Long-term Efficacy of Early Varenicline Use in Hospitalized Patients with Acute Myocardial Infarction: Taiwanese Population

Hsuan-Wei Chu[1,2], Chun-Hung Su[1,2], Chin-Feng Tsai[1,2], Chia-Yen Li[3], Shao-Fan Huang[1], Chi-Hua Yen[2,4], Ci-Wen Luo[5], Ying-Chao Lee[1], Meng-Hsun Yu[6,7], Kuei-Chuan Chan[1,2*], Chien-Hsien Lo[2,8*]

[1]*Division of Cardiology, Department of Internal Medicine, Chung-Shan Medical University Hospital, Taichung, Taiwan*
[2]*School of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[3]*Department of Nursing, Chung-Shan Medical University Hospital, Taichung, Taiwan*
[4]*Department of Family and Community Medicine, Chung-Shan Medical University Hospital, Taichung, Taiwan*
[5]*Department of Medical Research, Tungs' Taichung MetroHarbor Hospital. Taichung 435, Taiwan*
[6]*Department of Nutrition, Chung Shan Medical University, Taichung 402, Taiwan*
[7]*Department of Nutrition, Chung Shan Medical University Hospital, Taichung 402, Taiwan*
[8]*Division of Cardiology, Department of Internal Medicine, Dachien General Hospital, Miaoli, Taiwan*
**Dr. Kuei-Chuan Chan and Dr. Chien-Hsien Lo made identical contributions as co-corresponding authors to this paper*

Abstract

Background: Cardiovascular diseases (CVD) are a leading cause of death globally, with smoking being a major contributing factor. Varenicline, an effective aid for smoking cessation, has been proven to be effective even after acute myocardial infarction (AMI). However, in Taiwan, the evidence regarding immediate administration of varenicline to AMI patients, and its medium to long-term effects, still contains many aspects that remain unclear.

Methods: In this prospective, observational, single-center study, we collected data from smoking patients admitted for AMI and treated with percutaneous coronary intervention (PCI) from May 2018 to July 2021. These participants were tracked for a mean 3.3 years after medication with varenicline, focusing on successful cessation rate and cardiac events after treatment.

Results: Of the patients observed, 76.2% reported cessation at 24 weeks. At 3.3 years, the cessation rate was 50.3%. While patients with ST-segment elevation myocardial infarction (STEMI) and elderly patients achieved a significantly higher rate of cessation, there were no significant cardiac outcome differences between the successful cessation-experienced group and the failure group. Composite major events (including MI, non-fatal stroke and death) were significantly higher in the non-STEMI group than in the STEMI group (24.07% vs. 7.06% p<.005).

Conclusion: Our study suggests that early varenicline use is effective for smoking cessation after AMI in the Taiwanese population, yielding high long-term cessation rates, especially in STEMI and older patients.

Keywords: varenicline, smoking cessation, acute myocardial infarction, cardiovascular diseases, percutaneous coronary intervention

Received: Nov. 17, 2023; Accepted: Dec. 2, 2023
Address for correspondence: Dr. Chien-Hsien Lo
Division of Cardiology, Department of Internal Medicine, Da Chien General Hospital; No. 36, Gongjing Road, Miaoli City 360, Taiwan
Tel: +886-37-357125 ext. 64008; Fax: +886-37-362813; Email: myintoolwin@gmail.com

Introduction

In the past few decades, there have been significant improvements in mortality and risk associated with acute coronary syndrome (ACS).[1] However, despite these advances, cardiovascular diseases (CVD) remain a leading cause of death globally. For instance, in Taiwan, cardiovascular-related deaths rank second, according to data from the Ministry of Health and Welfare.[2] Clinicians, in addition to treating CVD, often emphasize the detrimental effects of smoking on cardiovascular health. For patients diagnosed with CVD, the risk of recurrence is notably higher for those who continue to smoke, compared to their non-smoking counterparts.[3] Disturbingly, smokers who undergo percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) suffer worse prognoses, compared to non-smokers.[4] In three cohorts comprising 6,519 patients (EPIC, EPILOG, and EPISTENT), smokers were more likely to suffer death, myocardial infarction (MI) or urgent vascular reconstruction within 30 days post-PCI.[5] Similarly, in the SYNTAX trial, smoking was identified as an independent predictor of adverse outcomes.[6] While Taiwan has witnessed a significant reduction in adult smoking habits over the last 12 years,[2] smoking will likely remain a principal cause of preventable deaths throughout this century. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, has emerged as a promising agent in the quest for effective smoking cessation therapy. However, despite its potential, research on the effects of Varenicline for immediate prescription after acute myocardial infarction (AMI) remains limited, especially in the Asian population.

While short-term safety and side effects of varenicline have been reported,[7] proof of long-term maintenance and protective effect is still extant. Our study aims to ascertain the long-term smoking cessation efficacy and secondary prevention benefits of early varenicline use for smoking cessation in post AMI patients.

Methods

This is a single-center, prospective observational study. Data on smoking patients admitted for and treated with PCI were collected and analyzed. These patients were tracked for their two-year outcomes post-procedure and their use of varenicline for smoking cessation. This research has been approved by the Research Ethics Committee of Chung Shan Medical University and Hospital [CS1-22034].

Study Participants

The primary study group consisted of patients who had experienced an AMI event and were current smokers. Data were collected from patients admitted between May 2018 and July 2021 who underwent emergency PCI for AMI, including ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (non-STEMI). The index date was defined as the date of the AMI indicated PCI procedure. The setting for this research was Chung Shan Medical University hospital. Consenting participants were offered high-intensity counseling and were prescribed varenicline for smoking cessation.

Study exclusion criteria included:

1. Patients with a previous MI event within 6 months before the index date.
2. Patients who smoked less than 10 cigarettes per day or had less than 10 pack-years of smoking.
3. Individuals aged less than 18 years old.
4. Patients who had used other smoking cessation medications within the last six months.
5. Patients who had previously used varenicline before the AMI.
6. Patients who could not be contacted or whose smoking status during the follow-up period was unconfirmed.

Intervention and Medication Details

The treatment course spanned an 8-week period. Varenicline dosage was scheduled as follows: 0.5 mg once daily for days 1-3, 0.5 mg twice daily for days 4-7, and 1.0 mg twice daily

from day 8 onward. Side effects, withdrawal symptoms, medication adherence and smoking status were recorded during the follow-up visits with dosage adjustments or termination made as needed. Smoking abstinence was defined as self-reported complete abstinence over 7 days, recorded through telephone contact or clinic visit.

Follow-up and Data Collection

The primary endpoint focused on the efficacy of varenicline. Other serious adverse cardiac events such as MI, non-fatal stroke, all-cause mortality, or coronary revascularization, were also collected and reviewed at two check points.

Additional counseling, phone calls and outpatient department (OPD) visits conducted up to the 24th week, defined as short-term, served as the first checkpoint — a common duration included and maintained in most studies for comparison. A telephone follow-up was scheduled for August 2023, defined as the long-term period, marking the second checkpoint, to assess the long-term outcomes. This long-term follow-up period ranged from a minimum of 2.2 years to a maximum of 5.5 years (mean 3.3 years) and included evaluations of smoking relapse and major health events, as previously mentioned.

Results

A flowchart of study participant selection is shown in Figure 1. From 2018 to 2021, we enrolled 602 participants in our study (STEMI: 330, non-STEMI: 272 patients) who were hospitalized due to AMI. A significant portion (412 patients, 68.4%) were non-smokers and were hence excluded from the study, leaving 190 current smokers that satisfied our criteria. Of these remaining patients, 6 declined to take varenicline, another 6 were on different smoking cessation

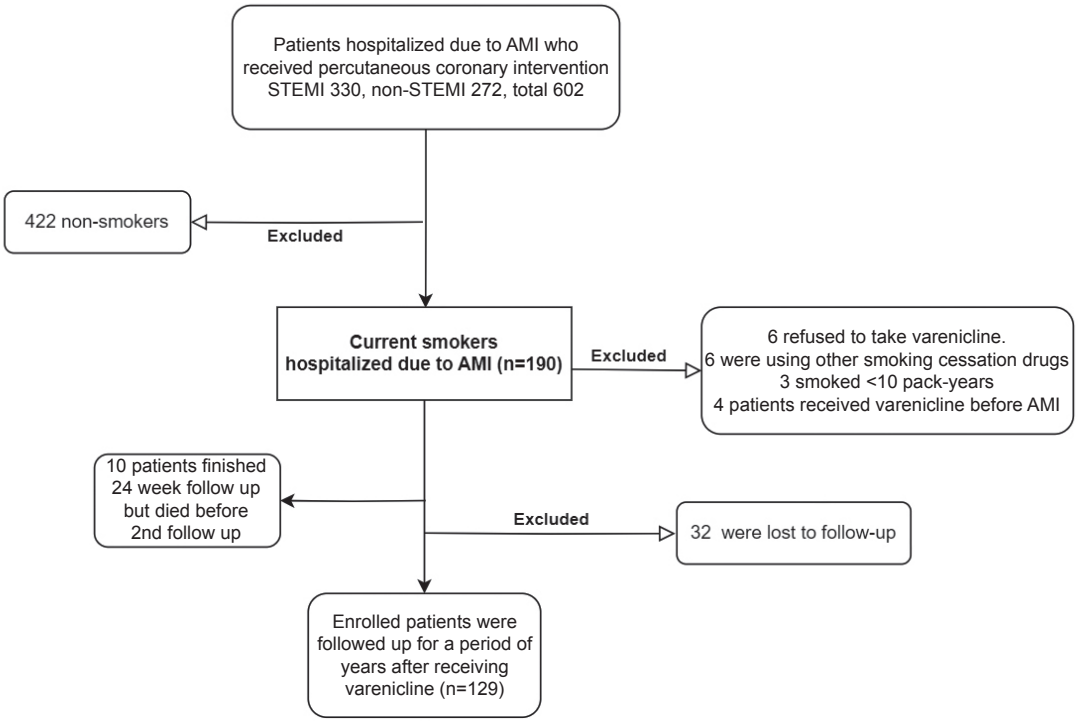


Figure 1. Flowchart of patient selection process.
STEMI: ST-segment elevation myocardial infarction; Non-STEMI: Non-ST segment elevation myocardial infarction.

medications, 3 were excluded because their smoking history covered less than 10 pack-years, and 4 patients had received varenicline before the AMI event. Furthermore, 13 participants were lost to follow-up before the 24th week, and 19 participants were lost to follow-up before August 2023. A total of 139 patients, all of whom had a smoking habit of ≥10 cigarettes per day and a history of ≥10 pack-years, completed the 24th week follow-up, and 10 patients died before August 2023. Among the 129 patients who completed both follow-up assessments, the mean follow-up duration since initiation of varenicline treatment was 3.27 years.

Patient Demographics and Baseline Characteristics

The demographics and baseline characteristics of the patients are comprehensively outlined in Table 1. The mean age of the participants was 56 years, with 134 of them being male (96%). All 139 patients underwent PCI, whereby 85 (61.15%) presented with STEMI and 54 (38.85%) with non-STEMI. The mean length of the hospital stay was 4.07 days. As regards the varenicline treatment details, the mean time

Table 1. Baseline characteristics of smokers with AMI.

Category	Variable	Value
Demographics	Age, mean ± SD, years	56 ±10.63
	Smoking duration, mean ± SD, years	32.6 ±10.10
	Cigarettes smoked per day at baseline, mean ± SD	26 ±14.67
	Cigarette pack-years at baseline, mean ± SD	44.25 ±31.42
	Male	134 (96%)
Medical history	Diabetes mellitus	60 (43.17%)
	Hypertension	72 (51.80%)
	Dyslipidemia	89 (64.03%)
	Prior ischemic stroke	4 (2.88%)
	Atrial fibrillation	9 (6.47%)
	Heart failure	13 (9.35%)
	Advanced chronic kidney disease (stage 3–5)	8 (5.76%)
	End-stage kidney disease	6 (4.32%)
Hospital admission	ST-segment elevation myocardial infarction	85 (61.15%)
	Non-ST-segment elevation myocardial infarction	54 (38.85%)
	Percutaneous coronary intervention	139 (100.00%)
	Mean length of hospital stay, days	4.07 ±1.85
Varenicline	Time from admission to first dose, mean ± SD, years	9.01 ±45.54
	Mean duration of medication intake, mean ± SD, weeks	7.08 ±5.03
	Patients who received first dose during hospitalization	125 (89.93%)
	Treatment course ≦ 1 week	19 (13.67%)
	Treatment course > 8 weeks	59 (42.45%)

SD: standard deviation.

from admission to the first dose was 9.01 days, and the mean duration of medication intake was 7.08 weeks. A significant majority, namely 125 patients (89.93%), received their first dose during hospitalization. Nineteen patients (13.67%) had a treatment course of 1 week or less, and 59 patients (42.45%) were treated for more than 8 weeks.

Outcomes:

Efficacy:

At the 24-week mark (short-term), the overall smoking cessation rate was 76.26% (106/139), while at the mean 3.3 years mark (long-term) the cessation rate was 54.26% (70/129). Success at both follow-up points was reported by 46.76% (65/139) of patients, while failure at both follow-up points was reported by 19.42% (29/139) of patients. For those administered medication for ≤1 week, the cessation rate was 73.7% (14/19) at the short-term mark, while at the long-term mark the overall cessation rate was 57.9% (11/19). Patients who took medication for >8 weeks, due to the initial treatment's ineffectiveness, had a cessation rate of 71.1% (42/59) at the short-term mark and 38.98% (23/59) at the long-term mark. We defined those who reported quitting successfully at any two follow-up time points as cessation-experienced patients, and those who never reported quitting as cessation-failure patients. Between the cessation-experienced group and the cessation-failure group there were no significant differences in smoking duration, daily consumed amount and pack-years. The cessation-experienced group seemed to be older but this difference did not reach statistical significance. As shown in Table 2, the cessation-failure group had a significantly higher prevalence of advanced chronic kidney disease (CKD) (stages 3-5) (14.29% vs. 3.6% p=0.0301) but not end-stage-renal-disease (ESRD) (0% vs. 5.41% p=0.208) or other baseline diseases, compared with the cessation-experienced group.

Table 2. *Possible predictors of the cessation-failure group and the cessation-experienced group.

		cessation-failure (n=28)	cessation-experienced (n=111)	Chi-Square
		N (%)	N (%)	*P*-value
Age	Mean ±SD	52.75 ±9.9	56.81 ±10.69	0.0706
Smoking duration	Mean ±SD	31.43 ±8.48	32.86 ±10.48	0.5033
Daily consumption	Mean ±SD	27.54 ±13.93	26.03 ±14.89	0.4270
Pack-years	Mean ±SD	45.5 ±31.61	43.94 ±31.51	0.7222
Baseline disease				
Diabetes mellitus		15 (53.57%)	45 (40.54%)	0.2135
Hypertension		14 (50%)	58 (52.25%)	0.8312
Dyslipidemia		17 (60.71%)	72 (64.86%)	0.6826
Stroke		0 (0%)	4 (3.6%)	0.3081
Atrial fibrillation		0 (0%)	9 (8.11%)	0.1192
Heart failure		1 (3.57%)	12 (10.81%)	0.2397
Chronic kidney disease		4 (14.29%)	4 (3.6%)	*0.0301
End-stage renal disease		0 (0%)	6 (5.41%)	0.2085

*Reaches statistical significance

Cardiac events around smoking cessation

After a mean 3.3 years of follow up, we recorded 10 mortality events, 4 strokes, 44 MIs and 58 coronary revascularizations, while similar all-cardiac events were detected in the two groups (Table 3 and Figure 2). The cessation-failure group (N=28) had slightly higher incidences of new stroke (3.57% vs. 2.7%), MI (35.71% vs. 30.63%), coronary revascularization (42.86% vs. 41.44%) and lower all-cause mortality (3.57% vs. 8.11%), compared to the cessation-experienced group (n=111). However, these differences were not statistically significant.

STEMI group vs. non-STEMI group

The outcomes for the two different MI groups are presented in Table 4. There were no significant age and sex differences between the groups. Both groups shared similar underlying diseases, such as diabetes, hypertension, lipid disorders, prior stroke, atrial fibrillation and heart failure. However, the STEMI group had a significantly lower proportion of advanced CKD at baseline than the non-STEMI group (5.88% vs. 16.67% $p < 0.05$), and was associated with a lower risk of developing composite major events (including MI, non-fatal stroke and death) (odds ratio: 0.274; 95% confidence interval: 0.095-0.791).

The smoking cessation rate is shown in Figure 3. In our study, STEMI patients (n=85) showed higher success rates than non-STEMI patients (n=54) in both short-term (80% vs. 70.37%) and long-term treatments (57.65% vs. 37.04%).

Discussion

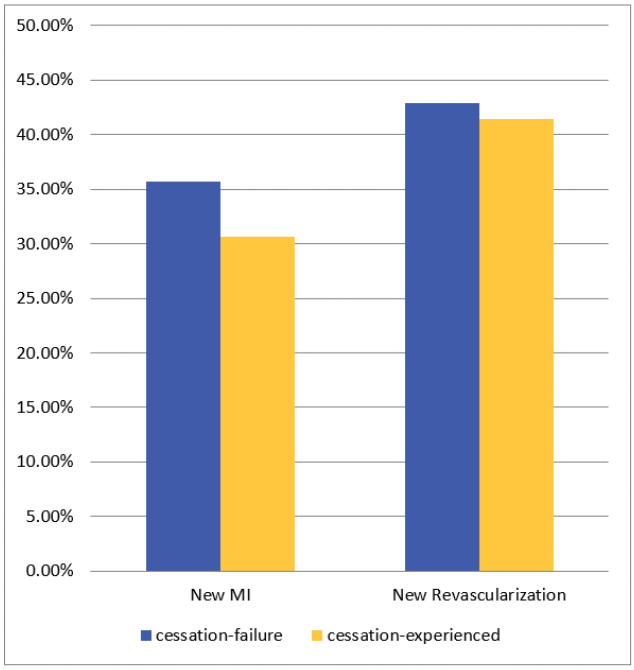
The study extends existing research,[7] which focused on the safety of early cessation strategy with varenicline prescription. To the best of our knowledge, this is the first long-term follow-up study of varenicline in a Taiwanese population after AMI. Varenicline's safety was confirmed in the 2016 EAGLES trial,[8] and it has been shown to be more effective in promoting smoking cessation than single nicotine replacement therapy (NRT) or bupropion through various clinical studies[9-11] that included a Taiwanese population (5.2% vs 10.3%, $p = .001$),[12,13] and it was also recommended in the 2019 ACC/AHA Guideline.[14] In patients with ACS, the EVITA trial demonstrated higher cessation rates with varenicline compared to placebo.[15] Recent studies have increasingly focused on medication administration to AMI patients during hospitalization,[16] highlighting that early intervention post-AMI admission is crucial for successful smoking cessation.

Cessation experience

Assessment methods for smoking cessation vary widely. Most trials prioritize point prevalence for cessation as the primary outcome and sustained cessation as a secondary endpoint. However, relapses are common among smokers and often occur multiple times before long-term cessation

Table 3. Comparison of new events occurring after medication between the cessation-failure group and the cessation-experienced group.

	cessation-failure (n=28)	cessation-experienced (n=111)	Chi-Squared
	N (%)	N (%)	*P*-value
Stroke	1 (3.57%)	3 (2.7%)	0.8059
Myocardial infarction	10 (35.71%)	34 (30.63%)	0.6053
Coronary revascularization	12 (42.86%)	46 (41.44%)	0.8920
All-cause mortality	1 (3.57%)	9 (8.11%)	0.4064



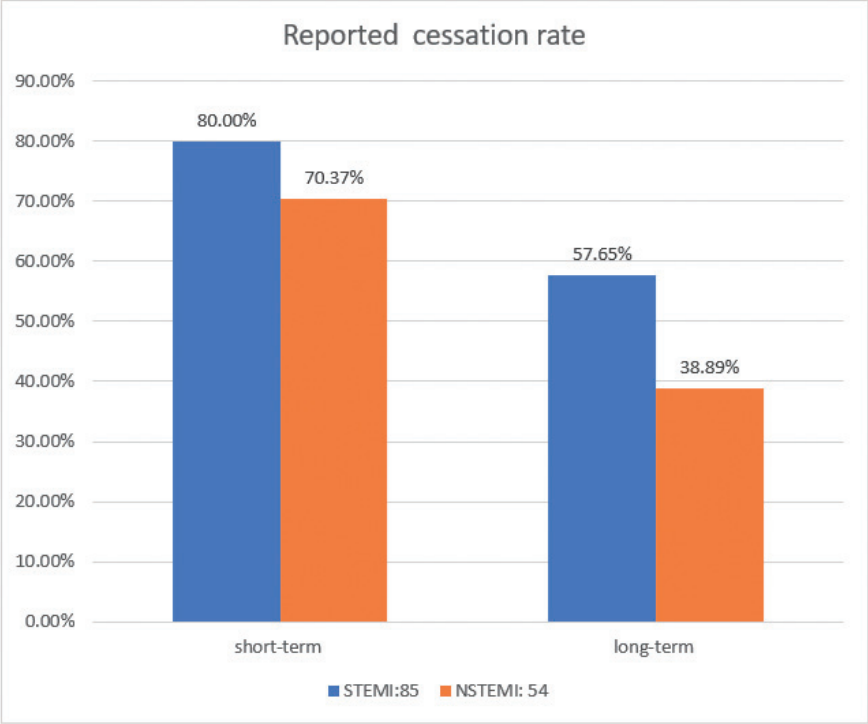
	cessation-failure (n=28)	cessation-experienced (n=111)	Chi-Squared
	N (%)	N (%)	*P*-value
Myocardial infarction	10 (35.71%)	34 (30.63%)	0.6053
Revascularization event	12 (42.86%)	46 (41.44%)	0.8920

Figure 2. Visualized outcome comparison between the cessation-failure group and the cessation-experienced group.

Table 4. Comparison of new events occurring after medication between the STEMI group and the non-STEMI group.

	NSTEMI (n=54)	STEMI (n=85)	*P*-value	Test
	N (%)	N (%)		
Revascularization	12 (22.22%)	23 (27.06%)	0.5220	Chi-Squared
Major events	13 (24.07%)	6 (7.06%)	0.0044	Chi-Squared
Myocardial infarction	8 (14.81%)	17 (20%)	0.4379	Chi-Squared
Smoking duration (years)	32.91 ±9.23	32.36 ±10.66	0.7461	Wilcoxon
Daily consumption	26.93 ±14.6	25.95 ±14.78	0.5392	Wilcoxon
Varenicline duration (weeks)	7.46 ±5.72	6.79 ±4.32	0.8943	Wilcoxon
Relapse smoking amount	6.46 ±10.27	3.92 ±7.88	0.2310	Wilcoxon
Consumption reduction	20.46 ±17.13	22.04 ±15.06	0.4167	Wilcoxon
Short-term success rate	38 70.37%	68 80%	0.2730	Chi-Squared
Long-term success rate	21 37.04%	49 57.65%	0.2664	Chi-Squared

*Reaches statistical significance



	non-STEMI (n=54)	STEMI (n=85)	Total (N=139)	
Short term successful rate	38 70.37%	68 80%	106	76.26%
Long term successful rate	21 37.04%	49 57.65%	70	50.36%

Figure 3. Visualized cessation rate comparison between the STEMI group and the non-STEMI group.

is achieved.[17] Some studies have even reported a 75% relapse rate within six months.[18] Therefore, we divided our comparison groups into those who had achieved cessation and those who failed.

Efficacy

In 2016, the EVITA trial reported a 70.5% smoking cessation rate at 24 weeks among patients who started varenicline treatment in-hospital following AMI, and other randomized controlled trials have demonstrated long-term (52 weeks) cessation rates of around 20-25%.[19,20] Even compared to the general population in Taiwan, where the cessation rate stands at 44.33% at 24 weeks,[21] our study demonstrates remarkable results. Over 50% of our study's participants reported having quit smoking at the long-term mark, and 76% reported having quit at 24 weeks, significantly exceeding the efficacy observed in previous studies.

In our study, 79.9% of patients experienced at least one cessation event. Even in those who had relapsed by the long-term mark, 38.71% (24/62) had reported a reduction of ≥50% in daily cigarette consumption. However, the benefit of simply reducing the quantity of smoking as regards cardiovascular endpoints in patients remains controversial in our study and in other reports.[22,23]

Data analysis has revealed that patients who reported having quit smoking at both check points had significantly shorter varenicline treatment durations than those who had relapsed. This likely reflects the adequate response of the successful patient group to the initial treatment, negating the need for extended therapy.

Despite the absence of statistical significance, patients in the STEMI group exhibited more pronounced benefits than those in the non-STEMI group, including higher rates of short- and long-term cessation success (80.46% vs. 70.91% at 24 weeks and 57.47% vs. 40.0% at the 3-year mark) and greater reduction in the quantity of cigarettes.

We hypothesize that sustained smoking cessation in our study may have been due to significant life events motivating patients, as previous research has suggested.[24] No significant differences between the groups were found in smoking duration or cigarette quantity. However, elderly patients seemed to have a higher chance of quitting smoking. Similar results have been reached by other studies,[25] indicating that it is worthwhile to encourage high risk elderly smokers to achieve long-term abstinence.

In our study, 129 out of 142 patients (90.8%) began treatment within the first week after PCI. Although we did not find a significant difference in the rate of major events between the early smoking cessation group (defined as those who reported cessation at the short-term mark) and those who did not quit smoking, the early cessation group exhibited a higher rate of cessation at the long-term mark (67.68% vs. 15.15%). This suggests that those who achieved early smoking cessation were more likely to maintain abstinence through the 3-years mark.

Clinical Outcomes

There was no statistically significant difference between the cessation-experienced group and the failure group. However, the cessation-experienced group seemed to have a lower incidence of cardiovascular events. Though the outcomes were not statistically significant, the cessation-experienced group was older and had a higher prevalence of hypertension, dyslipidemia, stroke, atrial fibrillation, heart failure and ESRD. Even with the comorbidities, the cessation-experienced group still demonstrated a trend of fewer recurrent MI and coronary revascularization events. Besides, according to previous research, it would take 10 to 15 years for former heavy smokers to no longer be significantly associated with elevated CVD risk, compared to lifetime non-smokers.[26] It is very likely that three years of smoking cessation is not enough to achieve statistical significance. Longer or large-scale studies are needed to confirm this effect.

STEMI vs. non-STEMI

As reported by several studies, short-term prognoses are worse for STEMI patients and long-term outcomes are worse for non-STEMI patients.[27-31] Our findings align with these results, showing that the STEMI group had a higher incidence of unexpected PCI during the three-year follow-up, while the non-STEMI group exhibited a greater risk of composite major events (including MI, non-fatal stroke and death). Although not statistically significant, patients who continued smoking at both follow-up points had a higher rate of recurrent MI and coronary revascularization, compared to those who had quit smoking at both points. The difference in risk was particularly apparent in the non-STEMI group, and less so in the STEMI group.

Limitations

This study is subject to several limitations. First, the small size of our sample curtailed our ability to perform subgroup analyses. Based on previous studies, longer and larger evaluation is needed to achieve accurate results. Second, as previously mentioned, opinions differ when it comes to assessing smoking cessation. Not only did we use prevalence at a single time period as our outcome, but also most of our results relied on patient self-reporting without confirmation based on carbon monoxide concentration. This carries the risk of underreporting due to concealment of smoking habits, thus causing an overestimation of the cessation rates in our study. Third, the absence of a control group in our study's design as a single-center, prospective, single-arm trial precludes any comparison with AMI patient findings.

Conclusion

Our findings indicate that early administration of varenicline during hospitalization in patients with AMI who received PCI yielded a high rate of smoking cessation, even at the mean 3-year follow-up. STEMI and older patients seem to have a higher rate of successful cessation.

Declaration of competing interest

The authors have no conflicts of interest to declare, relevant to this article.

References

1. Timmis A, Kazakiewicz D, Townsend N, et al. Global epidemiology of acute coronary syndromes. *Nature Reviews Cardiology* 2023;20(11):778-788.
2. 統計處. 109年18歲以上成人吸菸行為調查結果性別分析(國民健康署)- 統計處. Retrieved from https://dep.mohw.gov.tw/DOS/cp-5112-63459-113.html
3. Critchley J, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease. *JAMA* 2003;290:86.
4. Takahashi K, Thuijs DJFM, Gao C, et al. Ten-year all-cause mortality according to smoking status in patients with severe coronary artery disease undergoing surgical or percutaneous revascularization. *European Journal of Preventive Cardiology* 2020;29:312-320.
5. Cho L, Bhatt DL, Wolski K, et al. Effect of smoking status and abciximab use on outcome after percutaneous coronary revascularization: Pooled analysis from EPIC, EPILOG, and EPISTENT. *American Heart Journal* 2001;141(4):599–602.
6. Dai X, Gakidou E, Lopez AD. Evolution of the global smoking epidemic over the past half century: strengthening the evidence base for policy action. *Tobacco Control* 2022;31:129-137.
7. Lo C, Li L, Chang K, et al. Safety and efficacy of early varenicline prescription in hospitalized patients with acute myocardial infarction: East Asian population. *Journal of the Formosan Medical Association* 2023;122(10):1035-1041.
8. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *The Lancet* 2016;387(10037):2507-2520.
9. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2010.
10. Guo K, Zhou L, Shang X, et al. Varenicline and related interventions on smoking cessation: A systematic review and network meta-analysis. *Drug and Alcohol Dependence* 2022;241:109672.
11. Russo C, Walicka M, Caponnetto P, et al. Efficacy and safety of varenicline for smoking cessation in patients with type 2 diabetes. *JAMA Network Open* 2022;5(6):e2217709.
12. Hsueh KC, Tang PL, McRobbie H. Effectiveness of Varenicline Versus Combination Nicotine Replacement Therapy for Smoking Cessation: One-Year Outcomes in a Smoking Cessation Clinic in Taiwan. *Nicotine Tob Res* 2021;23:1094-1102.
13. Chang PY, Lo PC, Chang HC, et al. Comparative Effectiveness of Smoking Cessation Medications: A National Prospective Cohort From Taiwan. *PLoS One* 2016;11:e0166992.
14. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140(11).
15. Eisenberg MJ, Windle SB, Roy N, et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation* 2016;133(1):21-30.
16. Moiz A, Eisenberg MJ. Initiation of varenicline in people hospitalized for acute coronary syndrome Who smoke. *Circulation* 2023;147:1869-1871.
17. Nohlert E, Öhrvik J, Tegelberg Å, et al. Long-term follow-up of a high- and a low-intensity smoking cessation intervention in a dental setting–a randomized trial. *BMC Public Health* 2013;13(1).
18. Etter JF, Stapleton JA. Nicotine replacement therapy for long-term smoking cessation: a meta-analysis. *Tob Control* 2006;15(4):280-285.
19. Tonstad S. Effect of Maintenance Therapy With Varenicline on Smoking Cessation: A Randomized Controlled Trial. *JAMA* 2006;296:64.
20. Baker TB, Piper ME, Smith SS, et al. Effects of combined varenicline with nicotine patch and of extended treatment duration on smoking cessation. *JAMA* 2021;326(15):1485.
21. Wen Y, Wang I, Hu Y, et al. Duration of varenicline prescription and efficacy of smoking cessation treatment: an observational study in Taiwan. *Preventive Medicine* 2022;161:107091.
22. Chang J, Anic GM, Rostron BL, Tanwar M. Cigarette

Smoking Reduction and Health Risks: A Systematic Review and Meta-analysis. *Nicotine & Tobacco Research* 2020;23:635-642.
23. Jeong S, Jeon KH, Shin DW, et al. Smoking cessation, but not reduction, reduces cardiovascular disease incidence. European Heart Journal 2021;42:4141-53.
24. Höpner J, Junge U, Schmidt-Pokrzywniak A, et al. Determinants of persistent smoking after acute myocardial infarction: an observational study. *BMC Cardiovascular Disorders* 2020;20(1).
25. Hsu C, Hsueh K, Chou M, et al. Long-term smoking cessation rates in elderly versus other adult smokers: A 3-year follow-up study in Taiwan. *Addictive Behaviors Reports* 2018;8:62-65.
26. Duncan MS, Freiberg MS, Greevy RA et al, Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA* 2019;322(7):642.
27. Duncan MS, Freiberg MS, Greevy RA, Kundu S et al. Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA* 2019;322(7):642. https://doi.org/10.1001/jama.2019.10298
28. Singh M, Reeder GS, Jacobsen SJ, et al. Scores for Post–Myocardial Infarction risk stratification in the community. *Circulation* 2002;106(18):2309-2314.
29. Yan AT, Tan M, Fitchett D, et al. One-year outcome of patients after acute coronary syndromes (from the Canadian Acute Coronary Syndromes Registry). *American Journal of Cardiology* 2004;94(1):25-29.
30. Haim M, Behar S, Boyko V, et al. The prognosis of a first Q-wave versus non-Q-wave myocardial infarction in the reperfusion era. *The American Journal of Medicine* 2000;108(5):381-386.
31. Chang S, Lu C, Chen K, et al. Prognosis between ST-Elevation and Non-ST-elevation myocardial infarction in older adult patients. *Front Cardiovasc Med* 2022;8.