19 metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following ACS or PCI than with patients with normal CYP2C19 function.**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.**

Contraindications

- Active bleeding (e.g. peptic ulcer or intracranial hemorrhage (ICH))
- Hypersensitivity

Precautions

- Avoid concomitant use with strong or moderate CYP2C19 inhibitors (e.g. omeprazole)
- Bleeding: increased risk of bleeding; discontinue 5 days before elective surgery
- Premature discontinuation increases risk of cardiovascular events
- Recent TIA or stroke: Use of clopidogrel with aspirin in this population has not been shown to be more effective than clopidogrel monotherapy, but has a higher bleeding risk
- TTP has been reported with clopidogrel, with some fatal

Prasugrel:

Boxed Warning

- Effient can cause significant, sometimes fatal, bleeding
- Do not use Effient in patients with active pathological bleeding or a history of TIA or stroke.
- In patients ≥ 75 years of age, Effient is generally not recommended because of the increased risk of fatal and ICH and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered.
- Do not start Effient in patients likely to undergo urgent CABG. When possible, discontinue Effient at least 7 days prior to surgery.
- Additional risk factors for bleeding include:
 - Body weight < 60 kg
 - Propensity to bleed
 - Concomitant use of medications that increase the risk of bleeding
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG or other surgical procedures in the setting of Effient.
- If possible, manage bleeding without discontinuing Effient. Stopping Effient, particularly in the first few weeks after ACS, increases their risk of subsequent cardiovascular events.

Table 4. 15 month safety data, TRITON-TIMI 38²²

Endpoint	Prasugrel (n=6813)	Clopidogrel (n=6795)	HR for prasugrel (95% CI)	P Value
Non-CABG related TIMI major bleeding (key safety end point)	146 (2.4%)	111 (1.8%)	1.32 (1.03-1.68)	0.03
Major or minor TIMI bleeding	303 (5%)	232 (3.8%)	1.31 (1.11-1.56)	0.002
Bleeding requiring transfusions	244 (4%)	182 (3%)	1.34 (1.11-1.63)	< 0.001
CABG-related TIMI major bleeding	24 (13.4%)	6 (3.2%)	4.73 (1.90-11.82)	< 0.001

Contraindications

- Active bleeding
- Prior TIA or stroke
- Hypersensitivity

Precautions

- Bleeding risk is increased in patients who take prasugrel and undergo CABG
- Increased risk of stent thrombosis, MI and death with premature discontinuation
- TTP has been reported

Look-alike/Sound-alike Error Risk Potential:^{13-14, 25}

Clopidogrel:

Plavix may be confused with Elavil, Paxil

Prasugrel:

Effient may be confused with EtheDent

Prasugrel may be confused with pravastatin, propranolol

FDA Risk Evaluation and Mitigation Strategy (REMS):²⁶

Clopidogrel: None

Prasugrel:²⁷ Medication guide, communication plan

Goal: To mitigate the serious risk of bleeding associated with its use.

Drug Interactions:¹¹⁻¹²

Clopidogrel:

- Warfarin-increased risk of bleeding (note: no effect on pharmacokinetics of warfarin or INR)
- Non-steroidal Anti-Inflammatory Drugs (NSAID)-increased risk of gastrointestinal bleeding
- CYP2C19 inhibitors-metabolized in part by CYP2C19, therefore CYP2C19 inhibitors reduce plasma concentrations of the active metabolite and reduce platelet inhibition.
- Omeprazole-reduced plasma concentration of the active metabolite and platelet inhibition

Prasugrel:

- Warfarin-increased risk of bleeding
- NSAID-increase risk of bleeding with chronic use

Conclusions:

Prasugrel appears to be an option to consider for patients with ACS, UA/NSTEMI and STEMI, when undergoing PCI. Pharmacodynamic and pharmacokinetic studies show a quicker onset and an enhanced antiplatelet effect when compared to currently utilized doses of clopidogrel. It appears to show no reduction in antiplatelet effect when used in patients who have reduced CYP2C19. An additional theoretical benefit in the IHS is its benefit in the diabetic population, a disease frequently encountered in IHS facilities. However, these effects come with a higher bleeding rate as compared to clopidogrel. It appeared to be less effective in patients ≥ 75 years old and those < 60 kg. Additionally, it was found to have a net harm when compared to clopidogrel, for patients with TIA or stroke. Clopidogrel has the added FDA approved indication for the treatment of stroke, PAD and recent MI. Since prasugrel does not carry the same approved indications, it would not seem feasible to have prasugrel as a sole agent from this class.

Recommendations:

While prasugrel appears to be a reasonable agent to use, it seems reasonable to recommend that clopidogrel remain as the named agent on the NCF for the reasons listed above.

Relevant Acronyms:

CAD	Coronary artery disease
CVD	Cardiovascular disease
AI/AN	American Indian/Alaska Native
LD	Loading dose
MD	Maintenance dose
EM	Extensive metabolizer

RM	Reduced metabolizer
ACS	Acute coronary syndrome
NSTEMI	non-ST segment elevation myocardial infarction
STEMI	ST segment elevation myocardial infarction
PCI	percutaneous coronary intervention
UA	unstable angina
MI	myocardial infarction
CABG	Coronary artery bypass grafting
INR	International normalized ratio
CYP	Cytochrome P450
NSAID	Non-Steroidal anti-inflammatory drug
REMS	Risk Evaluation and Mitigation Strategy
TIA	Transient Ischemic Attack
PPI	Proton pump inhibitor
VA	Department of Veterans Affairs
TRITON-TIMI	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction
ICH	Intracranial hemorrhage
TTP	Thrombotic Thrombocytopenic Purpura
GP IIb/IIIa inhibitor	abciximab/epitifibatide/tirofiban
DES	drug-eluting stent
BMS	bare-metal stent
NICE	National Institute for Health and Clinical Excellence
NNT	Number Needed to Treat
HR	Hazard Ratio
CI	95% confidence interval
PAD	Peripheral artery disease
FDA	United States Food and Drug Administration
NCF	IHS National Core Formulary
NICE	National Institute for Health and Clinical Excellence

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