Markov Modeling for Microvascular Renal Complication of NIDDM and Hypertension to Evaluate the Use of Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB)

Y. A. Hidayat, T. I. A Padmasawitri, and J. I. Sigit

Abstract— **In the case of chronic disease, randomized clinical trial (RCT) can only provide partial information due to the limitation of observation time. Markov Model is able to accommodate the need of RCT data extrapolation beyond the observation time. In this study, we utilize a Markov Model to investigate two drugs i.e. Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB), for the management of microvascular renal complication of Non-Insulin Dependent Diabetes Mellitus (NIDDM) and Hypertension. We obtain data from previous meta-analysis study of several RCTs. We divide renal complications into four Markov states which represent the albuminuria level. Medication with ACEI and ARB are the treatment decision options. The result shows that ACEI and ARB are effective in halting the progression of renal complication until cycle 9 or 32 years prior to drug treatment initiation. It also shows that, ACEI is more effective when it is used in earlier years (up to 17.5 years), but becomes less effective compared to ARB when the drug treatment is prolonged. A sensitivity analysis is performed and shows that the drug price and the initial disease prevalence influence the model significantly.**

Index Terms— **Markov Model, renal complication, ACEI, ARB**

I. Introduction

Non-Insulin Dependent Diabetes Mellitus (NIDDM) and Hypertension are two examples of chronic diseases which will persist throughout a patient's lifetime. Without a proper medication, such diseases will cause organ deterioration, or generally known as complication. One of the prominent NIDDM and Hypertension complications is the microvascular renal damage. Advance stage of this complication can be found in 27.8% of Diabetes Mellitus patient [1].

As the Renin-Angiotensin-Aldosterone System (RAAS) plays an important role in the renal damage of NIDDM and Hypertension patient [2], a class of drug known as RAAS inhibitor is suggested by some national guidelines as an option for halting the complication's progress. Two types of RAAS inhibitor i.e. Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB) are the current first line options of RAAS inhibitor.

Many RCTs has been performed to evaluate the two drugs efficacy in halting renal complication of NIDDM and Hypertension patient. Due to the slow progression nature of this complication, most RCTs are not able to follow until the endpoint of the disease [3]. Subsequently, a decision analytic model is necessary to be developed to extrapolate RCT data throughout a period which is comparable to patient's life expectancy. In this case Markov model can be utilized to evaluate the drug's performance in affecting the endpoints of the chronic disease.

In brief, we apply Markov decision analysis approach to represent the development of renal complication of NIDDM and Hypertension. We utilize the model to evaluate the use of two RAAS Inhibitors (ACEI and ARB) to halt such complication, from the perspective of Indonesia patients, which are not covered by national medical insurance. Besides evaluating each drug, the utilization of the model also allows direct comparison of the two RAAS Inhibitors, where such comparison is rarely conducted in previous similar studies.

II. Study Design

A Markov model is utilized in this study due to the ability to model long-term outcome, where cost and effects are spread out over a long period of time [3]. It is also used for modeling diseases with repetitive nature [3]. On the first stage of model development we identify parameters that construct the mode. The relationship among those parameters can be seen in the influence diagram (Figure 1).

The model is used to evaluate drug treatment options in order to determine one drug option with the lowest cost utility ratio. Two parameters i.e. cost of medication and utility are necessary to be calculated in order to determine the cost utility ratio. Utility is influenced by renal condition; furthermore, the renal condition will be influenced by the performance of drug treatment. On the other hand, cost of medication is influenced by drug treatment option, and other cost component such as cost of side-effect treatment.

Manuscript received March 18, 2013; revised April 10, 2013.

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ISBN: 978-988-19251-0-7
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

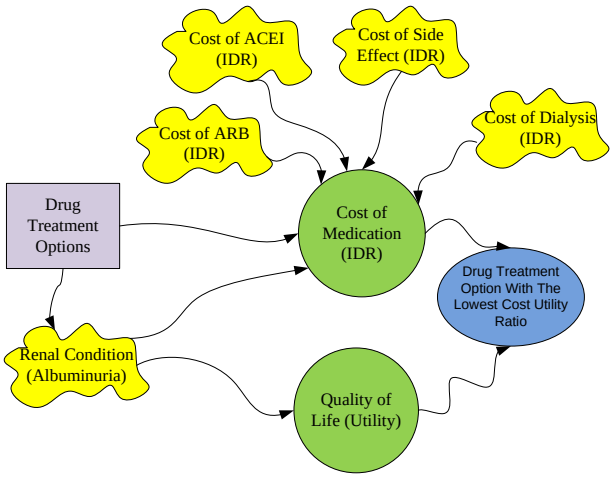

Fig. 1 *Influence diagram.*

In utilizing Markov model, we collect several data from previous studies. The process is described in Figure 2.

A. Markov States and Transition

An earliest clinical symptom of renal complication is the presence of albumin in urine or known as albuminuria. We divide renal complication into four Markov states based on the progression of albuminuria level which are: state 0 for normoalbuminuria (< 30 mg/d), state 1 for microalbuminuria (30-300 mg/d), state 2 for macroalbuminuria (>300 mg/d), and state 3 for doubling serum creatinine (hallmarked by the necessity for dialysis therapy). The possible transition is illustrated in Figure 3.

We assume that patient with normoalbuminuria has good compliance towards the drug, good blood pressure control and blood glucose level. Therefore, patient who reaches state 0 will be able to stay in this state during drug treatment period. We also assume that a regression is possible to occur from microalbuminuria to normoalbuminuria since the damage is reversible. Another assumption we make is the unlikely transition from macroalbuminuria or DSC to normoalbuminuria since the damage is irreversible. Last, we also assume that transition from microalbuminuria to DSC is unlikely to happen due to the low probability, so we do not consider it as a possible transition.

Transition probability is derived from Meta-Analysis study of several RCTs performed by [4]. Relative risk data (Table 1) from the previous study are used to calculate the probabilities.

TABLE I
MODEL CONSTRUCTION SUPPORTING DATA

Variable	Value	Reference
Disease Prevalence		
Normoalbuminuria	22.3%	[11]
Microalbuminuria	33.0%	[11]
Macroalbuminuria	44.7%	[11]
Relative Risk		
ACEI vs. Placebo		
State 2 to State 1	0.49	[4]
State 2 to state 3	0.62	[4]
State 1 to state 0	2.99	[4]
ACEI vs. ARB		
State 2 to State 1	1.2	[4]
State 2 to state 3	1.03	[4]
State 1 to state 0	1	[4]
Utility		
State 0	0.67	[10]
State 1	0.63	[10]
State 2	0.54	[10]
State 3	0.54	[10]

For ACEI, relative risk data in the study is derived from RCTs comparing the probability of ACEI arms to the probability of placebo arms in experiencing renal complication. Relative risk for each transition is derived from different combination of RCTs. First, probability of ACEI for each transition is calculated using (1) to (5).

$$RR = \frac{Probability\ for\ State\ Transition\ of\ ACEI}{Probability\ for\ State\ Transition\ of\ Placebo} = \frac{PACEI_a}{PPlac} \quad (1)$$

$$RR = \frac{PACEI_a}{1-PACEI_a} \quad (2)$$

$$RR - (RR)(PACEI_a) = PACEI_a \quad (3)$$

$$RR = PACEI_a \quad (4)$$

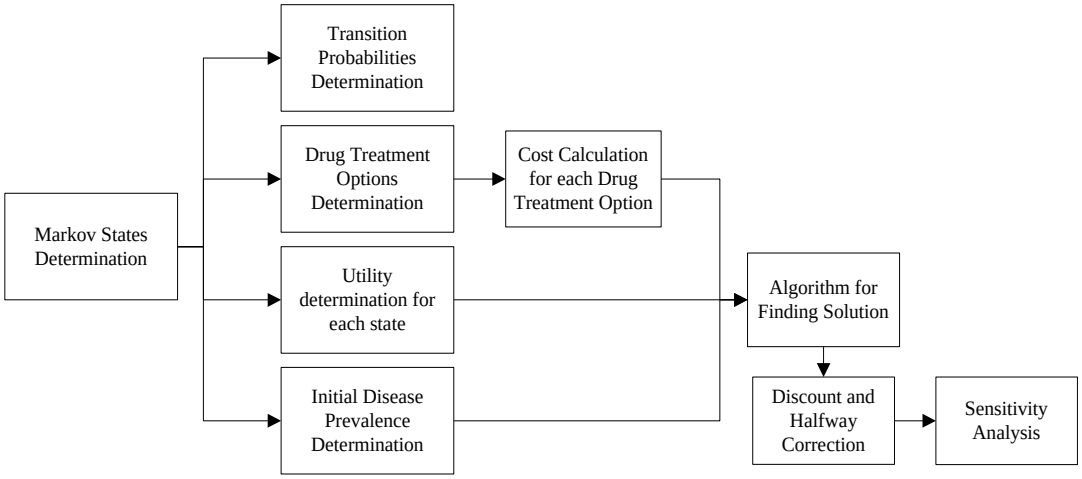

Fig. 2 Model construction and calculation process.

ISBN: 978-988-19251-0-7
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

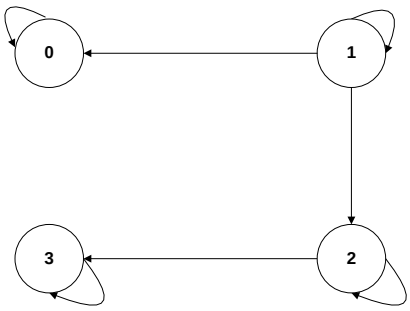

Fig. 3 Markov states transition representing health states transition.

$$PACEI_a = \frac{RR}{1+RR} \quad (5)$$

According to (5), it is not feasible to use $PACEI_a$ of each transition directly since the relative risk data is derived from different RCTs combination compared to placebo. Therefore, in order to derive the transition probability of ACEI, we need to find number of patient using ACEI for each transition using (6).

$$number\ of\ patient\ using\ ACEI = PACEI_a \times Total\ RCT\ participant \quad (6)$$

After the number of patient using ACEI for each transition is obtained, we can calculate the transition probabilities using (7).

$$PACEI = \frac{number\ of\ patients\ using\ ACEI\ ..(6)}{\sum number\ of\ patients\ using\ ACEI\ (from\ all\ RCTs)} \quad (7)$$

ARB transition probabilities are derived from ACEI transition probabilities. Using relative risk data of ACEI versus ARB from Table 1, we calculate ARB probabilities using (8).

$$PARB = \frac{PACEI}{RR} \quad (8)$$

Since the probabilities are taken from relative risk data of meta-analysis study, the cycle length is also based on the average length of the incorporated RCTs. Therefore, we determined that one cycle represents 3.5 years. During this period of time, health state transitions are observed significantly.

We calculate rewards for each drug treatment options, which are cost and utility. Cost depends on choice of drug and health state, while utility only depends on the health state.

B. Drug Treatment Option and Cost Determination

ACEI or ARB is used in every health state. We also consider ACEI high rate side effect, which is dry cough. We calculate the side effect cost by calculating the side effect prevalence derived from previous study [5] and dextromethorphan (DMP) cost which is assumed to be used in dry cough management. Annual cost for medication with ACEI is calculated using the average price of all available ACEI drug in Indonesia's market, incorporated with cost for side effect medications mentioned before. The same calculation is also applied in determining ARB cost but without the side effect cost. This is due to the fact that ARB usage does not produce such side effect. Since the cycle length is 3.5 years, the annual cost is calculated to suit this length of cycle.

For each group of drug (ARB and ACEI), first we calculate annual cost of individual drug using (9).

$$annual\ cost\ of\ drug = number\ of\ tablet\ \left(\frac{Tablet}{day.person}\right) \times Price\ \left(\frac{Rupiah}{tablet}\right) \times 30(days) \times 12 \quad (9)$$

For ACEI we add the cost with side effect treatment cost, calculate using (10).

$$annual\ side\ effect\ cost = number\ of\ DMP\ tablet\ \left(\frac{tablet}{day.person}\right) \times Price\ \left(\frac{Rupiah}{Tablet}\right) \times 30(days) \times 12 \quad (10)$$

In this study state 3 is hallmarked by RRT represented by dialysis treatment. Cost for dialysis is standardized based on The Indonesian Diatrans Kidney Foundation. The foundation provides average price data of dialysis treatment in Indonesia. The frequency for dialysis is two times a week. We calculate the dialysis price using (11).

$$dialysis\ annual\ cost = 12\ (months) \times number\ of\ dialysis\ treatment\ \left(\frac{treatment}{month}\right) \times Price\ for\ dialysis\ treatment\ \left(\frac{Rupiah}{Treatment}\right) \quad (11)$$

Drug Price is determined using the Indonesian highest retail price enclosed in standard book issued by professional organization and Ministry of Health [6], [7], [8]. The unlisted price is calculated using a published percentage of drug prices available in Table 2 derive from previous study [9].

TABLE II
type of drug and price percentage

Type of Drug	Percentage	Reference
Patent/*Off*-Patent	100%	[9]
Branded Generic	30%-80%	[9]
Generic	10%-30%	[9]

C. Utility

Utility data are obtained from previous study in [10]. We assume that patients in State 0 are NIDDM patients with no complication, while patients in State 1 are patients with one complication and patients in State 2 are patients with 2 complications or more. This assumption is based on the findings from epidemiology study [10], which states that patient in State 2 has at least one complication and one cardiovascular complication. Utility value can be seen in Table 1.

D. Initial Disease Prevalence

Epidemiology profile shows that during the initiation of medication most of the patients are in state 1 or state 2 [11]. The initial disease prevalence can be seen in Table 1.

ISBN: 978-988-19251-0-7
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

E. Discount Rate and Halfway Correction

Halfway correction is employed with the assumption that transition happens midway through each states. Since there is no standard in Indonesia, we applied 5% of discounting rate for each cycle to accommodate positive time preference of patients.

F. Sensitivity Analysis

Sensitivity analysis is conducted for several parameters including: *utility, price, and initial disease prevalence.* The purpose of this analysis is to determine parameters that affect the model significantly.

III. Results and Discussion

We multiply transition probabilities matrix and initial disease prevalence, and then replicate it for 20 cycles (representing 70 years). It is extrapolated way beyond life expectation years in order to evaluate the drug use effectiveness. From the calculation we derive numbers of patient in each state for each cycle. It can be seen from this calculation that transition for each cycle is quite similar for the two drugs. The mathematical operation to derive solution (S) is shown on (12) for ACEI and (13) for ARB.

$$number\ of\ patients\ in\ each\ cycle\ after\ 20\ cycles\ replication = ([Initial\ Disease\ Prevalence] \times [Transition\ Probabilities])^{20}$$

$$S_{ACEI} = \left([22 \quad 33 \quad 45 \quad 0] \times \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0.25 & 0.58 & 0.17 & 0 \\ 0 & 0 & 0.41 & 0.59 \\ 0 & 0 & 0 & 1 \end{bmatrix} \right)^{20} \quad (12)$$

$$S_{ARB} = \left([22 \quad 33 \quad 45 \quad 0] \times \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0.25 & 0.61 & 0.14 & 0 \\ 0 & 0 & 0.43 & 0.57 \\ 0 & 0 & 0 & 1 \end{bmatrix} \right)^{20} \quad (13)$$

At the end of cycle 9 (representing 32 years), in ACEI usage, most patients are experiencing DSC (58%), while 41% patients manage to regress and maintain their renal condition at normoalbuminuria. Hence 1% of patients experience microalbuminuria or macroalbuminuria. Similar pattern is found in ARB usage, but less patients experience DSC (56%) and more patient manage to regress to normoalbuminuria (43%). From the 10th cycle onward all patients have reached the absorbing state. At the 10th cycle, 57% of patients for ARB and 58% of patients for ACEI experience DSC, and another portion of patients managed to regress and stay in normal health state. This composition of patients remains stagnant until the end of the 20th cycle. Therefore ACEI and ARB is effectively used for halting renal complication progression only for 32 years prior to the starting of medication. This finding justifies the use of ARB and ACEI throughout the normal progression time of untreated renal complication to DSC state, which is 20 years according to American Diabetes Association [12].

It is important to point out that this finding is based on initial disease prevalence of Indonesia's population, where most patients already experience microalbuminuria or macroalbuminuria prior to ACEI or ARB medication [11]. There is a possibility that earlier intervention is able to prolong the effective usage period of these drugs.

To determine how long the drugs are able to maintain patient's health state in DSC or normoalbuminuria, a further investigation need to be conducted using another model. The model should include possible transition from normoalbuminuria to the worse health state i.e. microalbuminuria, despite maximum control of blood pressures and blood glucose. The model should also accommodate possibilities of death after patients experience the worst state of albuminuria which is DSC.

For further analysis, we multiply the number of patients in each state for each cycle with the rewards, which are the cost and utility. We calculate cost utility ratio for each cycle and each drug. Cost utility ratio describes the cost paid by a patient to gain 1 point of utility.

Cost utility ratio profile shows that in early cycles, up until the 2nd cycle (representing 7 years), the use of ACEI results in lower cost utility ratio. However, in long term use, ARB results in lower cost utility ratio.

When we calculated the cost utility ratio of accumulated cost and utility for 4, 5, and 6 cycles, we found that ratio of accumulated cost and utility for 5 cycles (representing 17.5 years) is lower for ACEI compared to ARB. However, the ratio of accumulated cost and utility of 6 cycles is lower for ARB compare to ACEI. Furthermore, the ratio of accumulated cost and utility of 20 cycle's shows that ARB users spare 0.05% of cost and gain 0.27% of utility value compare to ACEI users. Therefore, ACEI is more effective when used up until 17.5 years. Switching to ARB can be considered when the drug is used in a longer period.

A sensitivity analysis is performed and results in two sensitive parameters which are drug price and initial disease prevalence. Related to the drug price parameters, sensitivity analysis shows that when the price of branded generic drug is greater than or equal to 80% of the patent drug price, ARB's cost utility ratio becomes greater, and ACEI is more preferable. The same result is also found for generic drug price greater than or equal to 45% of the patent drug price. This is caused by the condition in which ARB patent drug price is marketed in Indonesia with higher price compared to ACEI. Therefore, if the available drug cost almost as high as patent drug, ACEI is preferable. Sensitivity analysis of price percentage is shown in Figure 4.

Branded generic price closely resembling patent drug price possibly happens in Indonesia due to the lack of government control [9]. Furthermore generic drug utilization is also limited in Indonesia due to several factors including government's inability to produce it [9].

Some insights are also found from the sensitivity analysis of initial disease prevalence. We test various disease prevalence ranging from the majority of patients already experiencing macroalbuminuria, to the majority of patients in microalbuminuria state. The minimum cost utility ratio of the two drugs is achieved when the composition of initial disease prevalence consist of 10% in macroalbuminuria, 54% in microalbuminuria and 36% in normoalbuminuria (Figure 5). Furthermore, it also shows that drug intervention employed in the early stage of albuminuria results in lower cost utility ratio. This finding emphasizes the need of an effective screening policy which allows early drug intervention. Another alternative is to employ 'treat all' policy, where all NIDDM and Hypertension patient regardless their albuminuria status should receive RAAS inhibitor. Ardakwah *et al*. [13] found that from the perspective of third party payer in The Netherlands, 'treat all' policy for NIDDM and Hypertension patients with ACEI is cost effective. A further investigation needs to be conducted to assure that same policy will gain same result in Indonesia.

ISBN: 978-988-19251-0-7
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

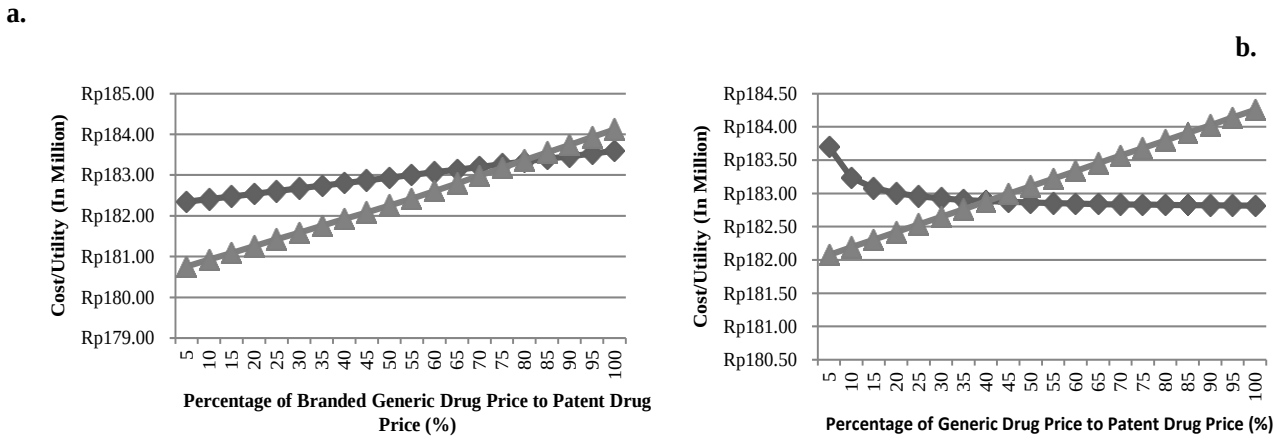

Fig. 4 Sensitivity analysis of price parameter, which are branded generic price (a) and generic price (b)

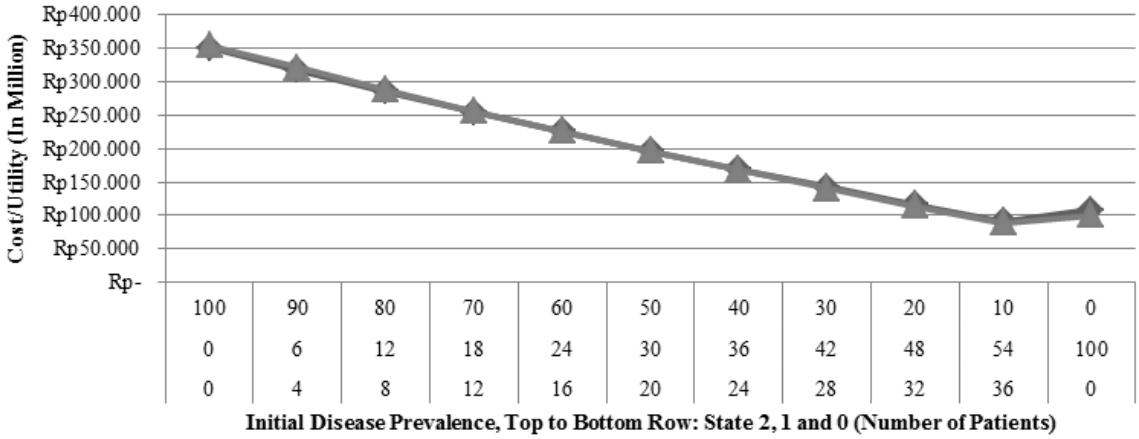

Fig. 5 Sensitivity analysis of intial disease prevalence parameter (▲: ARB, ◆: ACEI).

IV. Conclusion

A Markov model is used as an approach to select drug options in the case of Non-Insulin Dependent Diabetes Mellitus (NIDDM). This issue is a current theme in pharmacology science combined with operation research or engineering approach. A pharmacoeconomics consideration is considered in terms of cost and utility from the patient point of view, not only considering efficacy and quality of the drugs. We use meta-analytic data for testing our model instead of one-shot clinical data due to Markov model characteristics. We found that the RAAS inhibitor is effective in halting renal complication in NIDDM and Hypertension patient for 32 years period of use, starting from the first diagnosis of albuminuria. To ensure cost effective medication, early intervention with RAAS inhibitor to NIDDM and Hypertension patient is necessary, therefore there is a need of an effective albuminuria screening policy in Indonesia.

ACEI is the treatment option on early years up until 17.5 years prior to drug treatment initiation. For prolonged drug use, ARB can be considered. Sensitivity analysis shows that generic drug price, branded generic drug price and initial disease prevalence influence the model significantly.

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ISBN: 978-988-19251-0-7
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ISBN: 978-988-19251-0-7
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)