Formalization and Acquisition of Temporal Knowledge for Decision Support in Medical Processes

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Abstract

Background: In medical practice, long term interventions are common and they require timely planning of the involved processes. Unfortunately, evidence-based statements about time are hard to find in Clinical Practice Guidelines (CPGs) and in other sources of medical knowledge. At the same time, health care centers use medical records and information systems to register data about clinical processes and patients, including time information about the encounters, prescriptions, and other clinical actions. Consequently, medical records and health care information systems are promising sources of data from which we can detect temporal medical knowledge.
Objective: The objectives were to (1) Analyze and classify the sorts of time constraints in medical processes, (2) Propose a formalism to represent these sorts of clinical time constraints, (3) Use these formalisms to enable the automatic generation of temporal models from clinical data, and (4) Study the adherence of these intervention models to CPG recommendations.
Methods: In order to achieve these objectives, we carried out four studies: The identification of the sort of times involved in the long-term diagnostic and therapeutic medical procedures of fifty patients, the supervision of the indications about time contained in six CPGs on chronic diseases, the study of the time structures of two standard data models, as well as ten languages to computerize CPGs. Based on the provided studies, we synthesized two representation formalisms: Micro- and macro-temporality. We developed three algorithms for automatic generation of generalized time constraints in the form of micro- and macro-temporalities from clinical databases, which were double tested.
Results: A full classification of time constraints for medical procedures is proposed. Two formalisms called micro- and macro-temporality are introduced and validated to represent these time constraints. Time constraints were generated automatically from the data about 8,781 Arterial Hypertension (AH) patients. The generated macro-temporalities restricted visits to be between 1-7 weeks, whereas CPGs recommend 2-4 weeks. Micro-temporal constraints on drug-dosage therapies distinguished between the initial dosage and the target dosage, with visits every 1-6 weeks, and 2-5 months, respectively. Our algorithms obtained semi-complete maps of dosage increments and the maximum dosages for 7 drug types. Data-based time limits for lifestyle change counsels and blood pressure (BP) check-ups were fixed to 6 and 3 months, for patients with low- and high-BP, respectively, when CPGs specify a general 3-6 month range.
Conclusions: Experience-based temporal knowledge detected using our algorithms complements the evidence-based knowledge about clinical procedures contained in the CPGs. Our temporal model is simple and highly descriptive when dealing with general or specific time constraints' representations, offering temporal knowledge representation of varying detail. Therefore, it is capable of capturing all the temporal knowledge we can find in medical procedures, when dealing with chronic diseases. With our model and algorithms, an adherence analysis emerges naturally to detect CPG-compliant interventions, but also deviations whose causes and possible rationales can call into question CPG recommendations (e.g., our analysis of AH patients showed that the time between visits recommended by CPGs were too long for a proper drug therapy decision, dosage titration, or general follow-up).

Keywords: Temporal knowledge representation, time modelling, time constraints generation, decision support, medical procedural knowledge, clinical practice guidelines, cardiovascular diseases

1. Introduction

Time is intrinsic to medical practice. Therefore, time must be part of any representation of medical practice knowledge or only instantaneous clinical decisions could be made. Long-term interventions and planning in medicine are common and they demand a description of time constraints about the clinical

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actions involved. These actions are correct not only if they are done, but also if they are done at and during the right time. The health conditions of patients start and hold during a set time or over a time period. Clinical interventions occur at one or more points in time or over periods of time [42]. However, this temporal dimension is not always available, or is just partially considered, in Clinical Practice Guidelines (CPGs). CPGs are conceived to support decision-making processes in health care, covering health maintenance, prevention, diagnosis, treatment, patient self-care, and education. They describe medical procedures as a narrative set of recommendations for the management of patients who have a particular disease. CPGs dealing with chronic disorders require the patient's treatment to be continued over time, often for the remainder of the patient's life [6]. Some CPGs can include certain time-related parameters, such as the recommended time between two consecutive encounters during dosage titration. Nevertheless, very often, times are unspecified and, consequently, physicians are supposed to fill these information gaps with their own knowledge and experience.

Several studies have shown that the quality of health care is directly related to the experience of the physicians involved [8, 24, 25, 32]. The argued rationale is that physicians with experience can reason better than less experienced or inexperienced physicians because they have a greater ability to combine different sorts of knowledge acquired from several sources and from their own professional education, training, and experience. Consequently, they use to make wiser decisions. However, even senior physicians may have serious difficulties, or they might be reluctant to ascertain general time constraints for some diseases or clinical actions. To our knowledge, currently, there are no mechanisms to help physicians obtain evidence-based knowledge about the time constraints that should be included in CPGs. However, health care centers use medical records and information systems to register data about clinical processes and patients, including information about the times in which the encounters took place, the prescriptions that were made, or when other clinical actions happened [3, 5, 25, 27, 29, 30, 47, 48]. Information overload is becoming an issue as patients' data and medical information are being accumulated. We are heading towards an era of big data, where the issue is not only the amount of data available, but also the velocity of accumulation and sharing, as well as its variety. Many issues appear related to this data explosion, such as the complexity and heterogeneity of clinical data. The interest in discovering hidden information is emerging [28]. This information is not necessarily evidence-based, but gathered from the experience of daily medical practice. It can be recognized and transformed into medical knowledge with the help of computer intelligent data-analysis techniques and tools to support decision-making [3, 4, 5, 27, 29, 30, 47, 48, 49]. Consequently, medical records and health care information systems are promising sources of information to detect medical knowledge about time in medicine. When modelled, this experience-based knowledge about time can complement the evidence-based knowledge about clinical procedures contained in the CPGs, thus allowing Timed Medical Decision Support Systems' (TMDSS) development and exploitation.

In [21], Extended Timed Transition Diagrams (eTTDs) were proposed as an intuitive, easy, and efficient mechanism to formalize knowledge about medical procedures. eTTDs are state-transition diagrams in which states describe clinical situations in terms of a set of state variables with a clinical sense. Transitions between pairs of eTTD states are possible. They are represented as state-to-state edges that are labelled with (1) Clinical conditions that the patients crossing the edge satisfy, (2) Medical activities or actions describing the treatment provided to these patients, and (3) A time interval constraint representing the time for them to evolve to the next state. An eTTD can have transitions showing clinical situations in which a patient's condition remains the same following a clinical activity and time interval. Clinical actions in the transitions that correspond to pharmacological interventions can include a dose (e.g., 200 mg) and an intake frequency (e.g., every 8 hours). Both the dose and the intake frequency define the dosage of the pharmacological action.

In [21], eTTDs were used to represent knowledge about medical practice for the management of chronic patients at three levels of detail: Therapy strategy, dosage titration, and drug intolerance management. The modelling of these three levels of clinical knowledge was applied to offer help in decision-making processes for long-term treatments. The main limitation of that work was the lack of formalized representation for time constraints.

Here, in order to complement that work and to identify common time constraints in medical practice, we analyzed diagnostic and therapeutic medical procedures for 50 randomly chosen patients registered in

the primary care information system of the SAGESSA Health Care Group[1] (Spain) [41]. We also analyzed several CPGs about chronic diseases in order to detect the sorts of time constraints contained, and studied the time constructs of the standard data models EHRcom [11] and CDA HL7 [19], as well as several languages to computerize CPGs, to detect the sort of time constraints that they can represent. Based on this quadruple analysis, we synthesized two representation formalisms of time constraints in medicine: micro- and macro-temporality. Here, we also provide algorithms to generalize time constraints in the form of micro- and macro-temporalities from hospital datasets. When detected, constraints can be used to (1) complement evidence-based knowledge from CPGs with experience-based temporal knowledge obtained from data and to (2) study the adherence of physicians to the time constraints suggested in CPGs.

The rest of this paper is organized as follows. Section 2 deals with our proposal of time modelling for medical procedures. It begins with a classification of the time constraints for medical processes that we found after our analyses were conducted. It continues with a proposal on modelling the temporal dimension of medical procedures, and provides validation of the proposed temporal model. In Section 3, we propose computer algorithms for automatic generation of time constraints derived from data on medical processes. It also provides two types of tests and a discussion on the obtained results considering their medical correctness and adherence. Discussion and conclusions are presented in Section 4 and Section 5, respectively.

2. Time modelling of medical procedures

In order to formalize medical time constraints, we analyzed the sort of time indications that can be found in the medical processes registered in the medical records of several patients who were attended in the health care centers of the SAGESSA group. Moreover, we reviewed six clinical practice guidelines for three of the most prevalent cardiovascular diseases according to the World Health Organization (WHO) [50]. Finally, we also studied two of the most used standards for health care data representation (EHRcom and HL7 CDA) and ten of the most preferred languages used to computerize CPGs, and identified the constructs they use to represent time constraints. As a result of this multi-pronged analysis, we proposed a model to represent clinical time constraints in medical practice. The model is simple, but at the same time able to support temporal knowledge related to diagnostic and therapeutic medical processes.

2.1. Time constraints in medical processes

In order to identify the different sorts of time constraints managed by clinicians, we analyzed the medical processes surrounding the diagnoses and treatments of 50 patients suffering from chronic diseases. The study covered primary health care activities, and was based on information registered in the health care centers of the SAGESSA Group during the visits between patients and clinicians. On average, five encounters per patient were analyzed, each encounter describing relevant information about the assessment of the patient's condition and the course of action followed. The visits mainly dealt with diagnostic and therapeutic processes, including the observation of the signs and symptoms presented in the patients' medical history, the anamnesis, the identification of relevant information, and, if necessary, the performance of clinical tests and their results, which might help to make an appropriate diagnosis. On the other hand, therapeutic processes involved observations of different findings about patients (including signs and symptoms, primary and secondary diseases, and risk factors), but also about ordering and undergoing interventions and tests.

We found that during diagnosis, clinicians dealt with time constraints related to (1) The patient's observations (e.g., 'persistent high blood pressure for three days'), (2) The diagnostic procedures (e.g., 'measure blood pressure once a day for one week'), and (3) The patient's history (e.g., 'episode of myocardial infarction six months ago'). When investigating therapeutic encounters, we found that time constraints were related to (1) The observation of signs and symptoms (e.g., 'blood pressure stable for three months'), and

[1]The SAGESSA Group (http://www.grupsagessa.com/) is a public society comprised of more than 3,000 health care professionals, dedicated since 1989 to the provision of care services at the primary, secondary, tertiary, and educational levels in the region of Southern Catalonia (Spain).

(2) The performance of clinical actions such as drug administration or medical tasks (e.g., 'atenolol 50 mg once a day').

In summary, our study of clinical encounters at SAGESSA concluded that, during the diagnostic process, it is important to write down the date and time of the visit, the times when the related signs and symptoms began and ended, the times when clinical tests were performed, and, finally, the times when the results of clinical tests were obtained. During therapeutic processes, it is important to note the initiation and discontinuation of treatment, the date and time of visits, the time when the signs and symptoms justifying the treatment occurred and ended, the time when an intervention started, ended and its frequency, the times when medical tests were performed, and when the results were obtained. These results are organized in Table 1. It identifies ten sorts of time constraints and whether they were found related to diagnostic procedures, therapeutic procedures, or both.

	Sort of Time Constraint	Diagnosis	Treatment
T1	Date and time of the encounter	X	X
T2	Start of treatment		X
T3	End or duration of treatment		X
T4	Start of signs and symptoms	X	X
T5	End or duration of signs and symptoms	X	X
T6	Start of interventions (medication, tasks, ...)		X
T7	Frequency of interventions (medication, tasks, ...)		X
T8	End or duration of interventions		X
T9	Moment of medical tests realization	X	X
T10	Moment of receipt of medical tests results	X	X

Table 1: Sorts of time constraints used in diagnostic and therapeutic medical processes.

From a clinical perspective, the time constraints in Table 1 can be related to different sorts of clinical tasks. According to our analysis, medical practice can be based on two main tasks: Observations and actions. Clinicians can *observe* the patient's signs and symptoms, the results of clinical tests, and any information about past events that is available in the patient's record. They can also *act* on the patient by means of prescribing medication, starting clinical procedures (i.e., interventions), and performing clinical analyses or tests. Table 2 shows the different usages of each sort of time constraint in the identified clinical tasks, and the data elements involved. For instance, T6 (i.e., the start of interventions) is related to action tasks and it involves medication and procedures.

Clinical Task	Data Element	Sort of Time Constraint
Observation	Signs and symptoms	T4, T5
	Results of analyses/tests	T9, T10
	Past life events	T1, T2, T3
Action	Medication	T1, T2, T3, T6, T7, T8
	Procedures	T1, T2, T3, T6, T7, T8
	Analyses/tests	T9, T10

Table 2: Classification of sorts of time constraints considering observation and actuation.

2.2. Time constraints in Clinical Practice Guidelines

In order to determine how Clinical Practice Guidelines (CPGs) incorporate time constraints, we analyzed two CPGs for each one of the three most prevalent (as reported by WHO [50]) Chronic Cardiovascular Diseases (CVDs): Arterial Hypertension (AH) [16, 17], Heart Failure (HF) [12, 13], and Stable Ischaemic Heart Disease (SIHD) [14, 15]. The analyzed guidelines were published by the European Society of Cardiology and the European Society of Hypertension. In the analysis, we aimed to detect which time constraints appeared in the CPGs. These CPGs contained time constraints in the sections about diagnostic and pharmacological therapeutic procedures. No temporal restrictions were found in other CPGs sections. All the time constraints found can be classified into five categories: (1) Condition assessment, (2) Condition period, (3) Drug titration, (4) Drug titration period, and (5) Observation period. Table 3 relates these categories to the three chronic cardiovascular diseases considered. As observed in this table, the analyzed CPGs contain a

small number of time constraints regarding diagnostic procedures (i.e., condition assessment and condition period categories), while, in some cases, the pharmacological therapeutic procedures (i.e., drug titration, drug titration periods, and observation periods) are more frequent.

The meaning of these sorts of time constraints is the following. A *condition assessment* time constraint determines the frequency of assessment of a patient's condition while deciding on the diagnosis. For example, [16, 17] included two time constraints: 'Blood pressure should be measured every 2-3 visits' and '... 2 times per visit'. A *condition period* is defined as the duration that a measured condition should last for a physician to confirm a diagnosis. Thus, [12, 13] included two time constraints with regard to the diagnostic procedure: 'Unintentional weight loss during the last 6 months' and a '6-minute walk test for exercise testing'.

For clinical treatment, *drug titration* time constraints determine which drug dosage should be administered. For example, CPGs for HF [12, 13] indicate that, during the β-blocker titration, the dose should be doubled at each visit until the target dose is reached. *Drug titration time periods* are aimed to periodically reassess the effects of the treatment. If necessary, during these assessments, the treatment regimen is adjusted by increasing or reducing the dose, removing a drug, or adding other drugs. For example, according to [12, 13], HF drug titration periods must be fixed to 2-4 weeks in order to evaluate the treatment regimen when β-blockers are prescribed, but is changed to 4-8 weeks when either spironolactone or eplerenone are prescribed.

Finally, the *observation periods* keep track of the patient's condition. Once the target dosage is reached (i.e., the patient's condition is stable and the signs are controlled), a follow-up visit, or even a number of visits, for the patient may be necessary. For example, HF patient observation periods are recommended to be 1, 2, 3, and 6 months after achieving the target dosage for monitoring renal function and serum electrolytes [12, 13].

Table 4 captures which sort of time constraints in Table 1 can be found in the constraints seen in CPGs.

	CPGs			
Time Constraint	AH	HF	SIHD	Total
Condition assessment	2	0	0	2
Condition period	0	2	2	4
Drug titration	0	10	2	12
Drug titration period	1	5	0	6
Observation period	1	8	0	9
Total	4	25	4	33

Table 3: Number of time constraints provided in the CPGs of AH, HF and SIHD.

Sort of Time Constraint	Time Constraint in CPGs
T1	Observation period
T2	Observation period
T3	Observation period
T4	Condition period
T5	Condition period
T6	Drug titration period
T7	Drug titration
T8	Drug titration period
T9	Condition assessment
T10	Condition assessment

Table 4: Sorts of time constraints found in medical processes related to time constraints found in CPGs.

2.3. Time constraints in heath care data standards

We also analyzed the health care standards EHRcom Reference Model [11] and the HL7 CDA data model [19] and how they structure and cover the temporal restrictions of medical processes. Both models offer components that can save time constraints in clinical databases. They cover the date and time representation with regard to: (1) When data are recorded, (2) When encounters take place, (3) When the care events take place (e.g., procedures, observations, medication related events, acts, etc.), and (4) When patients' life events occur (e.g., signs and symptoms, previous diseases/health events, etc.). To represent time constraints in clinical databases, the EHRcom time components *time_committed*, *session_time*, and *obs_time*, and the HL7 CDA time components *effectiveTime* and *time* are used [11, 19]. Table 5 shows which EHRcom and HL7 CDA time components can be used to capture the sort of time constraints in Table 1.

Sort of Time Constraint	EHRcom Time Component	HL7 CDA Time Component
T1	time_committed, session_time	time, effectiveTime
T2	time_committed	time, effectiveTime
T3	time_committed	time, effectiveTime
T4	obs_time	effectiveTime
T5	obs_time	effectiveTime
T6	obs_time	effectiveTime
T7	obs_time	effectiveTime
T8	obs_time	effectiveTime
T9	obs_time	effectiveTime
T10	time_committed	time, effectiveTime

Table 5: Standard components used to annotate the sorts of time constraints in Table 1.

In particular, EHRcom proposes the component *item* that, together with *obs_time*, can be used to capture the temporal restrictions of clinical events represented by the time constraints T4-T9. In HL7 CDA, the component *entry*, used in combination with *effectiveTime*, captures temporal restrictions of clinical events such as observations, procedures, acts, substance administrations, etc.

2.4. Time constraints in languages to computerize CPGs

Medical decision support systems emerged to improve the application of CPGs in medical practice. This is based on the formalization of Computer-Interpretable Guidelines (CIGs), representing the knowledge contained in the CPGs [7, 9, 18, 20, 31, 33, 37, 38, 40, 43]. CIGs are computer structures, designed to be used through computer tools and not applied directly by health care professionals. We analyzed the knowledge structures used to represent time constraints by ten of the most frequently used CIG languages. These structures are start time, end time, duration, and frequency. Table 6 gathers the results of this analysis. The authors in [35] performed a similar analysis for six CIG languages (i.e., Asbru, EON, GLIF, GUIDE, PRODIGY, and PROFORMA) considering the start time, end time and duration structures for modelling time constraints about clinical actions.

	Start time	End time	Duration	Frequency
ARDEN SYNTAX [20]			X	
ASBRU [31]	X	X	X	X
EON [33]	X		X	X
GASTON [9]	X	X	X	X
GLIF [7]	X		X	X
GUIDE [38]	X	X	X	X
Decision tables [44]			X	
PRODIGY [37]	X	X	X	
PROFORMA [18]	X	X		X
SDA [40]	X	X	X	X

Table 6: Structures dealing with representation of time constraints in languages that formalize CPGs.

Table 7 captures which CIG languages can represent which sorts of time constraint in table 1.

	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	Total
ARDEN SYNTAX [20]	X		X		X			X	X	X	6
ASBRU [31]	X	X	X	X	X	X	X	X	X	X	10
EON [33]		X	X	X	X	X	X	X	X	X	9
GASTON [9]		X	X	X	X	X	X	X	X	X	9
GLIF [7]		X	X	X	X	X	X	X	X	X	9
GUIDE [38]		X	X	X	X	X	X	X	X	X	9
Decision tables [44]	X	X			X	X		X	X	X	7
PRODIGY [37]		X	X	X	X	X	X	X	X	X	9
PROFORMA [18]		X	X	X	X	X	X	X	X	X	9
SDA [40]		X	X	X	X	X	X	X	X		8

Table 7: Time constraints represented in languages that formalize CPGs.

2.5. Summary of the analyses

In the previous sections, we reported on the results of four analyses: (1) The sorts of time constraints found in medical processes and their relation to different sorts of clinical tasks, (2) The time constraints found in CPGs, (3) The time constructs in two standards of health care data representation, and (4) The structures of CIG languages to represent clinical time constraints.

Table 8 offers a summary of these results. The focus is on the sorts of time constraints and their relation to clinical tasks, CPGs, standard components, and structures of CIGs. For example, the time constraint T7 (i.e., frequency of interventions) is found in the action tasks about medication and clinical procedures; it covers drug titration in CPGs, *obs_time* and *effectiveTime* are standard components of EHRcom and HL7 CDA used to annotate it, and frequency structures in CIG languages represent it.

Sort of Time Const.	Clinical task						CPG					Standard component					CIG structures			
	Observation			Action								EHRcom			HL7 CDA					
	signs and symptoms	results of analysis/tests	past life events	medication	procedures	analysis/tests	condition assessment	condition period	drug titration	drug titration period	observation period	time_committed	session_time	obs_time	time	effectiveTime	Start time	End Time	Duration	Frequency
T1			X	X	X						X	X	X		X	X	X			
T2			X	X	X						X	X			X	X	X			
T3			X	X	X						X	X			X	X		X	X	
T4	X							X						X		X	X			
T5	X							X						X		X		X	X	
T6				X	X					X				X		X	X			
T7				X	X				X					X		X				X
T8				X	X					X				X		X		X	X	
T9		X				X	X							X		X	X			
T10		X				X	X					X			X	X	X			

Table 8: The fourfold analyses' summary.

2.6. Modelling the temporal dimension of medical procedures

Based on the previous analyses, we propose two representation formalisms for time constraints, called micro-temporality and macro-temporality [22, 23] which are capable of capturing and representing temporal knowledge found in the medical processes of diagnosis and treatment when dealing with chronic conditions.

For each disease D, V_D=$\{v_1, v_2, ..., v_n\}$ is the set of variables related to D. These are the variables describing the states, conditions, and actions of the medical processes of D. Thus, V_Σ is the subset of state variables in V_D that are used to determine the clinical condition of the patients having D. V_A is the set of action variables in V_D that represent the medical activities a clinician can perform during the treatment of D, and V_C the set of condition variables in V_D describing the evidence (i.e., the clinical causes) for concrete treatments.

Micro-temporality is a time constraint $[s_v, e_v, f_v, val]$ representing the start time, end time, frequency of occurrence, and the value of the measured variable v in V_D. When a micro-temporality is assigned to a state or condition variable v, val represents the observed value of v. For example, if the total daily measured cholesterol value is 195 mg/dl, the time constraint $[-, -, 24h, 195mg/dl]$ is related to the state variable 'Total Cholesterol', and if a prehypertension condition has been observed from four weeks ago until two days ago, and checked twice a day during this time, the time constraint $[4w, 2d, 12h,$ yes$]$ should be assigned to the state variable 'prehypertension'.

When a micro-temporality constraint is assigned to a clinical action variable in V_A corresponding to a drug prescription, val represents the dose, and $[s_v, e_v, f_v, val]$ states that a dose val of drug v is taken between times s_v and e_v (relative to the current time) with a frequency f_v. For example, the clinical order 'Carvedilol 6.25 mg three times a day for two weeks, starting tomorrow' has a micro-temporality $[1d, 2w, 8h, 6.25mg]$.

Sometimes, micro-temporality can take a generalized form when related to action variables describing drug prescriptions. If a drug has predefined values for *initial*, *maximum*, and *target* dosages, or standard dosage *increments* and *decrements*, the micro-temporality expression $[s_v, e_v, f_v, val]$ can be replaced by the corresponding generalized value, for the sake of simplicity. For example, Indapamide (diuretic) has a predefined standard initial dosage of 1.5 mg per day, which can be represented either as Indapamide [-, -, 24h, 1.5mg] or Indapamide [initial]. Notice that, if any diuretic is valid, then the expression Diuretic [initial] is also possible, with a different initial value that depends on the selected diuretic.

In our temporal model, *macro-temporality* is a time constraint $[t_{min}, t_{max}]$ representing a time range with minimum t_{min} and maximum t_{max} time values. It can be used to represent time delays before a clinical process can proceed. Figure 1 shows an example, where the constraint $[2w,4w]$ is assigned to a transition between the state *One drug* and the state *Two drugs*. The transition states that patients with Blood Pressure (BP) levels in the grades 1-3 HT (see table A.11 in Appendix A), with risk factors, and already taking β-blockers at the maximum dosage, must be prescribed with an additional diuretic drug at an initial dosage. However, a delay of 2 to 4 weeks is fixed before a next visit is made when the patient's state will be *Two drugs*.

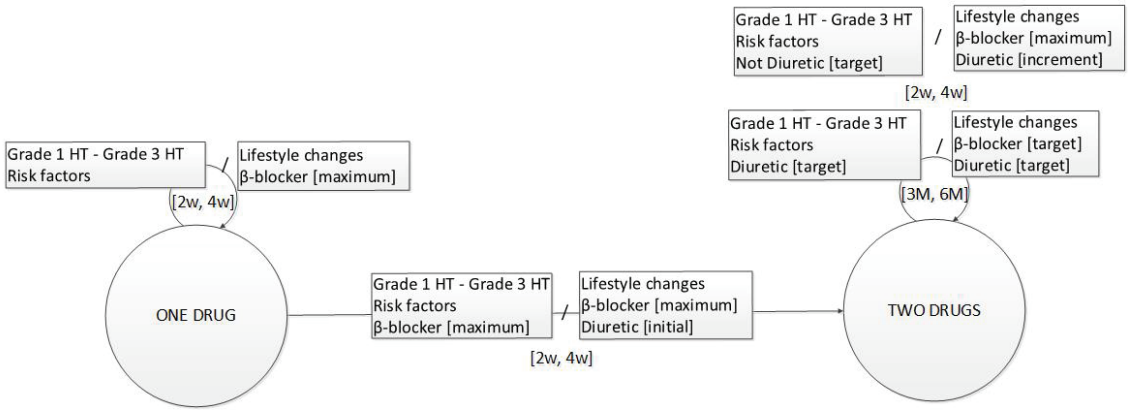

Figure 1: Example of partial AH treatment with time constraints.

Time units in micro-temporality and macro-temporality can be measured in seconds (s), minutes (m), hours (h), days (d), weeks (w), months (M), or years (y).

2.7. Validation of the model

Before accepting micro-temporality and macro-temporality as feasible expressions to model the temporal dimension of medical procedures, we performed a triple validation process consisting of checking whether they were able to cover all the time constraints found in the previous sections, all the drug titration actions of AH not covered by the CPGs [16, 17] but contained in expert consensus documents of the European Society of Cardiology [45, 46], and the AH clinical cases defined by two senior physicians.

Step-1 validation. The clinical time constraints T1-T10 in Table 1, CPG time constraints in Table 3, standard time components of EHRcom and HL7 CDA in Table 5, and CIG language structures in Table 6 were represented with micro-temporalities and macro-temporalities. The results are summarized in Table 9.

We can confirm micro-temporality as a powerful time representation structure which is capable of representing seven out of ten T1-T10 time constraints, four of the five time constraints found in CPGs, and three of the four time structures of CIG languages. On the contrary, macro-temporality proved essential in covering four of the standard components of EHRcom and HL7 CDA.

Temporal Constraint	Sort of Time Constraint										CPG					Standard component					CIG structures			
																EHRcom			HL7 CDA					
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	condition assessment	condition period	drug titration	drug titration period	observation period	time_committed	session_time	obs_time	time	effectiveTime	start time	end time	duration	frequency
Micro-temp				X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X		X
Macro-temp	X	X	X												X	X	X		X	X			X	

Table 9: Proposed temporal constraints and their time constraints representations.

Step-2 validation. We also checked whether micro-temporality and macro-temporality expressions were able to represent time constraints with regard to detailed drug titration procedures. This level of detail was not entirely found in the studied CPGs [16, 17], but contained in expert consensus documents of the European Society of Cardiology [45, 46] and the Drug Registry of the Republic of Slovenia [10]. For example, CPGs about AH recommend reconsidering drug titration every 2-4 weeks, and an observation of the patient's evolution every 3-6 months (see Figure 2). These time constraints correspond to the drug titration period and observation period, respectively. This broad information is complemented in [45, 46] with the description of a detailed titration procedure that recommends starting with an *initial dosage* that should be reconsidered every 2-4 weeks. These re-considerations can imply one or more *dosage increments*, until the *target dosage* or a *maximum dosage* is reached. This behavior, still imprecise, is also represented with micro- and macro-temporalities in the eTTD of Figure 2.

Drug titration time constraints were not found in the CPGs. Therefore, we considered the information provided in [45, 46] to find that ACEi and β-blockers should be administered at double dosage increments. Increments of other AH drugs were left to the clinicians' judgment. All this information on drug dosages was complemented with the Drug Registry of the Republic of Slovenia [10].

Our second step in the validation of micro- and macro-temporalities concluded with the representation of detailed information about specific drugs (e.g., ACEis, β-blockers, CCBs) and their initial dosages, increment of dosages, and maximum dosages, as suggested in [10]. The complete representation is available in [21] for interested readers.

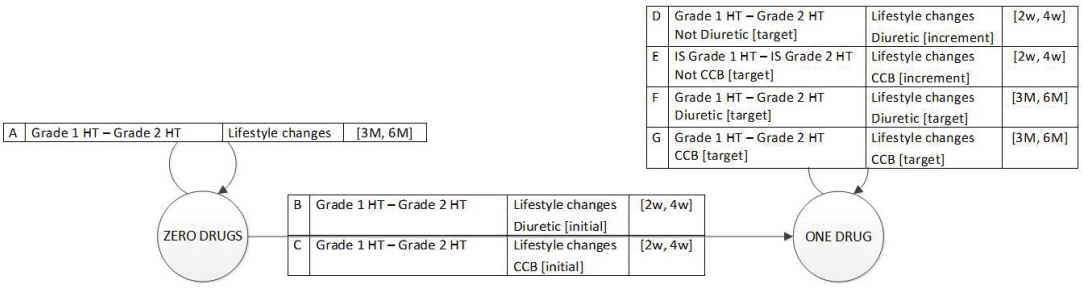

Figure 2: Example of partial AH treatment with time constraints.

Step-3 validation. The last validation step of micro- and macro-temporalities concerned their capacity to represent all the time constraints appearing in clinical cases described by two senior physicians. Ten clinical cases were defined with an AH treatment. They are shown in Appendix C. According to physicians, the cases are representative and diverse within the hypertension category of isolated systolic BP. Risk factors, such as age range and sex, dyslipidemia, glucose, obesity, smoking, and family history of premature CVD, were considered. Clinical cases did not reflect differences in treatments with regard to age and sex, and they did not include drug intolerances. Micro- and macro- temporal formats were used to represent all the time constraints detected in the cases. Figure 3 shows the full treatment of case 1, as an eTTD diagram.

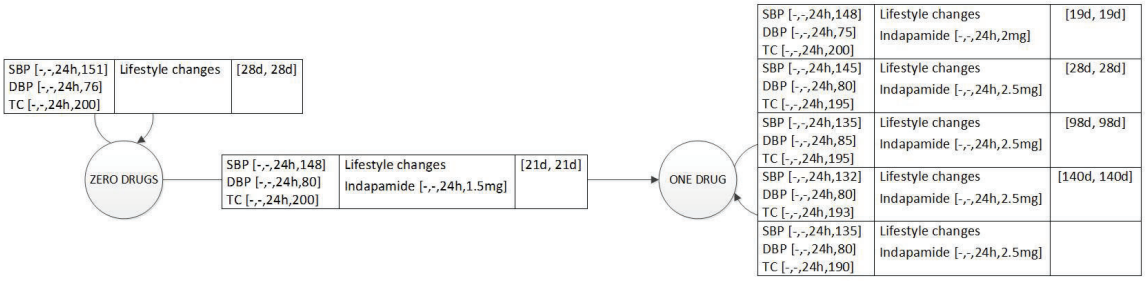

Figure 3: Temporal model for AH treatment - representing clinical case 1 from Table C.13.

All three validation steps and the corresponding micro- and macro-temporality capacities to represent specific and generalized clinical time constraints were supervised by the same two senior physicians. They were satisfied because of the simplicity of the temporal structures, their ability to represent generic and concrete time constraints, and their coverage of all the clinical time constraints conceivable.

3. Detecting time constraints of medical procedures from medical records

Physicians use their medical knowledge to make diagnostic and therapeutic decisions. Medical procedures followed in health care centers are registered in databases. In 2016, the authors of [28] argued that approximately 80% of saved data was unstructured and found in so-called clinical narratives. This constitutes a major challenge for information extraction where natural language processing emerges as a possible solution [28, 52], in combination with intelligent data analysis algorithms [4, 5, 29, 30, 47, 49] and knowledge representation technologies [6, 28], to capture the knowledge behind the data and to make it explicit.

Following from our temporal model, we developed algorithms for the automatic generation of generalized time constraints in the form of micro- and macro-temporalities from clinical datasets. The obtained temporalities were used to analyze the adherence between the experience-based temporal knowledge obtained from the data and the evidence-based knowledge recommended in the CPGs.

The data used to extract generalized time constraints was focused on patients suffering from AH, excluding comorbidities. Clinical data about treatments was organized as *Episodes Of Care* (*EOC*), where an EOC of a certain patient is defined as a sequence of encounters that refers to a patient's health problem. The evolution of the patient condition can be seen as a sequence of state transitions of the patient through the different encounters. The clinical data of each EOC describes a singular treatment, including temporal medical information about the medical processes followed.

A database describing 8,781 EOCs about AH patients was provided by SAGESSA. After a pre-processing phase in which clinical experts removed errors and supervised the medical correctness of the treatments described in the EOC data, 105,669 encounters with 4,052 pharmacological prescriptions remained. These data were used by our proposed algorithms to automatically generate the time constraints involved in the treatment of AH in SAGESSA.

3.1. Automatic generation of time constraints

Three algorithms were proposed to generate time constraints as micro- and macro-temporalities. The first algorithm takes the EOC database and generates macro-temporalities between evolving states of the patients as encounters follow one another. The second algorithm calculates the component frequency of the micro-temporalities related to pharmacological treatments, and the third algorithm complements the second one by calculating the dosages in micro-temporalities.

Macro-temporality generation. Algorithm 1 detects macro-temporality constraints from EOC data. A macro-temporality constraint is a time interval representing the minimal and maximal times that patients who satisfy a certain condition C can take to evolve between two consecutive states Σ_0 and Σ_1, when some clinical actions A are performed. The algorithm finds all pairs of consecutive encounters e_{ij} and $e_{i(j+1)}$ in the EOCs so that: (1) The state of the patient in e_{ij} is equivalent to Σ_0, (2) The state in $e_{i(j+1)}$ is equivalent to Σ_1, (3) The patient satisfies condition C, and (4) The clinical actions performed in e_{ij} are equivalent to A. For all the pairs of encounters found, the time between them is kept and used to calculate a time interval. The precision of the obtained interval (i.e., macro-temporality) can be adjusted using an elimination function based on an α-cut action. This function can be used to remove abnormal extreme clinical cases which demonstrate a serious time deviation from the norm, and to avoid or reduce overfitting.

Algorithm 1 Macro-temporality generation.

Require: Σ_0, Σ_1, A, C, $data$, α
  {Let Σ_0 and Σ_1 be two patient states}
  {Let A be a set of clinical actions}
  {Let C be the condition of the patients}
  {Let $data = \{EOC_1, ..., EOC_k\}$ be a list of episodes of care of disease D}
  {Let $EOC_i = \langle e_{i1}, ..., e_{in_i} \rangle$ be the sequence of encounters in EOC_i, i = 1...n$_i$}
  {Let α be a given percentage of time interval support}
  $dif = \varnothing$;
  for all EOC_i in $data$ **do**
    for all $e_{ij} \rightarrow e_{i(j+1)}$ pairs of consecutive encounters in EOC_i **do**

      if $e_{ij}.state \equiv \Sigma_0$ {the patient evolves from a state which is equivalent to Σ_0}
      and $e_{i(j+1)}.state \equiv \Sigma_1$ {the patient evolves to a state which is equivalent to Σ_1}
      and $e_{ij}.action \equiv A$ {the patient receives a treatment which is equivalent to A}
      and $e_{ij}.condition \equiv C$ {the patient satisfies condition C}
      and d_0 is the date-time of encounter e_{ij}
      and d_1 is the date-time of encounter $e_{i(j+1)}$ **then**
        Insert $(d_1 - d_0)$ in dif;
      end if
    end for
  end for
  Sort dif ascending;
  Calculate the elimination function according to equation: $elim = \frac{1}{2}(\#dif \times \frac{100-\alpha}{100})$;
  return interval $[dif[elim], dif[\#dif - elim]]$;

Micro-temporality generation - Frequency. Algorithm 2 obtains partial micro-temporal constraints representing frequencies of pharmacological actions. In medicine, the frequency of these actions use to be expressed in the 0-0-0-0 notation, with each 0 indicating the number of intakes in the morning, noon, afternoon, and evening, respectively. For example, 1-0-1-0 means two intakes per day, one in the morning and one in the afternoon. We define here the *clinical context* of a clinical action a as the current state Σ_0 of the patient receiving the action, the full treatment A received by the patient (notice that action a is part of the treatment A), and the conditions C justifying that treatment. The algorithm calculates whether a clinical action has to be performed once a day (i.e., *od* or [-, -, 24h, -]), twice a day (i.e., *bid* or [-, -, 12h, -]), three times a day (i.e., *tid* or [-, -, 8h, -]), or four times a day (i.e., *qid* or [-, -, 6h, -]), for a given clinical context, if the number of examples of these frequencies in the EOC database is above a calculated threshold. The final result is a set of common alternative frequencies. The result is used by algorithm 3 to generate micro-temporal constraints representing dosages (i.e., dose and frequency, together).

Algorithm 2 Partial micro-temporality generation - frequency.

Require: Σ_0, Σ_1, A, C, $data$, $drug$, α
{Let Σ_0 and Σ_1 be two patient states}
{Let A be a set of clinical actions}
{Let C be the condition of the patients}
{Let $data = \{EOC_1, ..., EOC_k\}$ be a list of episodes of care of disease D}
{Let $EOC_i = \langle e_{i1}, ..., e_{in_i} \rangle$ be the sequence of encounters in EOC_i, i = 1...n$_i$}
{Let $drug$ be the targeted drug}
{Let α be a given percentage of intake frequency support}
$freq = \varnothing$;
for all EOC_i in $data$ **do**
  for all $e_{ik} \rightarrow e_{i(j+1)}$ pairs of consecutive encounters in EOC_i **do**
    if $e_{ij}.state \equiv \Sigma_0$ {the patient evolves from a state which is equivalent to Σ_0}
    and $e_{i(j+1)}.state \equiv \Sigma_1$ {the patient evolves to a state which is equivalent to Σ_1}
    and $e_{ij}.action \equiv A$ {the patient receives a treatment which is equivalent to A}
    and $e_{ij}.condition \equiv C$ {the patient satisfies condition C}
    and $drug \in e_{ij}.action$ {drug is part of the treatment provided in e_{ij}}
    and f is the 0-0-0-0 frequency of $drug$ in e_{ij} **then**
      Insert f in $freq$;
    end if
  end for
end for
od = 0; bid = 0; tid = 0; qid = 0;
for all $f \in freq$ **do**
  if $f.intakes = 1$ **then**
    od++;
  else if $f.intakes = 2$ **then**
    bid++;
  else if $f.intakes = 3$ **then**
    tid++;
  else if $f.intakes = 4$ **then**
    qid++;
  end if
end for
$threshold = \alpha \times \frac{\#freq}{100}$
$frequencies = \varnothing$;
if od $\geq threshold$ **then**
  Insert od in $frequencies$;
end if
if bid $\geq theshold$ **then**
  Insert bid in $frequencies$;
end if
if tid $\geq threshold$ **then**
  Insert tid in $frequencies$;
end if
if qid $\geq threshold$ **then**
  Insert qid in $frequencies$;
end if
return $frequencies$;

Micro-temporality generation - Dosage. Algorithm 3 finds full generalized micro-temporal constraints representing dosages for a given target *drug*. It uses the drug properties *drug.initial* and *drug.maximum* that indicate the standard dosage to start a treatment, and the maximum dosage allowed for the *drug*. The algorithm searches the EOC database to find evidences of [initial] and [maximum] dosages for the provided clinical context of the target drug. If the patient's state is stable, the generalized dosage [target] is returned. The final result of the algorithm is a list of generalized dosages related to the target drug.

Algorithm 3 Micro-temporality generation - dosage.

Require: Σ_0, Σ_1, A, C, $data$, $drug$, $frequency$
{Let Σ_0 and Σ_1 be two patient states}
{Let A be a set of clinical actions}
{Let C be the condition of the patients}
{Let $data = \{EOC_1, ..., EOC_k\}$ be a list of episodes of care of disease D}
{Let $EOC_i = \langle e_{i1}, ..., e_{in_i} \rangle$ be a sequence of encounters in EOC_i, i = 1...n_i}
{Let $drug$ be the targeted drug}
{Let $frequency$ be one among {od, bid, tid, qid} representing a $drug$ daily intake returned by the algorithm 2}
$daydosages = \varnothing$;
for all EOC_i in $data$ **do**
  for all $e_{ij} \rightarrow e_{i(j+1)}$ pairs of consecutive encounters in EOC_i **do**
    if $e_{ij}.state \equiv \Sigma_0$ {the patient evolves from a state which is equivalent to Σ_0}
    and $e_{i(j+1)}.state \equiv \Sigma_1$ {the patient evolves to a state which is equivalent to Σ_1}
    and $e_{ij}.action \equiv A$ {the patient receives a treatment which is equivalent to A}
    and $c_{ij}.condition \equiv C$ {the patient satisfies condition C}
    and $drug \in e_{ij}.action$ {drug is part of the treatment provided in e_{ij}}
    and (d, f) are the dose and frequency of $drug$ in e_{ij} **then**
      dpd = daily_dosage(d,f); {calculates the equivalent dosage per day of [-, -, f, d]}
      Insert dpd in $daydosages$;
    end if
  end for
end for
$dosages = \varnothing$;
if drug.initial $\in$ $daydosages$ **then**
  Insert [initial] in dosages;
end if
if drug.maximum $\in$ $daydosages$ **then**
  if stable_state(Σ_0) **then**
    Insert [target] in dosages;
  else
    Insert [maximum] in dosages;
  end if
end if
if (drug.initial $\notin$ $daydosages$) **and** (drug.maximum $\notin$ $daydosages$) **then**
  if stable_state(Σ_0) **then**
    Insert [target] in dosages;
  else
    Insert [increment] in dosages;
  end if
end if
return dosages;

3.2. Testing the algorithms

The algorithms were tested in combination with the system described in [22] to generate timed transition diagrams as eTTDs. Two types of tests were considered: One supervised, where the EOC database was formed by the clinical cases proposed by senior physicians and depicted in Appendix C, and the other one, unsupervised, where a database provided by SAGESSA with 105,669 encounters and 4,052 pharmacological prescriptions was used, after first undergoing a data cleansing process.

3.2.1. Supervised test

Ten clinical cases suggested by senior physicians, described in Appendix C, and used in section 2.7 for the third-step of the model validation, were taken to test the correctness of the previous algorithms. The results are gathered in the eTTD diagram of Figure 4, representing the temporal model for the AH treatment of these clinical cases.

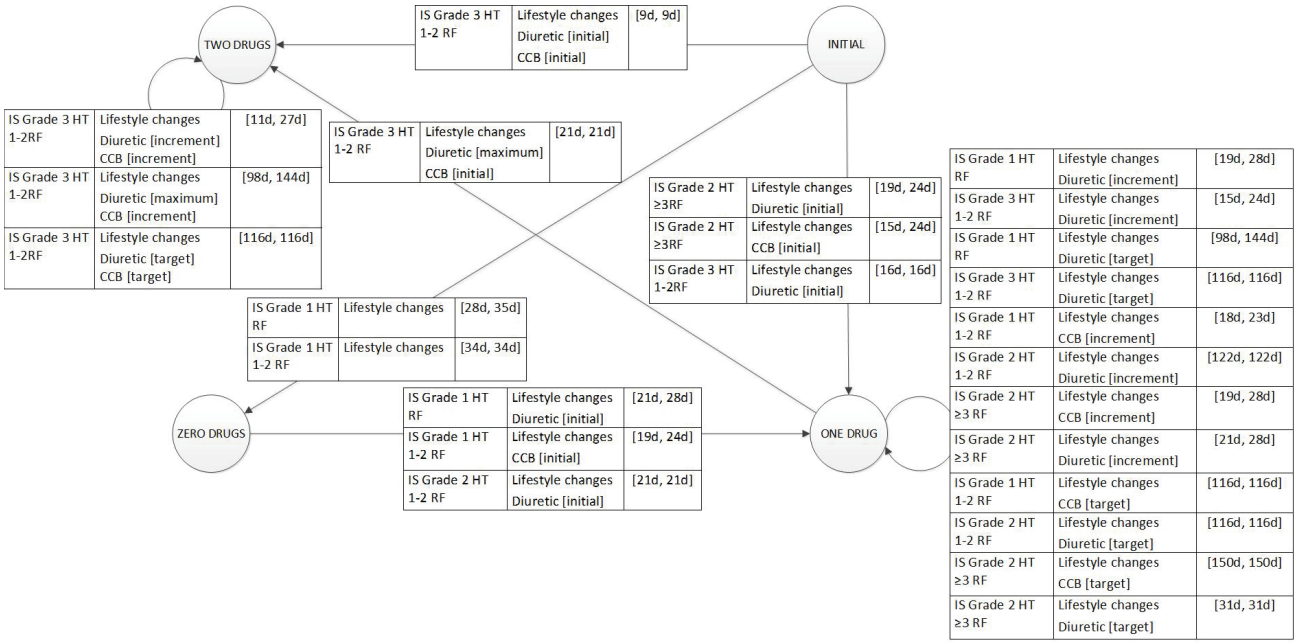

Figure 4: Temporal model for AH treatment obtained from clinical cases.

All the time constraints found adhere to the constraints in the CPG-based temporal model. This is not a surprising result, since the clinical cases represent clinical situations supervised by senior physicians, who are experts in the recommendations contained in the CPGs and in other medical documents.

3.2.2. Unsupervised test

Algorithms 1-3 were also tested using EOC data from the SAGESSA Group [41]. The data was limited to patients suffering from AH, excluding comorbid cases. The database contained 105,669 encounters of 8,781 patients who were treated for AH in the year 2011. These involved 4,052 prescriptions of pharmacological therapy relevant for AH treatment. Each prescription included a drug name, a dose, and an intake frequency. Some missing data regarding the frequency of medication was detected, and complemented. In some cases, the frequency was present, but the sample of complete data was not representative enough to confirm that the algorithms could produce correct frequencies. Having complete correct times in the data about prescriptions is crucial for micro-temporal constraint generation. Consequently, the time constraints for some clinical actions could not be obtained. However, in the next lines, we comment on nine interesting results of our analysis of the data with the algorithms. These can be seen as relevant contributions of our algorithms to the analysis of the adherence of clinicians to CPGs or as a means to determine the lines of actuation of clinicians in a health care centre. Table 10 summarizes them and identifies the adherence issues between the treatments registered in the data and the recommendations in the CPG.

Type of contribution	Adherence Issue	Data	CPG
(1) Macro-temporality confirmation	Observation period	1-7 weeks	2-4 weeks
(2) Detect missing macro-temporalities			
(3) Implicit detection of micro-temporalities (by macro-temporality discretization)	Initial or increment dosage	1-6 weeks	2-4 weeks
	Maximum or target dosage	4-6 months	3-6 months
(4) Confirm lack of micro-temporality information			
(5) Change of clinical standard detections	High normal BP condition	Prescribed	Not recommended
(6) Identification of variability	ACEi + ARB drug combination	Prescribed	Not recommended or possible, but less well tested
(7) Identify theoretical and practical clinical discrepancies	Statin	Prescribed first line therapy	Second line therapy to treat risk factors
(8) Polypharmacy coherence	Polypill	Prescribed	Recommended
(9) Time validation of routine clinical actions	Lower BP categories	Up to 6 months	3-6 months
	Higher BP categories	Up to 3 months	

Table 10: Summary of the adherence analysis considering nine contribution types.

1. *Macro-temporality confirmation.* Algorithm 1 can be used to confirm whether clinicians apply the same macro-temporality as indicated in CPGs or not. In our unsupervised test, visits occur every 1-7 weeks, while the CPG recommends 2-4 weeks.
2. *Detect missing macro-temporalities.* If clinicians do not follow all possible treatments between visits, algorithm 1 can fail to detect some macro-temporal patterns. In extreme cases, this could be an indication of the lack of standard clinical criteria. In our data analysis, we identified two reasons for this lack of macro-temporality detection. Firstly, our input data registered entries in 2011 only, but some patients evolved from previous (or subsequent) years. Therefore, some evolutions could not be reflected in the obtained temporal model. Secondly, physicians do not necessarily prescribe all the possible alternatives contained in the CPGs. Alternatives that are not followed by clinicians, are not registered in the data, and they are not captured in our temporal model.
3. *Implicit detection of micro-temporalities.* Micro-temporal constraints can be generated implicitly as a result of discretizing macro-temporalities. We observed this very often during drug dosage titration, when wide ranged periods are obtained. For example, in one specific patient state transition, ACEi was prescribed with the time constraints 8, 12, 15, 20, 122 and 147 days. These constraints refer to two periods: 1-3 weeks or 4-6 months, which we identified as separate time periods encapsulating short-term and long-term treatments, respectively. Physicians confirmed that both time periods are in accordance with the constraints recommended in the CPGs, and that they followed the time standards for short- and long-term chronic disease treatments.
4. *Confirm lack of micro-temporality information.* When the information about dosages is not registered systematically, algorithms 2 and 3 can fail to detect correct micro-temporalities. In our analysis, source data lacked annotations about the usage frequency of many prescribed drugs. Due to this limitation, we were not able to detect the full dosages of all the prescriptions found, and some of the therapy models had to be partially constructed at a broader level of drug therapy.
5. *Change of clinical standard detections.* Our algorithms can be used to detect CPG knowledge updates and upgrades. During our analysis, for example, we detected that clinicians prescribed drug therapy to patients with a high-normal BP, while the CPG [17] advises against it. This CPG was published in 2013, after the treatments recorded in the database took place. A previous CPG [16], published in 2007, recommended starting drug therapy if certain risk factors are present when BP levels are normal or high-normal, which is the exact behavior found by our algorithms when analyzing the data.
6. *Identification of variability.* Our algorithms can generate models that may contain alternative drug therapies. Table B.12 summarizes the information provided in CPG [17] related to the possible combination of AH drugs. Some of them were detected by our algorithms. They also detected combinations of ARB and ACEi drugs, which the CPG [17] states explicitly as *not recommended*. An earlier CPG [16] allowed this sort of combination due to a lack of evidence against it. Again, we could conclude that clinical treatments followed the CPG recommendations in [16].
7. *Identify theoretical and practical clinical discrepancies.* One of the most interesting uses of the introduced algorithms is to detect deviations from standard treatments. For example, in the generated temporal model, *statins* appear as a first line drug therapy of AH, whilst CPGs recommend statins only as a complement to AH therapy (i.e., as a second line therapy) to treat risk factors such as cholesterol levels (e.g., reduce LDL-C levels below 1.8 mmol/l). Our analysis detected this discrepancy between clinical data and CPGs.
8. *Polypharmacy coherence.* Our algorithms are sensitive to combinations of drugs in a single pill. Single-pill drug combinations were used in 29.21% of cases. These pills (polypills) can combine two or more drugs. CPGs [16, 17] about AH, recommend the use of polypills. When the EOC data is analyzed, we need to take this fact into account, particularly when we differentiate between patient states according to the number of drugs prescribed. See, for example, the treatment in Figure 4 with the states zero, one, and two drugs. Polypill treatments are represented in the state two-drugs.
9. *Time validation of routine clinical actions.* Routine clinical actions, such as *recommend lifestyle changes* or *measuring BP*, are actions that clinicians make systematically. In our analysis, clinicians perform these suggestions between every *few days* to every *few months*, while CPGs recommend

them in a range from *three to six months*. There are different interpretations of the observed high frequency. For example, the visit of chronic AH patients can be caused by a reason other than AH, but the clinician can use the visit to follow-up on the AH condition of the patient, and check the values of BP and other risk factors, thereby augmenting their frequency of observation. In the data, 90% of AH patients received a recommendation of changing their lifestyle every *three months* or less. If only normal and high-normal BP patients are considered (see Table A.11), the frequency changes to *six months*. The conclusion is that clinicians follow CPG indications, but they prefer to monitor the patient's condition in shorter time periods than CPGs recommend, for patients with higher BP values.

Physicians validated the generated temporal model. The results are presented as eTTDs in Appendix D (Figures D.5 to D.8). In Figure D.6, for example, we can observe some of the above stated adherence issues, such as prescribing statin as a first-line therapy, detecting micro-temporal general constraints for some clinical actions such as the prescription of ACEi at [initial], [maximum] or [target] dosages, etc. The assignment of two micro-temporalities to one drug (e.g., ACEi [initial] [increment]) indicates that the micro-temporality values were obtained implicitly by macro-temporality discretization (see contribution type number 3 in the previous paragraph and in Table 10). We also detected a short-term time constraint pattern but we were not able to conclude whether this pattern belongs to an initial or increment dosage. The same idea is behind the [maximum] and [target] dosages assigned at the same time to one drug (e.g., β-blocker [maximum][target]).

4. Discussion

In medicine, procedural knowledge permits a physician to determine the best course of action possible. This procedural knowledge can be extended with a temporal component and therefore become time-dependent. Time plays a major role in the clinical domain, as it helps us to understand the chronological sequence of medical procedures [28]. Physicians use their medical knowledge to make diagnostic and therapeutic decisions. Decision-making processes depend on whether clinicians can recall, find, understand, and use a vast amount of medical knowledge and information [32, 34]. Temporal knowledge about medical processes is rarely published, and physicians are compelled to rely on their own experience to make decisions about recommended times. The aim of our research was to make implicit temporal knowledge become explicit by extracting and representing missing time constraints in CPGs, thus complementing the evidence-based knowledge of CPGs with the experience-based temporal knowledge obtained from the automatic analysis of retrospective data about clinical treatments. Our technology also provides a framework to study the adherence of clinical interventions to the time constraints that can be found in CPGs.

More concretely, this paper focuses on the formalization of medical time constraints and the automatic generation of temporal models for medical procedures. In order to provide a successful formalization of medical time constraints, we analyzed the sort of time indications that can be found in the medical processes registered in the medical records of the SAGESSA group health care centers. We also studied two of the most used standards for health care data representation (i.e., EHRcom RM and HL7 CDA) and identified their constructs to represent time constraints. We reviewed six clinical practice guidelines for three of the most prevalent cardiovascular diseases. In addition, ten languages to computerize CPGs were studied, to detect the sort of time constraints that they can represent. This fourfold analysis resulted in a temporal model proposal with two representation formalisms of time constraints, called macro-temporality and micro-temporality.

The authors in [28] emphasize the importance of time granularity or the ability to represent time at different levels of detail. They argue that the time constraints of medical and clinical events may require diverse and mixed specificity and conclude that different levels of detail in time instants and intervals are barely supported by the currently proposed temporal models. The validation tests of our temporal model showed that it offers temporal knowledge representation for different specificities, thus achieving the necessary requirements to capture and represent any temporal knowledge found in the medical processes of diagnosis and treatment when dealing with chronic diseases.

Three complementary algorithms for the automatic generation of time constraints were proposed. These algorithms obtain the time constraints of the medical procedures which are represented in the databases of the health care centers. Our tests showed that the automatic learning process obtained the correct results; i.e., our algorithms produced complete and relevant temporal models for the treatment of Arterial Hypertension. Other studies with similar results for Heart Failure and Ischaemic Heart Disease can be found in [21], with indications on the sequence of clinical actions and the titration processes represented as eTTDs. These studies confirm the possible extension of our algorithms to cover other CVDs. Some other chronic diseases, such as Diabetes Mellitus and Clinical Obstructive Pulmonary Disease could not be analyzed due to the low quality of the data available in SAGESSA. Our methods are sensitive to the quality of the data, which should be structured, correct, complete, and representative of the clinical treatments performed [26] in order to obtain the correctly timed treatment models in a particular clinical setting. Ensuring that these properties are present in the data is the most critical part of our proposal. Data quality can be improved with complex pre-processing step such as the one described in [26].

The proposed algorithms can be used for clinical adherence analysis. Our final adherence analyses showed deviations in the generated time constraints with regard to the time recommendations found in the CPGs. According to our interpretations, different reasons provoked these deviations. Real life circumstances about patients, physicians, and the proper health care system influence time constraints. For example, deciding the date of the next encounter depends on the agenda of both the physician and the patient, but also on the patient's adherence to the treatment. Following CPG recommendations also depends on whether the physicians are aware of, and familiar with, the latest versions of these guidelines. In [51], the authors concluded that a standard panel of 2,500 patients would need 21.7 hours per day(!) for a General Practitioner (GP) to offer guidelines recommended health care. In [1], the authors argue that the traditional clinical practice model would be viable only if a GP could care for a panel of fewer than 1,000 patients. According to these results, deviations from CPGs are possible due to overwork. Additionally, the health care system itself may influence time constraints: limited resources at the health care institutions (e.g., waiting lists) or different levels of accessibility to health care are common examples affecting clinical times. The most appropriate duration between two consecutive follow-ups can be based not only on the knowledge and experience of clinicians, but also on the limitation of resources. Authors in [2] demonstrated a negative impact of large panel sizes on the available appointment access and a greater probability of poor-quality rankings. Also, patients from rural and urban areas can experience different limitations with regard to the frequency of their visits. It is important that patients understand their condition and the treatment decisions in order to increase their therapy adherence. In [36], the authors identify the necessary components to introduce patient-centered care. These components aim to improve the understanding and participation of patients in the medical decision process as well as to follow the instructions contained in the treatments. Technological support for health care can also affect the adherence of clinical practice to CPGs. For example, the authors in [6] argue that none of the available computerized systems for Clinical Practice Guidelines' management address issues of communication and interaction between the involved persons (e.g., physicians, specialists, patients, caregivers, etc.). Sometimes the responsibility of notifications between clinical experts is left to the patient and a verification of a correct-complete communication is not implemented (e.g., after being discharged from a hospital, the GP is not notified directly by the hospital physician about the recommended follow-ups).

We have shown that health care databases can be a source of information to detect temporal medical knowledge of the medical procedures followed in health care centers. The implicit temporal knowledge contained in these databases can be made explicit as eTTDs through the use of automatic learning techniques.

This knowledge can be used to review the current clinical protocols in health care institutions and, taking into account the patients' evolution and satisfaction, to improve the cost-effectiveness and acceptance of the treatments. For example, our results indicate that physicians prefer more frequent visits from chronic patients than is recommended in CPGs, particularly while deciding the proper therapy, titrating drug dosages, and performing general follow-ups. Moreover, the obtained models can be incorporated as knowledge bases of new timed medical decision support systems (TMDSS) to help young clinicians with less experience in their training, and more experienced clinicians to remind the necessary actions.

The presented work does not include comorbidity analysis (i.e., treatments for patients suffering from

multiple diseases). Due to the aging of the population and the increase of chronic diseases, one of the main challenges for modern health care is dealing with comorbid patients [3]. Our future actions include using the proposed algorithms to develop temporal models for comorbid patients. A first attempt to consider the management of comorbidities with computer technology has been already published in [39]. Our next objective is to combine these technologies with the ones described in this paper. Furthermore, we are currently formalizing a randomized experimental study with a control group in which clinicians in the intervention group will apply the knowledge obtained with our algorithms to manage clinical cases while the clinicians in the control group will be using their own criteria. The respective medical practice results will be compared in order to determine whether the usage of those models imply a direct benefit on patients' care and safety, as a means of final validation of the knowledge obtained. We expect that our technology and these future complementary studies could contribute to improve the clinical protocols in SAGESSA and to optimize the organization of the centers.

5. Conclusion

Our work showed that the lack of evidence about temporal indications in CPGs can be complemented with the use of computer technology for the intelligent analysis of the data about the clinical treatments registered in health care information systems. All this knowledge that comes from clinical experiences can be captured with two types of structures (micro- and macro-temporality) that have been shown not only able to describe all kind of temporal constraints in the management of cardiovascular diseases, but also easily understood by clinicians. The application of three proposed algorithms confirms that clinical data can be transformed into temporal knowledge to manage new chronic patients, to audit the clinical actions performed in health care centers, and to analyze the adherence of clinical actions to the standard procedures described in CPGs.

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Conflict of interest statement

The authors declare that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Appendix A. Blood Pressure Classification

Category	Blood pressure (mmHg) SBP	DBP
Normal	120-129	80-84
High normal	130-139	85-89
Grade 1 HT	140-159	90-99
Grade 2 HT	160-179	100-109
Grade 3 HT	≥ 180	≥ 110
Isolated systolic Grade 1 HT	140-159	< 90
Isolated systolic Grade 2 HT	160-179	< 90
Isolated systolic Grade 3 HT	≥ 180	< 90

Table A.11: Blood Pressure Classification of AH patients [17].

Appendix B. Possible combinations of classes of AH drugs

Drug combination	Preferred	Useful (with some limitations)	Possible (but less well-tested)	Not recommended
β-blocker + Diuretic		+		
β-blocker + ARB			+	
β-blocker + CCB			+	
β-blocker + ACEi			+	
Diuretic + ARB	+			
Diuretic + CCB	+			
Diuretic + ACEi	+			
ARB + CCB	+			
ARB + ACEi				+
CCB + ACEi	+			

Table B.12: Possible combinations of classes regarding antihypertensive drugs [17].

Appendix C. Clinical cases

3/6/2011	1/7/2011	22/7/2011	10/8/2011	7/9/2011	1/12/2011	17/4/2012
SBP=151 DBP=76 TC = 200	SBP=148 DBP=80 TC = 200	SBP=148 DBP=75 TC = 200	SBP=145 DBP=80 TC = 195	SBP=135 DBP=85 TC = 195	SBP=132 DBP=80 TC = 193	SBP=135 DBP=80 TC = 190
LSC	LSC Indapamide 1,5 mg 1-0-0-0	LSC Indapamide 2 mg 1-0-0-0	LSC Indapamide 2,5 mg 1-0-0-0	LSC Indapamide 2,5 mg 1-0-0-0	LSC Indapamide 2,5 mg 1-0-0-0	LSC Indapamide 2,5 mg 1-0-0-0

Table C.13: Clinical case 1 (66-year-old female).

2/3/2012	28/3/2012	18/4/2012	16/5/2012	5/9/2012
SBP=163 DBP=85 Smoker Waist=110cm	SBP=150 DBP=83 Smoker Waist=110cm	SBP=145 DBP=80 Smoker Waist=109cm	SBP=138 DBP=82 Smoker Waist=109cm	SBP=135 DBP=85 Waist=106cm
LSC Hidroclorotiazide 12.5 mg 1-0-0-0	LSC Hidroclorotiazide 18 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0

Table C.14: Clinical case 2 (75-year-old male).

15/2/2013	15/3/2013	8/4/2013	6/5/2013	10/10/2013
SBP=150 DBP=76 Smoker TC = 195	SBP=155 DBP=83 Smoker TC = 195	SBP=150 DBP=83 Smoker TC = 190	SBP=135 DBP=80 Smoker TC = 190	SBP=130 DBP=85 Smoker TC = 190
LSC	LSC Hidroclorotiazide 12,5 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0

Table C.15: Clinical case 3 (57-year-old-male).

5/11/2012	11/2/2013	7/3/2013	25/3/2013	17/4/2013	27/8/2013
SBP=156 DBP=79	SBP=153 DBP=75	SBP=148 DBP=80	SBP=142 DBP=85	SBP=130 DBP=84	SBP=136 DBP=82
LSC	LSC Amlodipin 5 mg 1-0-0-0	LSC Amlodipin 7,5 mg 1-0-0-0	LSC Amlodipin 10 mg 1-0-0-0	LSC Amlodipin 10 mg 1-0-0-0	LSC Amlodipin 10 mg 1-0-0-0

Table C.16: Clinical case 4 (58-year-old-female).

2/2/2011	18/2/2011	14/3/2011	29/3/2011	19/4/2011	15/4/2012
SBP=190 DBP=85	SBP=188 DBP=89	SBP=175 DBP=79	SBP=160 DBP=80	SBP=138 DBP=83	SBP=135 DBP=86
LSC Hidroclorotiazide 12,5 mg	LSC Hidroclorotiazide 18 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0	LSC Hidroclorotiazide 12,5 mg 1-0-0-0 Amlodipin 5 mg 1-0-0-0	LSC Hidroclorotiazide 12,5 mg 1-0-0-0 Amlodipin 5 mg 1-0-0-0	LSC Hidroclorotiazide 12,5 mg 1-0-0-0 Amlodipin 5 mg 1-0-0-0

Table C.17: Clinical case 5 (69-year-old-female).

1/2/2012	5/3/2012	26/3/2012	26/4/2012	6/8/2012
SBP=172 DBP=74 Smoker Waist=92cm	SBP=170 DBP=85 Smoker Waist=92cm	SBP=150 DBP=83 Smoker Waist=92cm	SBP=123 DBP=80 Smoker Waist=92cm	SBP=120 DBP=75 Smoker Waist=92cm
LSC	LSC Hidroclorotiazide 12,5 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0

Table C.18: Clinical case 6 (54-year-old-female).

3/8/2010	16/18/2010	4/1/2011	24/1/2011
SBP=146 DBP=76	SBP=150 DBP=80	SBP=145 DBP=80	SBP=125 DBP=85
LSC	LSC Nifedipine 20 mg 0-0-0-1	LSC Nifedipine 40 mg 0-0-0-1	LSC Nifedipine 40 mg 0-0-0-1

Table C.19: Clinical case 7 (83-year-old-male).

2/12/2012	11/12/2012	7/1/2013	18/1/2013	22/5/2013
SBP=190 DBP=85	SBP=170 DBP=86	SBP=150 DBP=79	SBP=123 DBP=77	SBP=135 DBP=86
LSC Hidroclorotiazide 12,5 mg 1-0-0-0 Amlodipin 5 mg 1-0-0-0	LSC Hidroclorotiazide 18 mg 1-0-0-0 Amlodipin 7,5 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0 Amlodipin 10 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0 Amlodipin 10 mg 1-0-0-0	LSC Hidroclorotiazide 25 mg 1-0-0-0 Amlodipin 10 mg 1-0-0-0

Table C.20: Clinical case 8 (63-year-old-male).

20/6/2012	3/7/2012	31/7/2012	21/8/2012	5/9/2012	7/1/2013
SBP=150 DBP=88	SBP=147 DBP=80	SBP=148 DBP=75	SBP=148 DBP=75	SBP=135 DBP=85	SBP=132 DBP=80
LSC	LSC Indapamide 1,5 mg 1-0-0-0	LSC Indapamide 2 mg 1-0-0-0	LSC Indapamide 2,5 mg 1-0-0-0	LSC Indapamide 2,5 mg 1-0-0-0	LSC Indapamide 2,5 mg 1-0-0-0

Table C.21: Clinical case 9 (73-year-old-male).

4/4/2011	21/4/2011	18/5/2011	6/6/2011	16/11/2011
SBP=163 DBP=85 LDL-C=130 Family history of CVD	SBP=150 DBP=83 LDL-C=130 Family history of CVD	SBP=145 DBP=87 LDL-C=130 Family history of CVD	SBP=128 DBP=73 LDL-C=130 Family history of CVD	SBP=135 DBP=85 LDL-C=130 Family history of CVD
LSC	LSC Diltiazem 80 mg 1-0-1-1	LSC Diltiazem 100 mg 1-0-1-1	LSC Diltiazem 120 mg 1-0-1-1	LSC Diltiazem 120 mg 1-0-1-1

Table C.22: Clinical case 10 (70-year-old-female).

Appendix D. Temporal models for AH treatment obtained from data

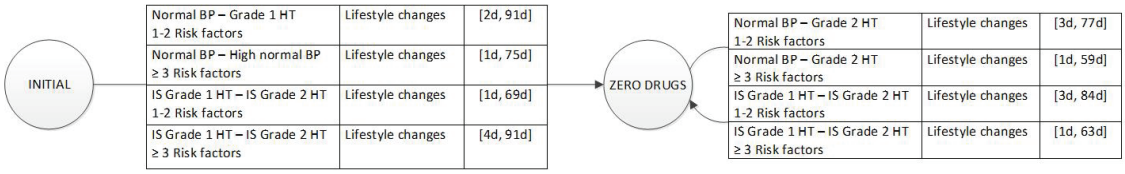

Figure D.5: Temporal model for AH treatment obtained from data - part1.

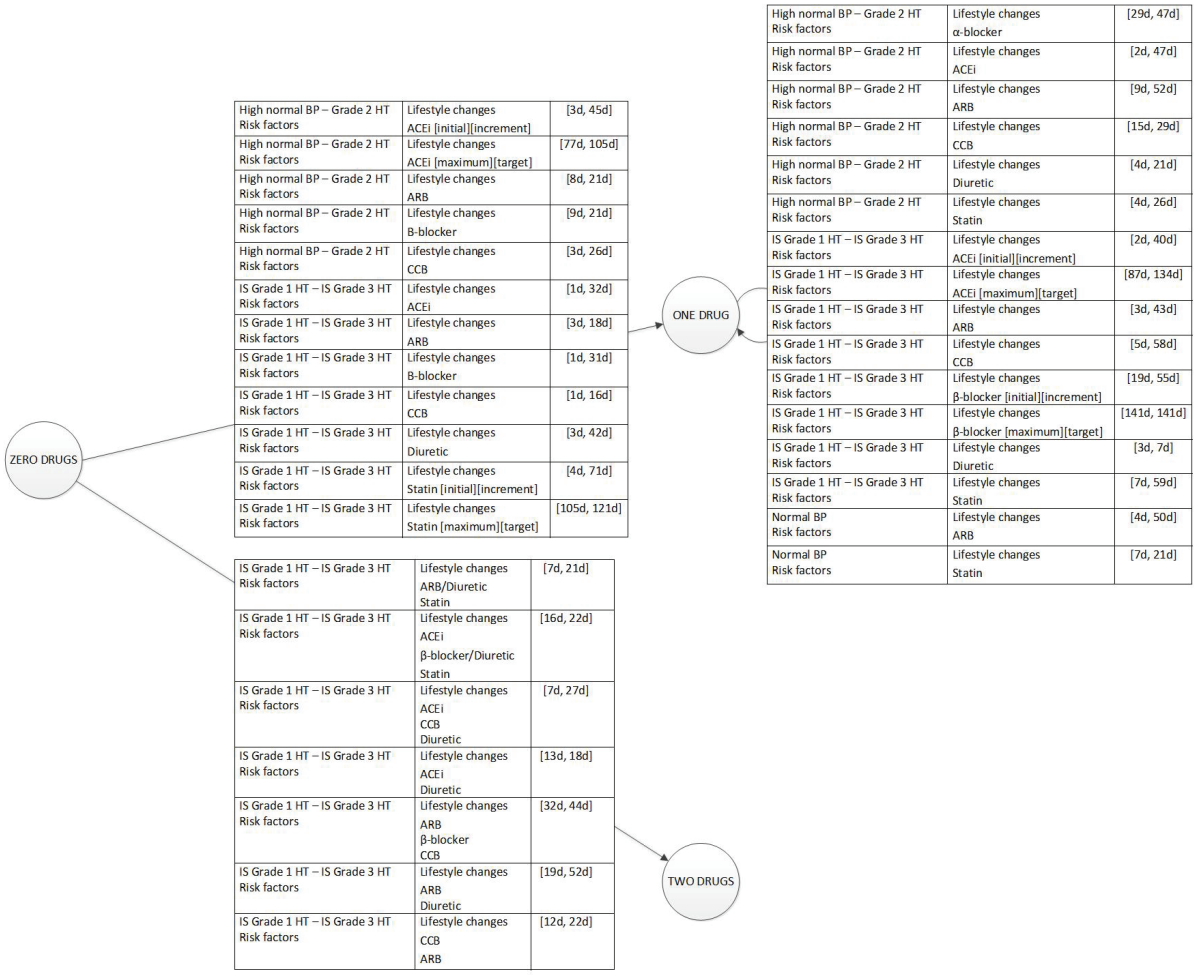

Figure D.6: Temporal model for AH treatment obtained from data - part2.

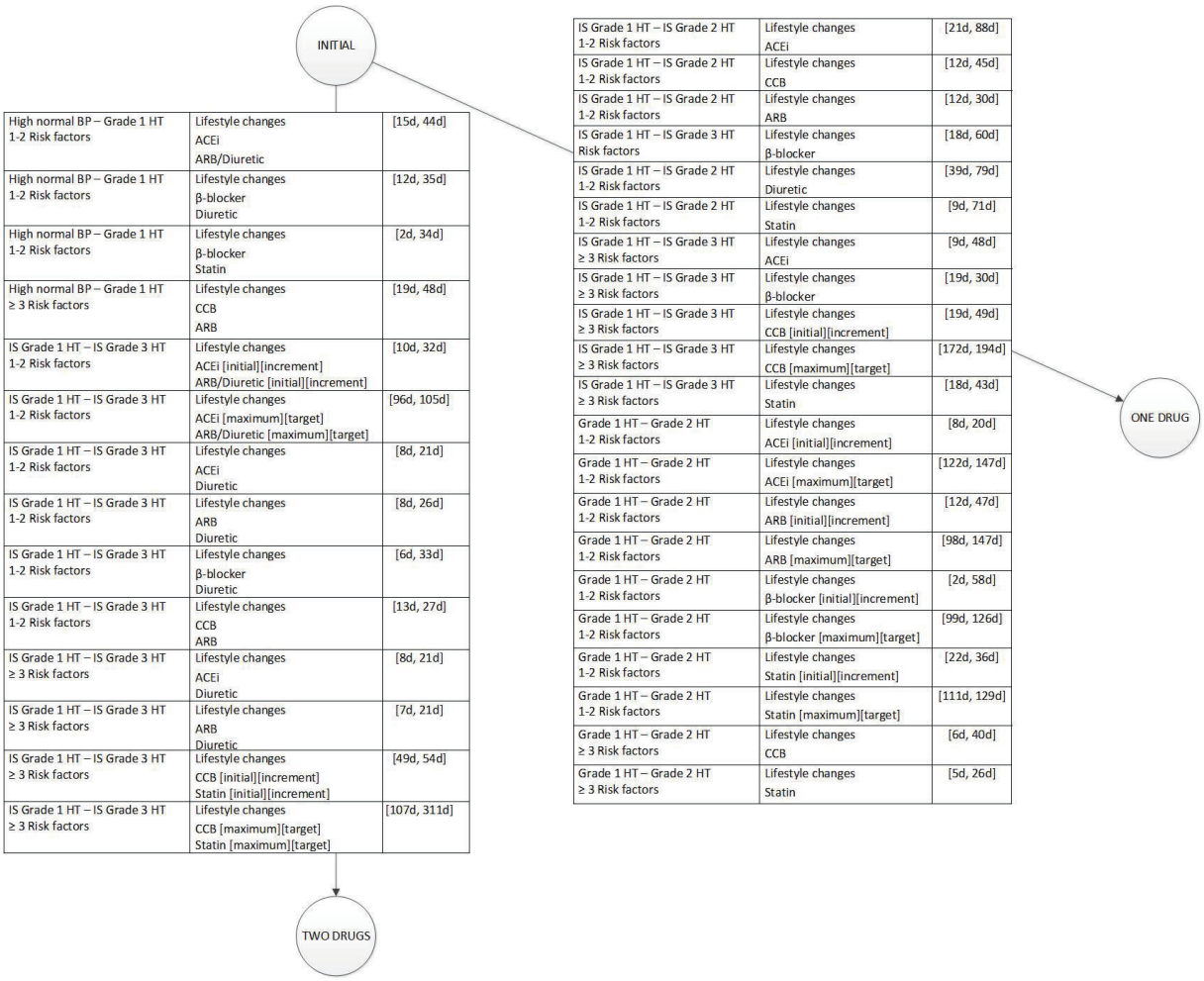

Figure D.7: Temporal model for AH treatment obtained from data - part3.

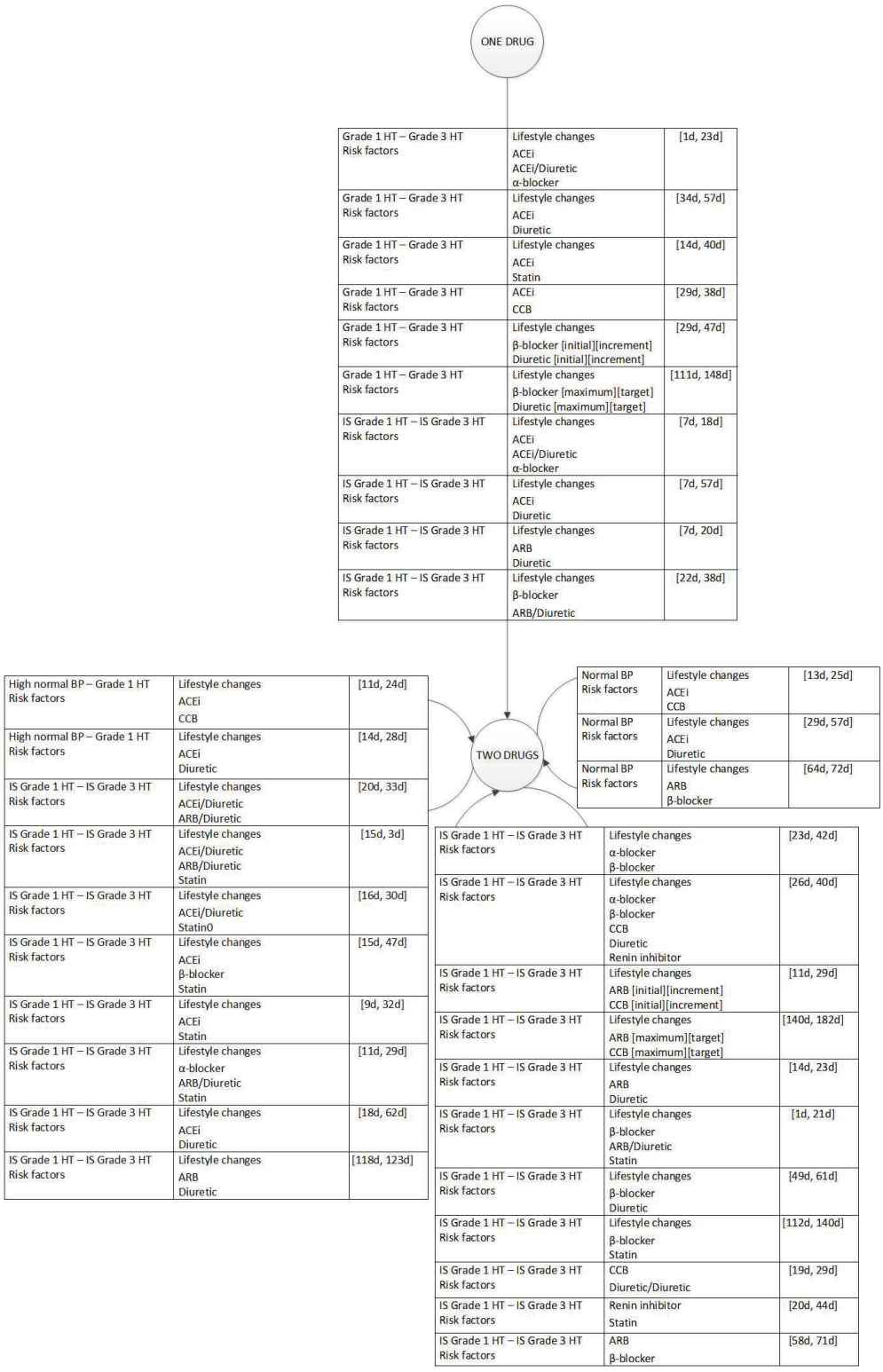

Figure D.8: Temporal model for AH treatment obtained from data - part4.

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