의학박사 학위논문

무증상 죽상동맥경화증에 대한 당뇨병 조절의 효과: 컴퓨터 단층촬영을 이용한 관상동맥 조영술 등록연구의 분석

Impact of Diabetes Control on Subclinical Atherosclerosis: Analysis from Coronary Computed Tomographic Angiography Registry

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이 논문을 의학박사 학위 논문으로 제출함

2017 년　12 월

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국문요약

연구목적

무증상 관상동맥 죽상경화증 환자에서 혈당조절의 영향을 연구하고자 한다.

연구배경

컴퓨터 단층촬영을 이용한 관상동맥 혈관조영술로 진단된 무증상 관상동맥 죽상경화증환자와 당뇨조절과의 연관성에 대한 연구가 부족하다.

연구방법

관상동맥질환의 과거력이 없고, 자발적으로 컴퓨터 단층촬영을 이용한 관상동맥 혈관조영술을 시행했던 무증상의 6,434 명의 환자를 분석하였다 (평균나이 53.7 ±7.6, 남자 4,694 명 [73.0%]). 이들은 당뇨병이 없는 환자 5,409 명, 당화혈색소가 7% 미만으로 조절되는 당뇨병 환자 666 명, 당화혈색소가 7% 이상으로 조절되지 않은 당뇨병 환자 359 명이었다. 관상동맥이 50% 이상 좁아진 정도를 의미있는 협착소견으로 정의하였고, 심장사건은 사망, 심근경색, 불한정 협심증과 관상동맥 혈관재개통술을 복합하여 정의하였다.

연구결과

당뇨가 없는 환자보다 조절되는 당뇨환자에서 죽상경화반의 위험도가 더 높았지만(승산비 1.23, 95% 신뢰구간 1.02-1.47,p=0.029) 관상동맥의 유의한 협착은 통계적으로 차이가 없었다 (승산비 1.24, 95% 신뢰구간 0.93-1.66, p=0.145). 그러나 조절되지 않은 당뇨환자에서는 당뇨가 없는 환자보다 죽상경화반의 위험도 높았고 (승산비 2.26, 95% 신뢰구간 1.76-2.91, p<0.001) 관상동맥의 유의한 협착의 위험도 높았다 (승산비 3.46, 95% 신뢰구간 2.57-4.68, p<0.001). 추적관찰기간동안 (중앙값 21.8 개월) 당뇨가 없는 환자와 조절되는 당뇨환자에서 심장사건의 발생 빈도는 통계적유의성은 없었다 (위험비 1.12, 95% 신뢰구간 0.60-2.11, p=0.726). 그러나 조절되지 않은 당뇨환자가 당뇨가 없는 환자와 비교해서 심장사건의 발생 위험이 유의하게 높았다 (위험비 2.71, 95% 신뢰구간 1.50-4.91, p=0.001).

결론

무증상 죽상경화 환자에서 당뇨가 조절되지 않을 경우 관상동맥의 죽상경화와 심장사건의 발생 위험이 높았다. 이런 연구결과는 무증상 관상동맥 죽상경화 환자에서 당뇨병이 있을 경우 혈당조절이 중요하다는 것을 제시한다.

차 례

표 및 그림 차례

서론 (INTRODUCTION)

Glycemic control is fundamental to diabetes management [1]. Previous studies have demonstrated that improved glycemic control is associated with significantly reduced onset or progression of microvascular complications in diabetic individuals [2-6]. In addition, individuals with diabetes showed a higher prevalence, extent, and severity of coronary atherosclerosis than those without [7-9]. Coronary artery disease (CAD) is a leading cause of death among diabetic individuals [10]. Recent long-term follow-up studies have also shown cardiovascular benefits of intensive glycemic control [3, 11, 12]. However, there are limited data regarding the impact of the diabetes control on the risk of subclinical coronary atherosclerosis in asymptomatic individuals. Recently, with the advent of multidetector row computed tomography, coronary computed tomography angiography (CCTA) has proven to be effective in providing the comprehensive evaluation of coronary atherosclerosis, including lesion location, severity and plaque characteristics [13]. Thus, in this study, we sought to evaluate the impact of diabetes control on the risk of subclinical coronary atherosclerosis through a large cohort of asymptomatic Korean individuals who voluntarily underwent CCTA.

연구방법 (METHODS)

Study Population

In total, 9,269 consecutive South Korean individuals aged 20 years and older who had undergone self-referral CCTA evaluation as part of a general health examination in the Health Screening and Promotion Center at Asan Medical Center from January 2007 to December 2011. Among these, 7,129 (76.9%) individuals agreed to participate in this study. Possible risks associated with CCTA were explained and informed consent was obtained.

Exclusion criteria include subjects with 1) a previous history of angina or myocardial infarction; 2) abnormal rest electrocardiographic results, i.e., pathological Q waves, ischemic ST segments or T wave changes, or left bundle-branch blocks; 3) insufficient medical records; 4) structural heart diseases; 5) a prior history of open heart surgery or percutaneous coronary intervention; 6) a previous cardiac procedure; or 7) renal insufficiency (creatinine >1.5 mg/dL). Finally, 6,434 subjects were enrolled (**Figure 1**). The study was approved by the local Institutional Review Board of the Asan Medical Center, Seoul, Korea.

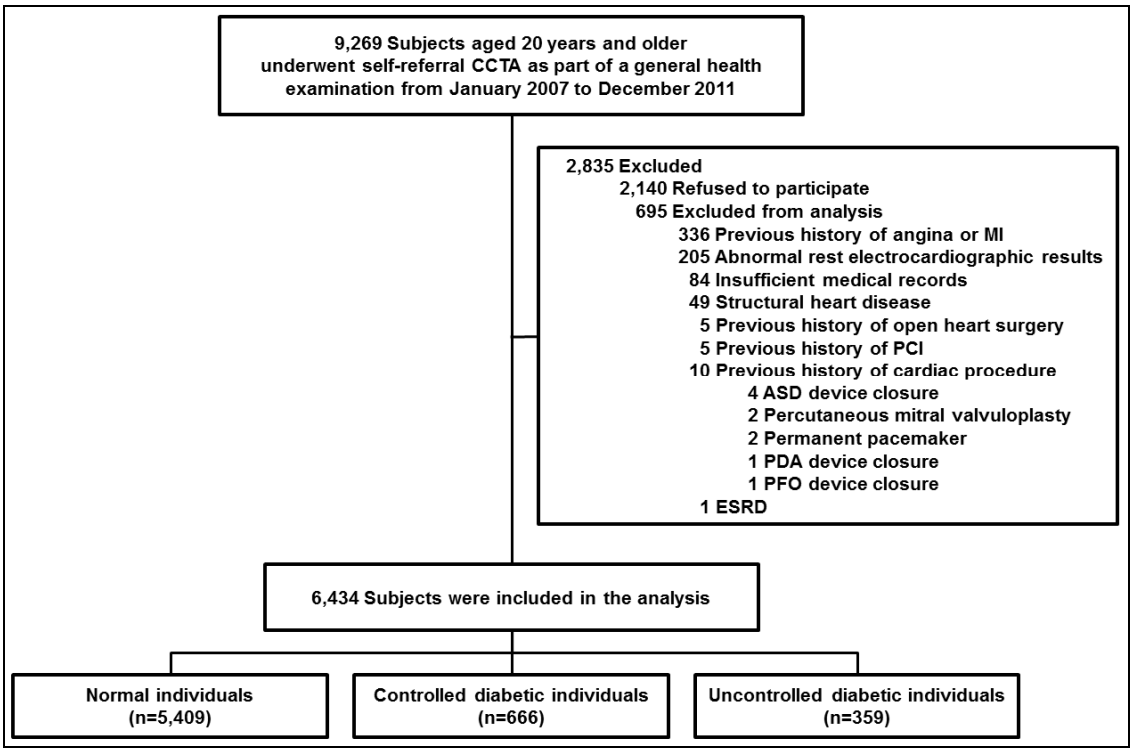

Fig. 1. Overview of the study population.

The demographic information was collected from a database maintained by the Health Screening and Promotion Center at the Asan Medical Center. Medical history including angina, myocardial infarction, stroke, structural heart disease, open heart surgery, percutaneous coronary intervention, previous cardiac procedures, diabetes mellitus, hypertension, or hyperlipidemia; a family history of CAD; and smoking status was taken from the responses in the systemized self-report questionnaire issued prior to the general health examination. A family history of CAD was defined as having a first-degree relative of

any age on the self-report questionnaire [14]. Diabetes was defined as a fasting plasma glucose (FPG) ≥126 mg/dL or a hemoglobin A1C (HbA1C) level ≥6.5% [1]. In addition, subjects who reported the use of anti-diabetic medications on a self-report questionnaire were considered to have diabetes [15]. By their diabetes control, study participants were categorized as normal, controlled diabetes (diabetes with HbA1C <7%), or uncontrolled diabetes (diabetes with HbA1C ≥7%), respectively [1]. Hypertension was defined as a blood pressure ≥140/90 mmHg or a self-reported history of hypertension and/or use of anti-hypertensive medication. Hyperlipidemia was defined as total cholesterol ≥240 mg/dL or use of an anti-hyperlipidemic treatment.

Clinical and Laboratory Measurements

Height and weight were obtained while subjects wore light clothing without shoes. The body mass index was calculated as weight in kilograms divided by the square of the height in meters. The waist circumference was measured midway between the costal margin and the iliac crest at the end of a normal expiration. The blood pressure was measured on the right arm after a rest of ≥5 min using an automatic manometer with an appropriate cuff size [16].

After overnight fasting, early morning blood samples were drawn from the antecubital vein into vacuum tubes and subsequently analyzed in the central, certified laboratory of the Asan Medical Center. Measurements included the concentrations of FPG, uric acid, creatinine, C-reactive protein and several lipid parameters. Fasting total cholesterol, high density lipoprotein cholesterol, low density lipoprotein (LDL) cholesterol, triglyceride, uric acid and creatinine were measured by an enzymatic colorimetric method using a Toshiba 200FR Neo (Toshiba Medical System Co., Ltd., Tokyo, Japan). FPG were measured by an enzymatic colorimetric method using a Toshiba 200 FR autoanalyzer (Toshiba). Ion-

exchange high-performance liquid chromatography (Bio-Rad Laboratories, Inc., Hercules, CA, USA) was used to measure HbA1C levels. Serum C-reactive protein level was measured according to a high-sensitivity assay by using a latex particle–enhanced immunoturbidometric assay (Roche Diagnostics, Mannheim, Germany). All enzyme activities were measured at 37°C [16].

CCTA Image Acquisition and Analysis

CCTA was conducted using either single-source 64-slice CT (LightSpeed VCT, GE, Milwaukee, WI, USA) or dual-source CT (Somatom Definition, Siemens, Erlangen, Germany). Subjects with no contraindication to β-adrenergic blocking agents and with an initial heart rate greater than 65 beats per minute received an oral dose of 2.5 mg bisoprolol (Concor, Merck, Darmstadt, Germany) 1 hour before the CT examination. CT scanning was performed in the prospective ECG-triggering mode or the retrospective ECG-gating mode with ECG-based tube current modulation. Two puffs (2.5 mg) of isosorbidedinitrate (Isoket spray, Schwarz Pharma, Monheim, Germany) were sprayed into the patient's oral cavity before contrast injection. During CCTA acquisition, 60-80 mL of iodinated contrast (Iomeron 400, Bracco, Milan, Italy) was injected at 4 mL/second, followed by a 40 mL saline flush. A region of interest was placed in the ascending aorta, and image acquisition was automatically initiated once a selected threshold (100 HU) had been reached using bolus tracking. A standard scanning protocol was used, and the tube voltage and tube current-time product were adjusted according to the patient's body size as follows: 100 kVp or 120 kVp tube voltage; 240 to 400 mAs per rotation (dual-source CT); and 400 to 800 mA (64-slice CT) tube current [13].

All CCTA scans were analyzed using a dedicated workstation (Advantage Workstation, GE; or Volume Wizard, Siemens) by experienced cardiovascular radiologists (D.H.Y., J.-W.K., and T.-H.L.). According to the guidelines of the Society of Cardiovascular Computed

Tomography, a 16-segment coronary artery tree model was used [17]. A coronary artery calcium score was measured as described**,** with categorized by scores of 0, 1 to 10, 11 to 100, 101 to 400, and >400 [18]. Plaques were defined as structures >1 mm^2 within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques containing calcified tissue involving more than 50% of the plaque area (density >130 HU) were classified as calcified, plaques with <50% calcium were classified as mixed, and plaques without calcium were classified as non-calcified lesions [19]. The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the site of maximal stenosis and compared with the mean value of the proximal and distal reference sites [20]. Stenosis ≥50% was defined as significant. The overall plaque burden was determined from coronary artery plaque scores calculated from modified Duke prognostic scores, segment stenosis scores, and segment involvement scores, as described [21]. In addition, high-risk CAD was defined as at least 2-vessel coronary disease with proximal left anterior descending (LAD) artery involvement, 3-vessel disease, or left main (LM) disease [22].

Clinical Outcomes

Follow-up clinical data were obtained by review of medical records at the end of August 2012. Clinical events were defined as a composite of all-cause death, non-fatal myocardial infarction (MI), acute coronary syndrome requiring hospitalization, or coronary revascularization. Deaths were identified by using identification numbers, which were assigned to the subjects at birth certificates, in the National Statistical Office [14]. The diagnosis of MI was based on the presence of new Q waves in at least two contiguous leads, or an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of the normal range at follow-up. Revascularization was performed if there was a stenosis of at least 50% of the diameter with a positive stress test or if there was a stenosis of at least 70%

[23].

Statistical Analysis

Categorical variables are expressed as frequencies with percentages, and continuous variables as the mean and standard deviation. Between-group comparisons were performed by using the Pearson's chi-square test or Fisher's exact test for categorical variables, and by using the one-way analysis of variance or Kruskal–Wallis test for numerical variables, as appropriate. Logistic regression analyses were performed to evaluate the independent relationships between the diabetes control and subclinical coronary atherosclerosis on CCTA. For the multivariable analyses, we adjusted for the all predictor variables in **Table 1**. Unadjusted and adjusted odds ratios with 95% confidence intervals for the logistic regression were calculated. The effect of diabetes control on cardiac events was assessed by Cox proportional hazard regression, using the normal group as a reference. All reported p-values are two sided, and p-values of <0.05 were considered statistically significant. Data manipulation and statistical analyses were conducted using SAS® Version 9.1 (SAS Institute Inc., Cary, NC).

결과 (RESULTS)

Population Characteristics

The mean age of study participants was 53.7±7.6 years and 4,694 (73.0%) were male. Of them, 5,409 (84.1%), 666 (10.4%), and 359 (5.6%) were categorized as normal, controlled diabetes, and uncontrolled diabetes, respectively. The baseline characteristics of the study population according to the diabetes control are listed in **Table 1**. In controlled diabetes, the mean FPG and HbA1C were 122.9±18.2 mg/dL and 6.2±0.5%. On the other hand, in uncontrolled diabetes, the mean FPG and HbA1C were 159.6±40.7 mg/dL and 8.1±1.3%.

Table 1. Baseline characteristics of study participants according to the diabetes control

Variables	Normal	Controlled Diabetes	Uncontrolled Diabetes	p-value
Number of patients, (%)	5,409 (84.1)	666 (10.4)	359 (5.6)	
Demographics				
Age, years	53.3±7.5	55.6±7.5	55.9±7.6	<0.001
Gender, no. (%)				
Men	3,832 (70.8)	573 (86.0)	289 (80.5)	<0.001
Women	1,577 (29.2)	93 (14.0)	70 (19.5)	
Clinical characteristics or coexisting conditions				
Body mass index, kg/m^2	24.5±2.9	25.3±2.8	25.5±3.3	<0.001
Waist circumference, cm	85.3±8.3	88.6±7.6	89.2±8.4	<0.001
Systolic blood pressure, mmHg	119.5±12.9	122.7±13.2	124.6±14.3	<0.001
Diastolic blood pressure, mmHg	76.6±10.4	78.1±10.1	78.4±10.1	<0.001
Hypertension, no. (%)	1,818 (33.6)	364 (54.7)	170 (47.4)	<0.001
Hyperlipidemia, no. (%)	1,549 (28.6)	296 (44.4)	158 (44.0)	<0.001
Current smoker, no. (%)	1,209 (22.4)	187 (28.1)	129 (35.9)	<0.001
Previous stroke, no. (%)	41 (0.8)	11 (1.7)	4 (1.1)	0.056
Family history of CAD*, no. (%)	854 (15.8)	89 (13.4)	40 (11.1)	0.021
Total cholesterol, mg/dL	197.2±33.1	185.9±38.5	187.3±40.0	<0.001
LDL cholesterol, mg/dL	123.0±29.2	112.3±32.8	112.9±33.5	<0.001
HDL cholesterol, mg/dL	54.0±13.7	51.6±12.2	48.4±11.9	<0.001
Triglyceride, mg/dL	129.3±77.0	148.6±105.3	180.1±137.6	<0.001
Creatinine, mg/dL	0.9±0.2	0.9±0.1	0.9±0.2	0.010
Uric acid, mg/dL	5.6±1.4	5.7±1.3	5.3±1.3	<0.001
hsCRP ≥2 mg/dL, %	43 (0.8)	8 (1.2)	7 (1.9)	0.056
Ejection fraction, %	63.3±4.1	63.4±4.1	63.5±4.4	0.665

Values are given as mean±standard deviation or number (%).

*Coronary artery disease in a first-degree relative of any age.

CAD = coronary artery disease; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

CCTA Findings

Table 2 shows the CCTA findings according to the diabetes control. The mean coronary artery calcium score of study participants was 40.8±139.5. There were significant differences in coronary artery calcium score according to the diabetes control ($p<0.001$). In addition, the prevalence of any atherosclerotic, calcified, non-calcified, or mixed plaque increased with the diabetes control (p for all<0.001). Plaque burden scores such as segment involvement score, segment stenosis score, and modified Duke prognostic score also increased with the diabetes control (p for all<0.001).

Of study participants, 494 (7.7%) had significant coronary arteries stenosis (≥50% diameter stenosis) in at least 1 coronary artery on CCTA. Significant stenosis in the LM, LAD, left circumflex artery and right coronary arteries was observed in 23 (0.4%), 328 (5.1%), 161 (2.5%) and 143 (2.2%), respectively. The prevalence of significant stenosis, multi-vessel disease, significant stenosis in the LM or proximal LAD artery, high-risk CAD also increased with the diabetes control (p for all<0.001).

Association between the Diabetes Control and Subclinical Atherosclerosis

Univariate analyses showed that controlled diabetic individuals had a significantly higher prevalence of subclinical coronary atherosclerosis than normal individuals. Multivariate analyses also revealed that controlled diabetic individuals had more any atherosclerotic, calcified, and mixed plaques than the normal individuals. However, there were no statistically significant differences in the adjusted odds ratios for non-calcified plaque, significant stenosis, multi-vessel disease, significant stenosis in the LM or proximal LAD, and high-risk CAD between the normal and controlled diabetic individuals (**Table 3**).

In uncontrolled diabetic individuals, univariate analyses showed a significant association between uncontrolled diabetes and any subclinical coronary atherosclerosis (p for all<0.001). Multivariate analyses also revealed the consistent association of uncontrolled diabetes with any subclinical coronary atherosclerosis (p for all<0.05) (**Table 3**).

Table 2. Coronary computed tomographic angiographic findings according to the diabetes control

Characteristics	Overall	Normal	Controlled Diabetes	Uncontrolled Diabetes	p-value
Mean coronary artery calcium score	40.8±139.5	33.3±123.8	73.7±209.5	92.3±176.5	<0.001
Coronary artery calcium score classification, no. (%)					<0.001
0	4,145 (64.6)	3,656 (67.8)	339 (51.2)	150 (41.8)	
1-10	598 (9.3)	483 (9.0)	81 (12.2)	34 (9.5)	
11-100	1,028 (16.0)	811 (15.0)	133 (20.1)	84 (23.4)	
101-400	490 (7.6)	342 (6.3)	78 (11.8)	70 (19.5)	
>400	151 (2.4)	99 (1.8)	31 (4.7)	21 (5.8)	
Any atherosclerotic plaque, no. (%)	2,691 (41.8)	2,096 (38.8)	360 (54.1)	235 (65.5)	<0.001
Plaque characteristics, no. (%)					
Calcified plaque	1,810 (28.1)	1,376 (25.4)	270 (40.5)	164 (45.7)	<0.001
Non-calcified plaque	1,180 (18.3)	923 (17.1)	134 (20.1)	123 (34.3)	<0.001
Mixed plaque	570 (8.9)	404 (7.5)	90 (13.5)	76 (21.2)	<0.001
Segment involvement score	1.1±1.7	0.9±1.6	1.5±1.9	2.2±2.4	<0.001
Segment stenosis score	0.6±1.9	0.5±1.7	0.9±2.4	1.8±3.2	<0.001
Modified Duke prognostic score	1.2±0.6	1.2±0.6	1.2±0.7	1.5±1.0	<0.001
Significant stenosis, no. (%)	494 (7.7)	345 (6.4)	69 (10.4)	80 (22.3)	<0.001
Multi-vessel disease, no. (%)	126 (2.0)	87 (1.6)	20 (3.0)	19 (5.3)	<0.001
Significant stenosis in the left main or proximal LAD artery, no. (%)	170 (2.6)	122 (2.3)	25 (3.8)	23 (6.4)	<0.001
High-risk disease, no. (%)	125 (1.9)	86 (1.6)	17 (2.6)	22 (6.1)	<0.001

Values are given as mean±standard deviation or number (%).

LAD = left anterior descending aretry.

Table 3. The association between the glycemic control and subclinical atherosclerosis on coronary computed tomographic angiography.

	Univariate		Multivariate	
Variables	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Any atherosclerotic plaque				
Uncontrolled diabetes	3.00 (2.39-3.75)	<0.001	2.26 (1.76-2.91)	<0.001
Controlled diabetes	1.86 (1.58-2.19)	<0.001	1.23 (1.02-1.47)	0.029
Normal (reference: normal)	1	-	1	-
Calcified plaque				
Uncontrolled diabetes	2.47 (1.99-3.06)	<0.001	1.82 (1.43-2.32)	<0.001
Controlled diabetes	2.00 (1.69-2.36)	<0.001	1.32 (1.09-1.59)	0.003
Normal (reference: normal)	1	-	1	-
Non-calcified plaque				
Uncontrolled diabetes	2.53 (2.01-3.19)	<0.001	2.12 (1.65-2.71)	<0.001
Controlled diabetes	1.22 (1.00-1.50)	0.050	0.96 (0.78-1.19)	0.707
Normal (reference: normal)	1	-	1	-
Mixed plaque				
Uncontrolled diabetes	3.33 (2.53-4.37)	<0.001	2.53 (1.88-3.41)	<0.001
Controlled diabetes	1.94 (1.52-2.47)	<0.001	1.40 (1.08-1.81)	0.012
Normal (reference: normal)	1	-	1	-
Significant stenosis in at least one coronary artery				
Uncontrolled diabetes	4.21 (3.21-5.52)	<0.001	3.46 (2.57-4.68)	<0.001
Controlled diabetes	1.70 (1.29-2.23)	<0.001	1.24 (0.93-1.66)	0.145
Normal (reference: normal)	1	-	1	-
Multi-vessel disease				
Uncontrolled diabetes	3.42 (2.06-5.68)	<0.001	2.66 (1.53-4.63)	0.001
Controlled diabetes	1.89 (1.16-3.10)	0.011	1.29 (0.77-2.17)	0.335
Normal (reference: normal)	1	-	1	-
Significant stenosis in the left main or proximal left anterior descending artery				
Uncontrolled diabetes	2.97 (1.88-4.69)	<0.001	2.29 (1.40-3.75)	0.001

Controlled diabetes	1.69 (1.09-2.62)	0.019	1.25 (0.79-1.98)	0.336
Normal (reference: normal)	1	-	1	-
High-risk coronary artery disease*				
Uncontrolled diabetes	4.04 (2.50-6.54)	<0.001	3.34 (1.97-5.66)	<0.001
Controlled diabetes	1.62 (0.96-2.75)	0.072	1.15 (0.67-1.99)	0.612
Normal (reference: normal)	1	-	1	-

Values are given as mean±standard deviation or number (%).

CI = confidence interval

*Defined as at least 2-vessel coronary disease with proximal left anterior descending artery involvement, 3-vessel disease, or left main disease.

Clinical Outcomes

During the follow-up period (median 21.8 months [interquartile range, 15.2-33.4 months]), a total of 118 cardiac events occurred in 115 patients: 21 all-cause deaths, 2 non-fatal MI, 2 acute coronary syndrome requiring hospitalization, and 93 coronary revascularizations. Normal, controlled diabetic, and uncontrolled diabetic individuals experienced 83 (1.5%), 15 (2.3%), and 17 (4.7%) cardiac events, respectively.

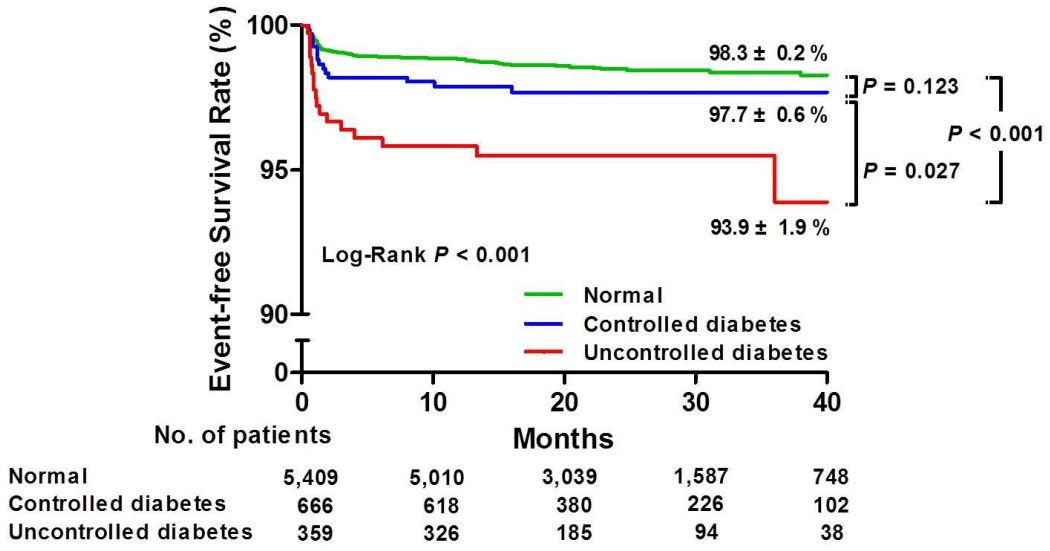

Fig. 2. Kaplan-Meier event-free survival curve according to the diabetic control.

The uncontrolled diabetic patients had significantly lower event-free survival rate than normal (98.3±0.2 vs. 93.9±1.9%, p<0.001) and controlled diabetic patients (97.7±0.6 vs. 93.9±1.9%, p=0.027) (Fig. 2). Assessing by Cox proportional hazard regression, there was no significant difference in cardiac events between normal and controlled diabetic individuals (hazard ratio 1.12, 95% CI 0.60–2.11, p=0.726). However, uncontrolled diabetes was associated with an increased risk of cardiac events compared with normal individuals (hazard ratio 2.71, 95% CI 1.50–4.91, p=0.001).

고찰 (DISCUSSION)

The main findings of this study were as follows: 1) in asymptomatic individuals, uncontrolled diabetes was independently associated with significant subclinical coronary atherosclerosis compared with normal and controlled diabetic individuals; 2) consequently, uncontrolled diabetic individuals experienced more cardiac events; 3) there findings suggest that diabetes control had a beneficial effect on the risk of subclinical coronary atherosclerosis in asymptomatic individuals.

In this study, uncontrolled diabetic individuals had a higher prevalence, extent, and severity of coronary atherosclerosis on CCTA than normal individuals. Even after adjustments for clinical and laboratory variables, uncontrolled diabetes was consistently associated with any subclinical coronary atherosclerosis. Moreover, uncontrolled diabetes was an independent risk factor for significant stenosis in the LM or proximal LAD, multi-vessel disease and high-risk CAD, which have been known to be associated with a worse prognosis [24]. As a result, uncontrolled diabetic individuals experienced more cardiac events. By contrast, compared with normal individuals, controlled diabetic individuals were more likely to have non-significant subclinical coronary atherosclerosis confined to atherosclerotic

plaques. In addition, cardiac event rates may have been comparable because of the lack of any difference between the normal and controlled diabetes groups in terms of significant coronary artery stenosis (e.g., at least one coronary artery, significant stenosis in the LM or proximal LAD, multi-vessel disease, or high-risk CAD). Therefore, our findings support that diabetes control is important in preventing significant subclinical coronary atherosclerosis and cardiac events in asymptomatic diabetic individuals.

In earlier studies, intensive glucose control was not shown to have a significant effect on the rates of major cardiovascular events in diabetic individuals [4, 25]. However, recent long-term follow-up studies have demonstrated that intensive glucose control may be effective in decreasing cardiovascular events in diabetic individuals [3, 11, 12]. Given that cardiac events are thought to occur after long periods of subclinical disease, our study provides some insights into these results. This study showed that control of diabetes was associated with beneficial effects for significant subclinical coronary atherosclerosis, which may have led to the differences in cardiac events between uncontrolled and controlled diabetic individuals. Therefore, emphasis should be given on diabetes control to prevent future cardiac events in asymptomatic diabetic individuals.

To date, randomized trials have failed to demonstrate that routine screening for CAD can decrease cardiac events in relatively well-controlled asymptomatic diabetic populations [26, 27]. In these trials, the study participants were treated by contemporary medical practice, achieving HbA1C, LDL cholesterol, and systolic blood pressure levels at or near the target ranges (HbA1c 7.0–7.5%, LDL cholesterol 86–114 mg/dL, and systolic blood pressure 129–133 mmHg). Eventually, intensive intervention for current cardiac risk factors resulted in lower cardiac event rates in these patients. A previous study also demonstrated resolution of myocardial ischemia resulted from more aggressive treatment of cardiovascular risk factors[12]. In this present study, controlled diabetic individuals also had near targeted levels for HbA1C (6.2%), LDL cholesterol (112 mg/dL), and systolic blood pressure (123 mmHg).

As a result, controlled diabetes was not associated with significant subclinical coronary atherosclerosis on CCTA and an increased risk of cardiac events. Since previous and our studies showed that the adherence to current guidelines could improve subclinical coronary atherosclerosis and clinical outcomes in asymptomatic diabetic individuals, further implementation of established guidelines is needed in this population.

Our study has several limitations. First, the current study was based in a single center. Moreover, because all study participants voluntarily went to the hospital for general health examination, there was a potential for selection bias. Second, calcified plaques and higher coronary artery calcium score may lead to overestimation of significant coronary arteries stenosis. Third, our study population was exclusively Korean. Ethnic differences and clinical differences in diabetes have been noted between Asian and Western populations. Therefore, the generalization of our findings to other ethnic groups may be limited. Finally, CCTA itself has limitations including radiation hazard, use of contrast, and higher cost. Although our study enrolled only volunteers, the use of CCTA in asymptomatic individuals has not yet been justified.

결론 (CONCLUSIONS)

In this large observational study of asymptomatic individuals undergoing CCTA, uncontrolled diabetes was associated with significant subclinical coronary atherosclerosis and an increased risk for cardiac events. However, controlled diabetes was only associated with non-significant subclinical coronary atherosclerosis without an increase in cardiac events. These findings should be validated in additional studies.

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STRUCTURED ABSTRACT

Objectives We sought to evaluate the impact of diabetes control on the risk of subclinical coronary atherosclerosis.

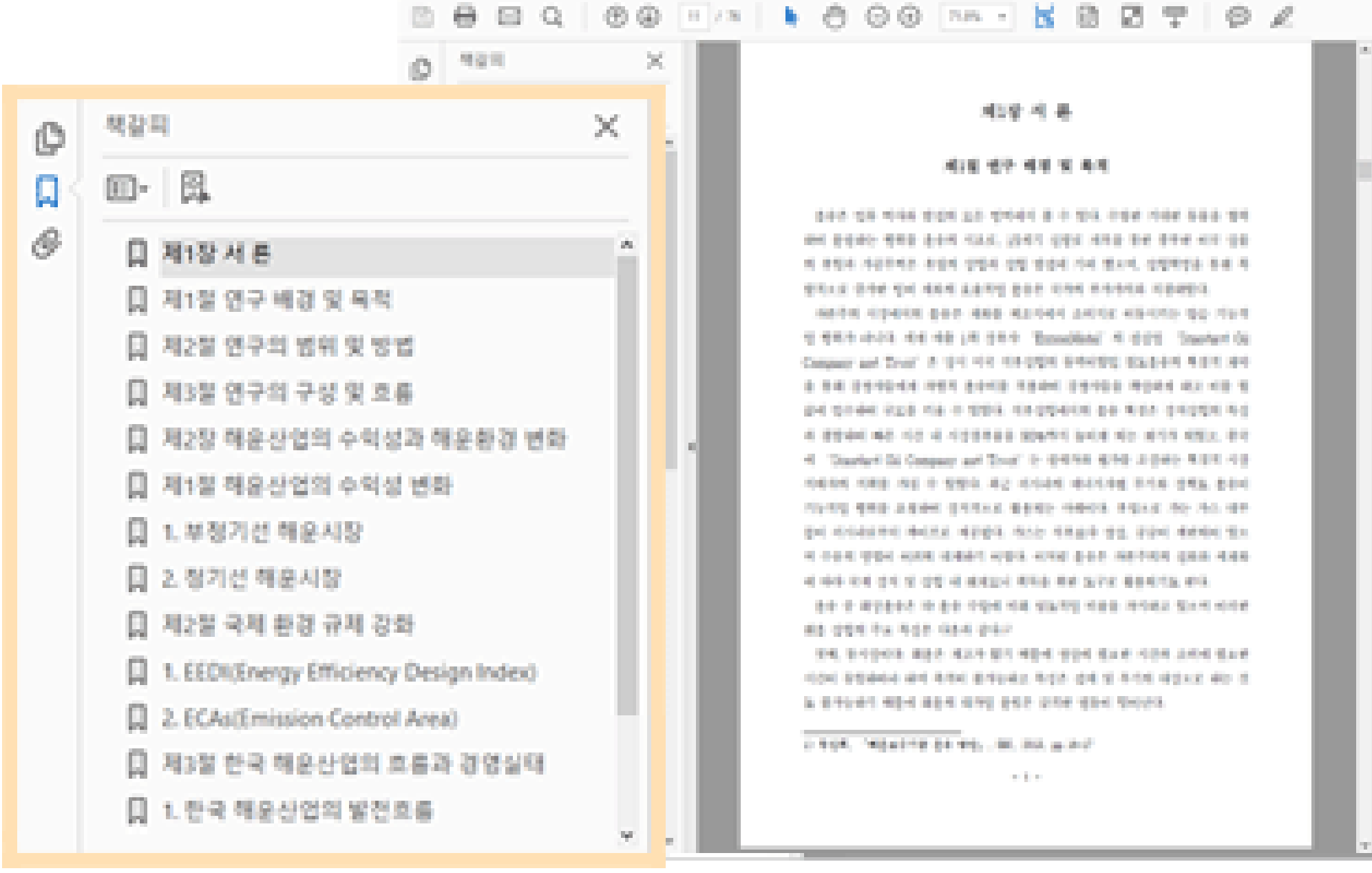
Background There are limited data regarding the relationship between diabetes control and the risk of subclinical coronary atherosclerosis assessed by coronary computed tomographic angiography (CCTA).

Methods We analyzed 6,434 consecutive asymptomatic individuals without previous history of coronary artery disease who underwent CCTA (mean age, 53.7±7.6 years and 4,694 men [73.0%]). The degree and extent of subclinical coronary atherosclerosis were assessed by CCTA, and ≥50% diameter stenosis was defined as significant. A cardiac event was defined as a composite of all-cause death, myocardial infarction, unstable angina, or coronary revascularization. Study participants were categorized as normal (n=5,409), controlled diabetes (hemoglobin A1C <7%, n=666), or uncontrolled diabetes (hemoglobin A1C ≥7%, n=359), respectively.

Results Compared with normal individuals, controlled diabetic individuals had a higher risk for any atherosclerotic plaque (odds ratio 1.23, 95% confidence interval [CI] 1.02–1.47, p=0.029), but there was no difference in significant coronary artery stenosis (odds ratio 1.24, 95% CI 0.93–1.66, p=0.145). In contrast, uncontrolled diabetic individuals had consistently higher risks of any atherosclerotic plaque (odds ratio 2.26, 95% CI 1.76–2.91, p<0.001) and significant coronary artery stenosis (odds ratio 3.46, 95% CI 2.57–4.68, p<0.001) than normal individuals. During a median follow-up of median 21.8 months, there was no significant difference in cardiac events between normal and controlled diabetic individuals (hazard ratio 1.12, 95% CI 0.60–2.11, p=0.726). However, uncontrolled diabetes was associated with increased risk of cardiac events compared with normal individuals (hazard ratio 2.71, 95% CI 1.50–4.91, p=0.001).

Conclusions Among asymptomatic individuals, uncontrolled diabetes was associated with significant subclinical coronary atherosclerosis with subsequent high risk for cardiac events. These findings suggest the importance of diabetes control in asymptomatic individuals.

Key words: Diabetes; control; atherosclerosis; coronary artery disease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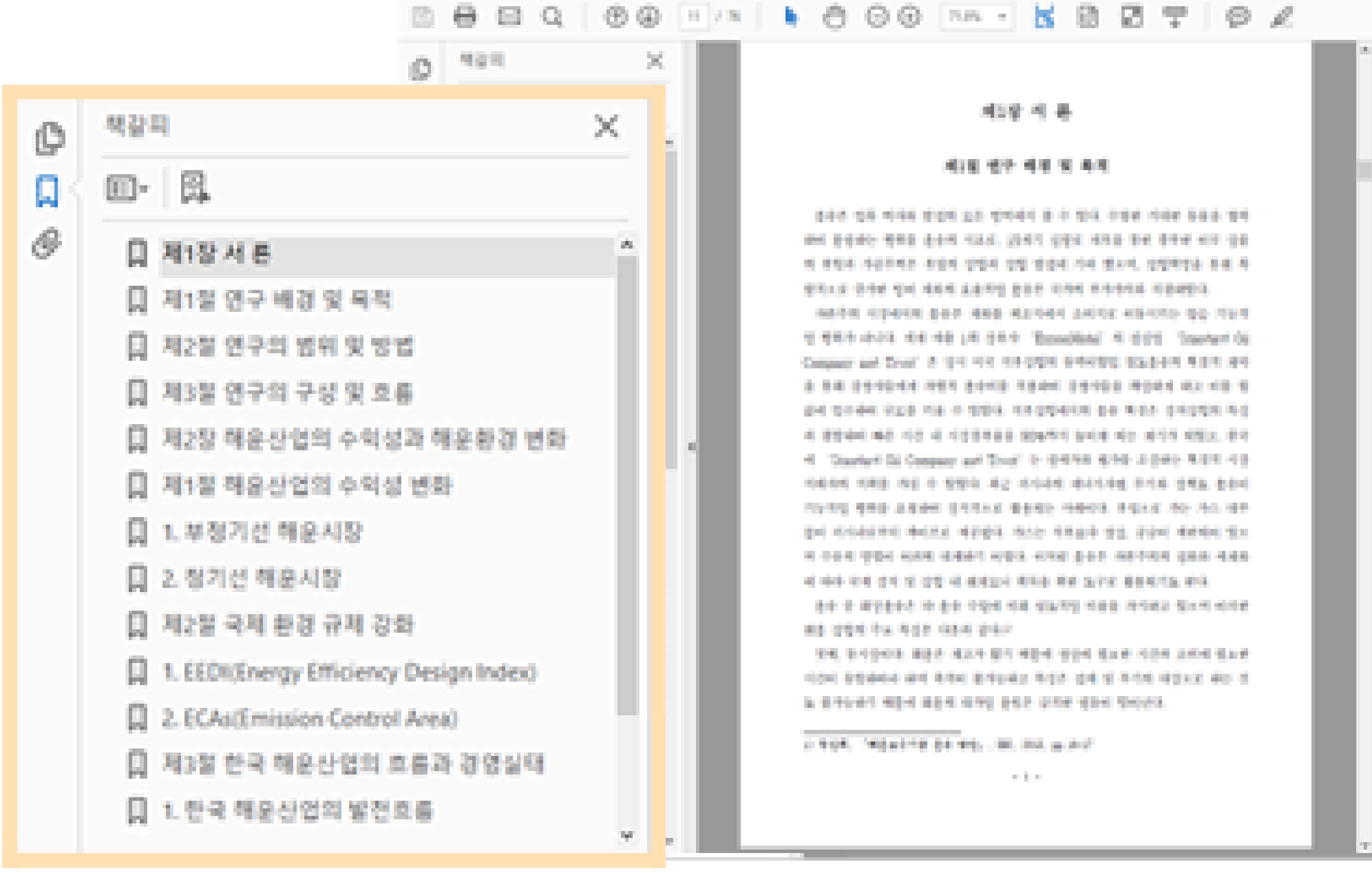
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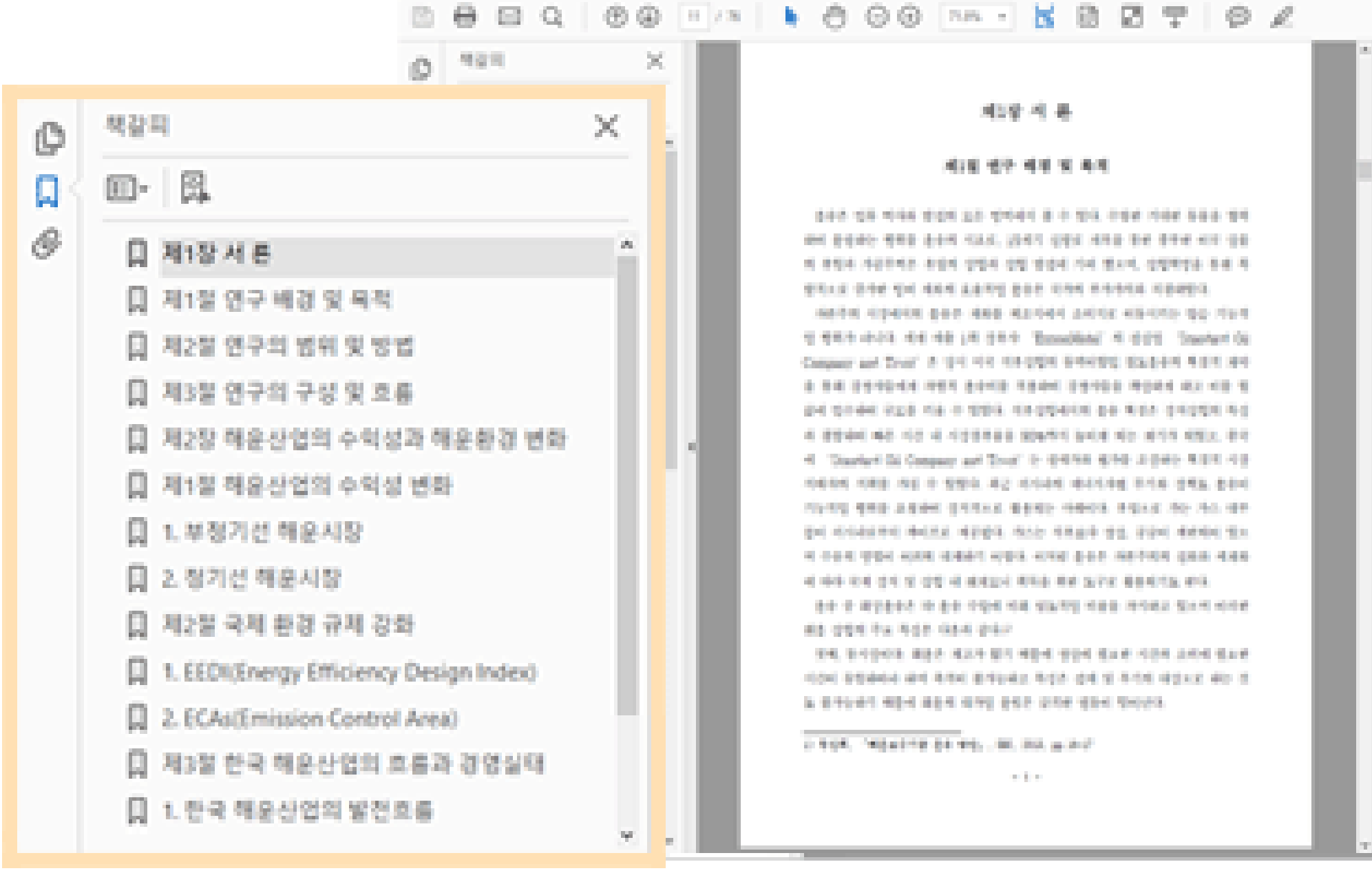
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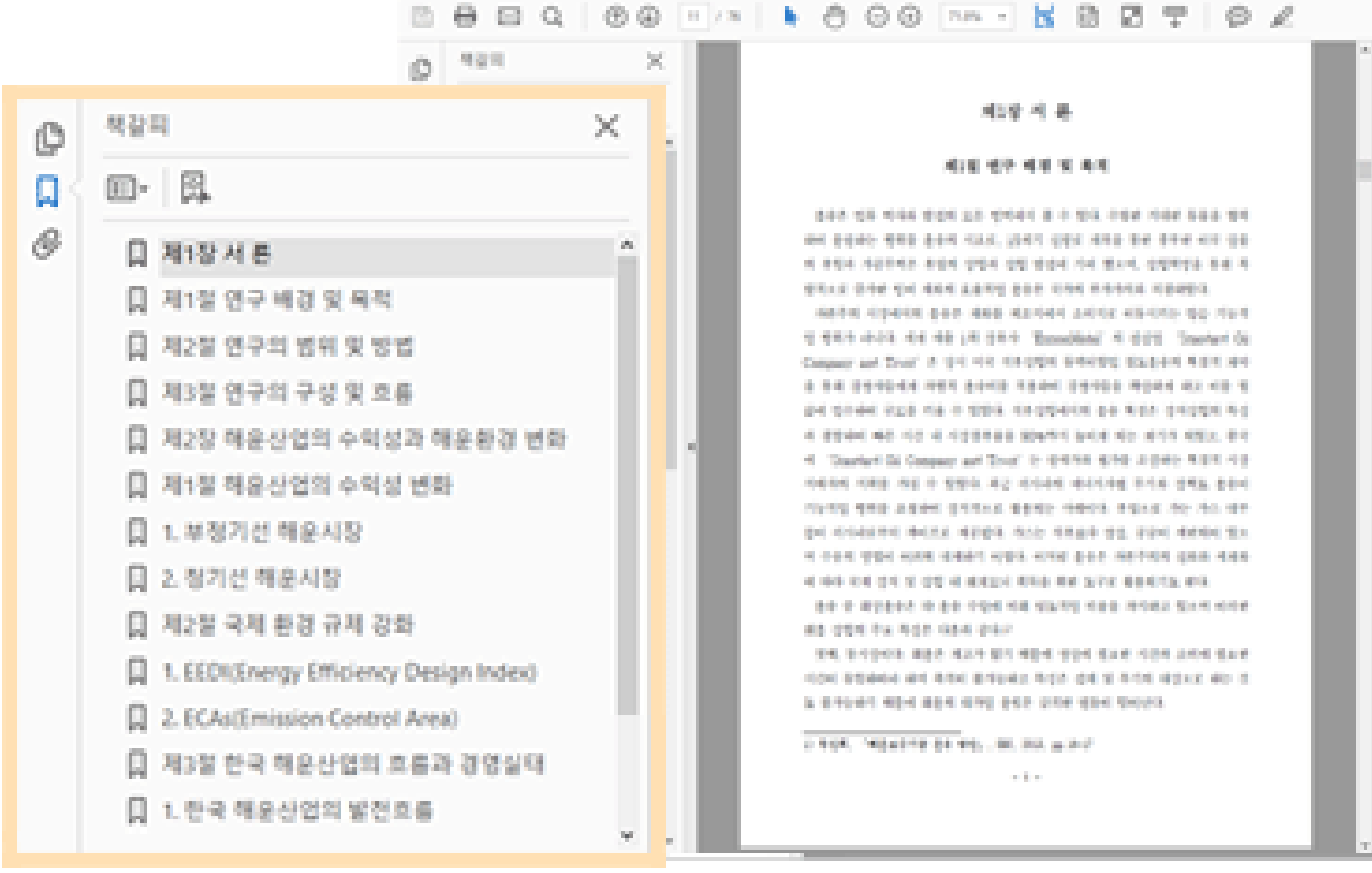
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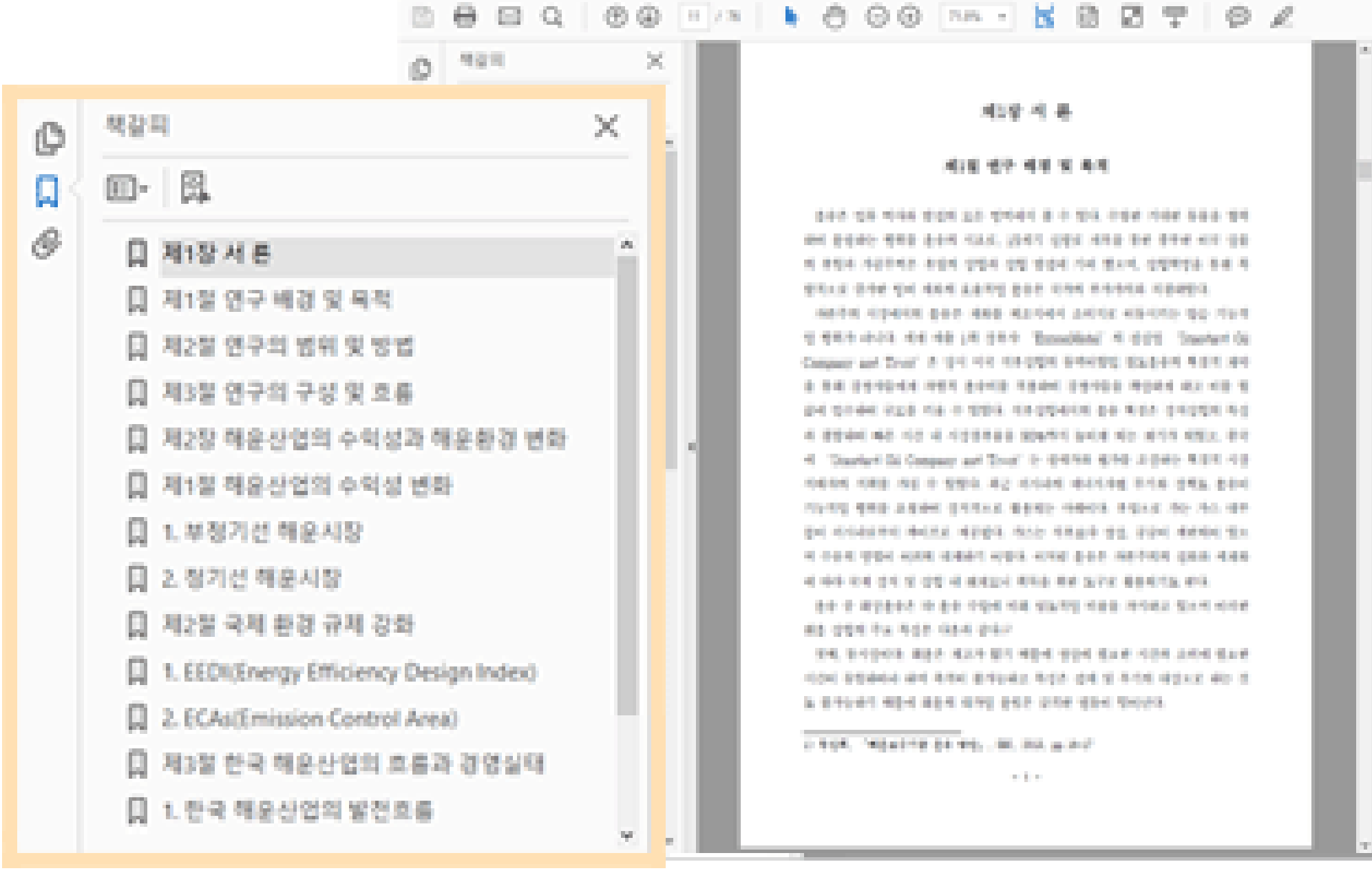
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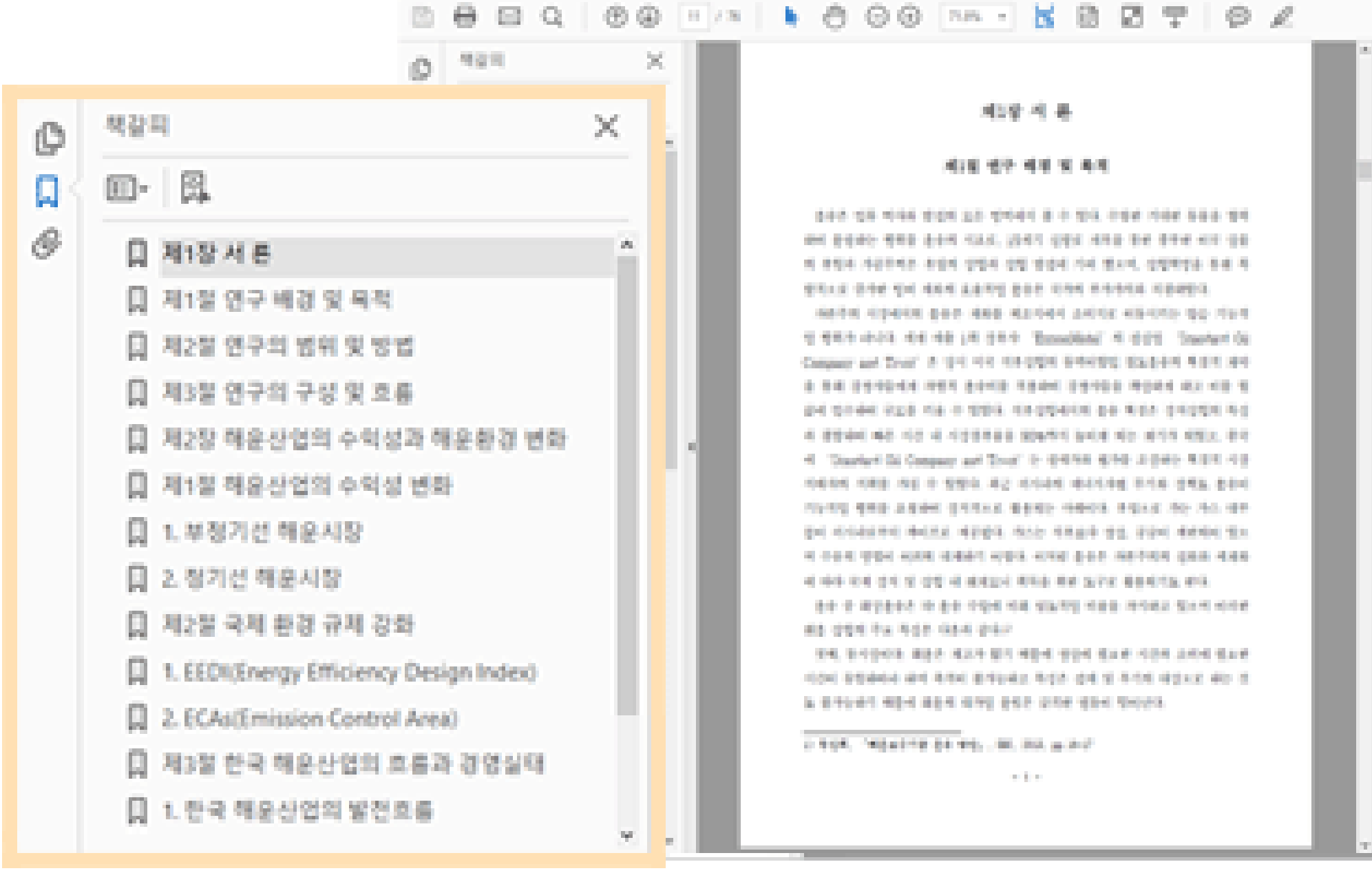
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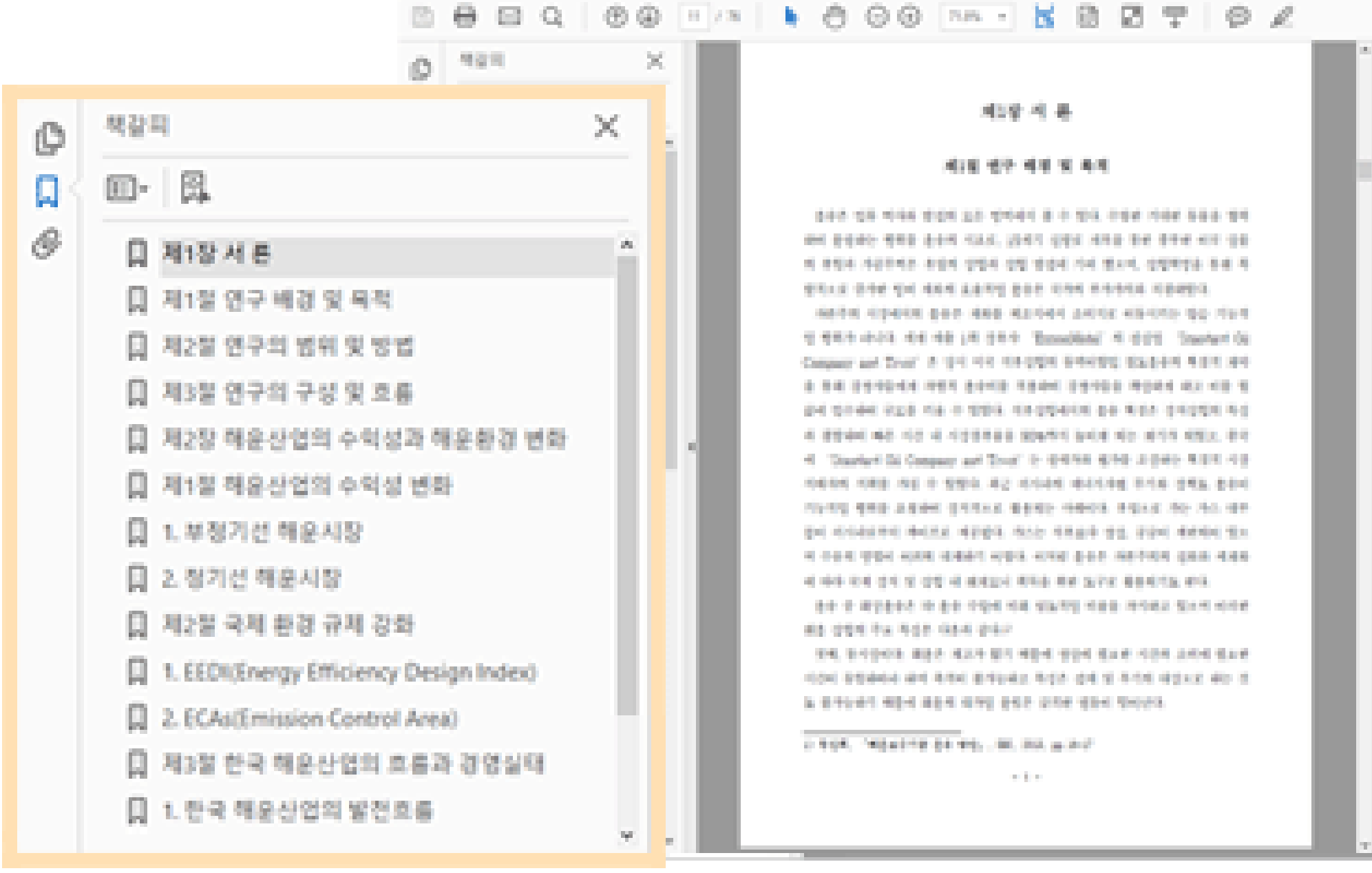
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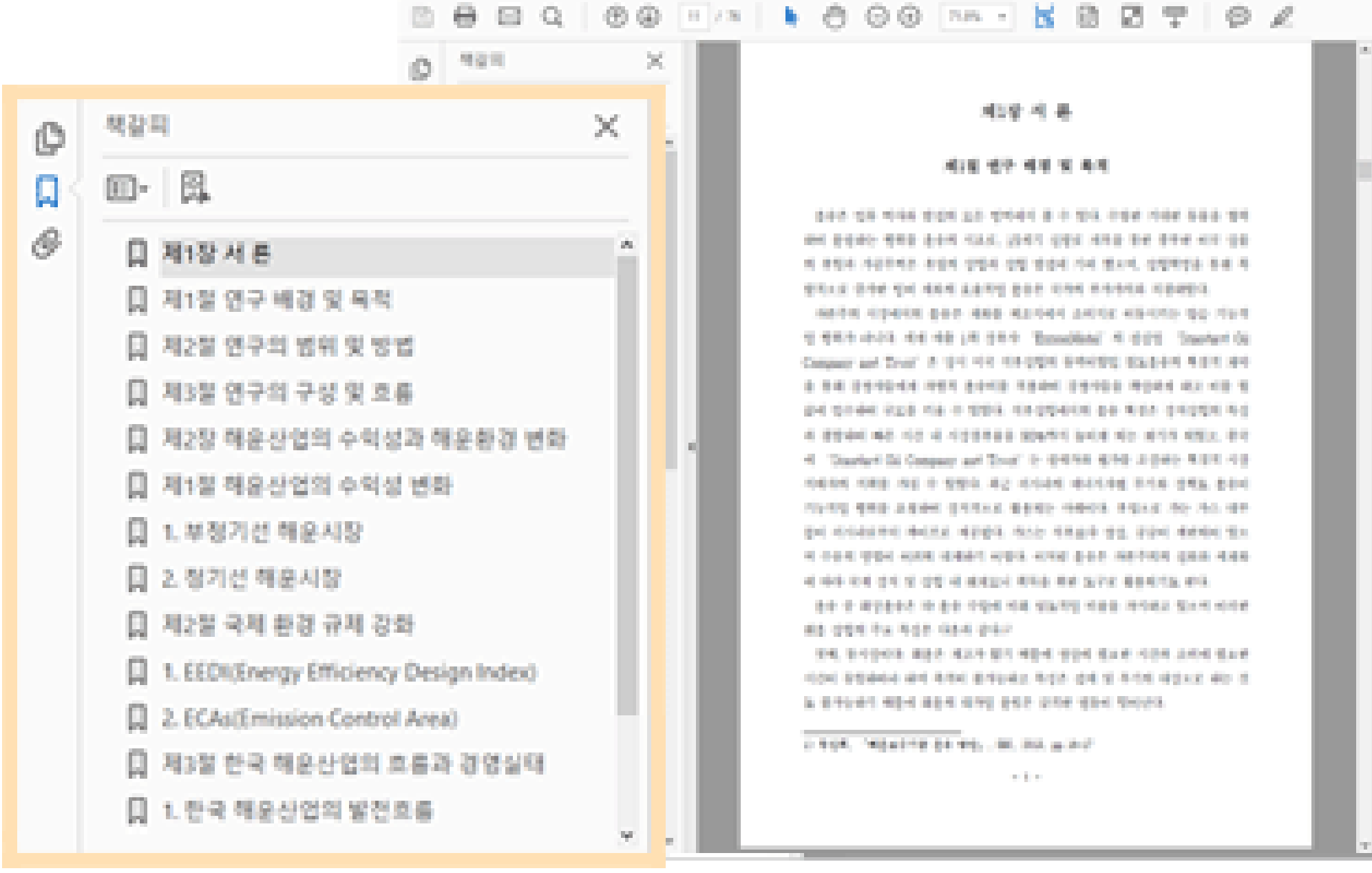
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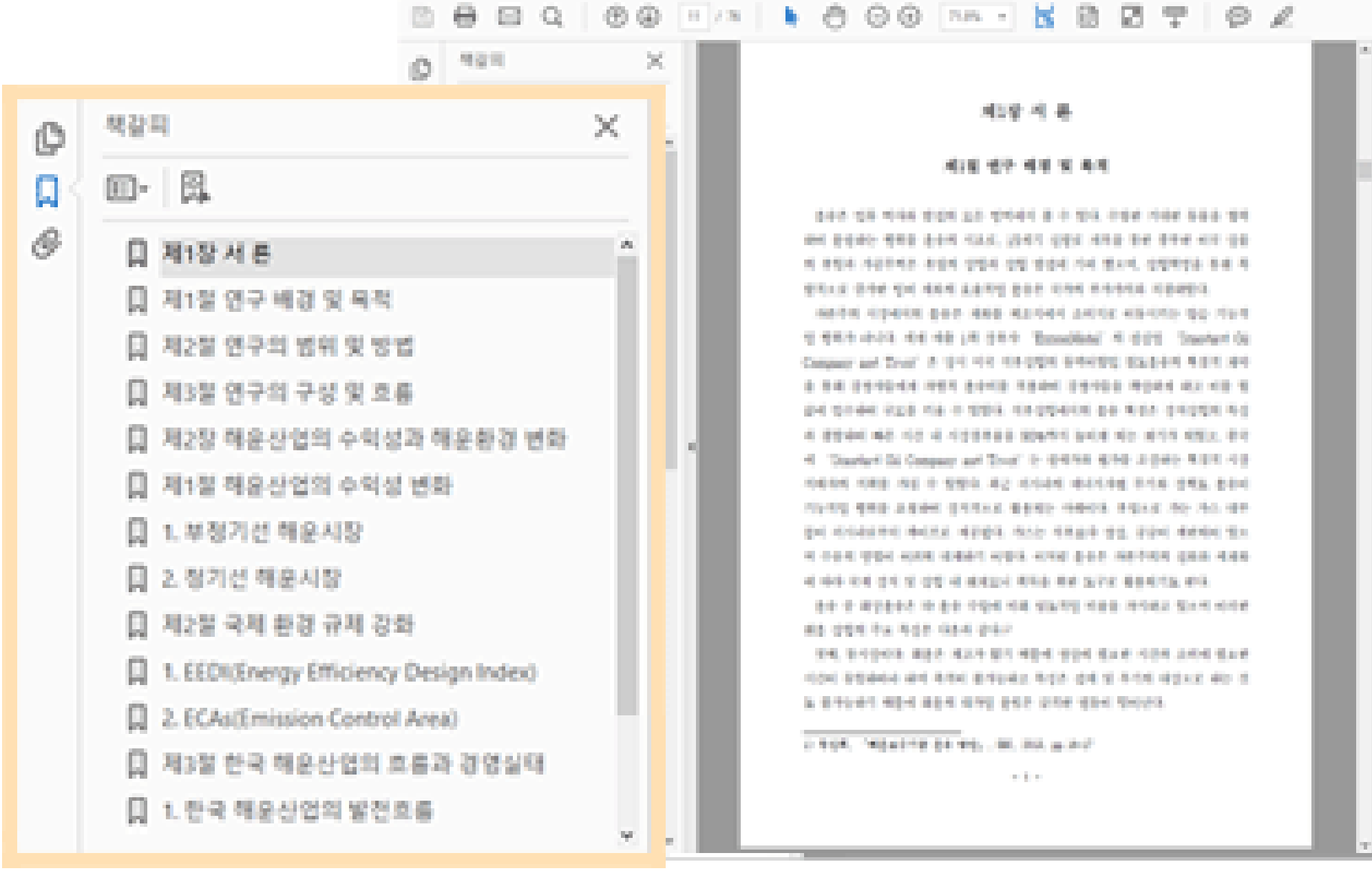
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