Multi-level Medical Knowledge Formalization with eTTDs to Support Medical Practice for Chronic Diseases

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Abstract

Medical processes combine medical actions which are performed by health care professionals while they observe signs and symptoms, and decide about interventions, prescriptions, tests, etc. in order to deal with the health problem that affects a particular patient. The capability of physicians to propose an appropriate treatment depends on their awareness of similar clinical cases and their knowledge about advances in the treatment of the involved diseases. Clinical practice guidelines (CPGs) are narrative sets of recommendations for treating patients suffering from a particular disease. With CPGs, physicians can stay up to date on the best evidence-based medical care and with the recommendations of experts. However, the access to (and the application of) the contents in the CPGs is difficult during the actual care process.

Our research was centred in the knowledge representation for the purposes of decision making in medical processes. The objective was to represent knowledge for medical processes of chronic diseases. In order to achieve this objective, we have followed three steps: (1) We made an analysis and comparison of formal languages for procedural knowledge representation from a decision making perspective. This was driven by 15 basic questions of medical practice. (2) We proposed an intuitive, ease, and efficient mechanism of medical knowledge formalization. And, (3) we defined a methodology to model medical procedures from stored data about individual, multi-level, medical processes. Proposed mechanism is called the extended Timed Transition Diagram (eTTD) and it can represent three basic levels of decision making in a long term treatment: therapy strategy, dosage, and intolerances.

We have validated eTTDs with CPGs of three chronic cardiovascular diseases: arterial hypertension, heart failure, and stable ischemic heart disease. For the sake of containment, only the results for arterial hypertension are presented. The obtained models can be used as a baseline framework for medical procedural decision support systems development.

Keywords: knowledge representation, decision-making, medical processes, procedural knowledge modelling, knowledge-based framework, medical decision support

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1. Introduction

Medical processes use to be based on the encounters between health care professionals and patients in a short or long term basis. When these processes are therapeutic, the objectives can be diverse; e.g., to heal the patient (curative treatment), to contain the progression of a disease (chronic treatment), to reduce a patients suffering (palliative treatment), to relieve observed signs and symptoms (symptomatic treatment), or to impede a disease to occur (preventive treatment). Medical processes and their health care actions combine to allow clinicians to provide daily medical practice [57]. In this task, clinicians' skills to propose appropriate treatments depend on their awareness of similar clinical cases and their knowledge about the advances in the treatment of the diseases involved. These therapeutic advances can be found in clinical practice guidelines (CPGs). CPGs are documents that describe medical procedures as a narrative set of recommendations for the management of patients who have a particular disease. They are designed to support the decision making process in health care, covering health maintenance, prevention, diagnosis, treatment, patient self-care, and education. Using CPGs, physicians can stay up to date on the best evidence-based medical care and, in the cases where evidence is not available, with the recommendations of experts [37]. The aim of CPGs is to improve the quality of care by bringing new research findings into practice. They are meant to limit undesirable practice variations and reduce health care costs by optimizing health care delivery [16, 70]. However, the access and application of their content is difficult during the care process. Medical decision support systems (MDSSs) emerged to improve the application of CPGs in medical practice, but developing these MDSSs requires the formalization of computer-interpretable guidelines (CIGs), representing the knowledge contained in the CPGs [11, 12, 23, 41, 47, 49, 52]. CIG-based MDSSs combine guideline knowledge with patient clinical data to provide patient specific advice during the actual care process. These systems increase the chance to impact physician's behaviour in contrast to the usage of traditional (narrative) CPGs. CIGs are designed to be used through computer tools and not directly applied by health care professionals. The approach is knowledge engineering and it consists of a knowledge conveyance from human experts to machine structures. Access and exploitation of the conveyed knowledge is offered with computer tools. Consequently CIGs are computer structures rather than medical structures that clinicians cannot easily understand [36, 48].

But knowledge about medical processes is also contained in the data stored in health care databases and electronic health records [3, 37, 38, 39, 40, 63, 68]. This knowledge is not necessarily based on medical evidence but on the experience of medical practice and it can be recognized and transferred from computers to health care professionals with the help of computer data-analysis techniques and tools [3, 38, 39, 40, 54, 58, 68]. Part of the data stored in these clinical information systems refer to clinical treatments, such as those related to chronic cardiovascular diseases (CVDs); e.g., arterial hypertension (AH), heart failure (HF), or stable ischemic heart disease (SIHD).

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According to the World Health Organisation (WHO) [71], CVDs are the number one cause of death in the world. Of the 56 million global deaths in 2012, 38 million (68%) were due to noncommunicable diseases (NCDs) and the greatest share of these deaths with 17.5 million (31%) were due to CVD. A WHO latest report [27] is projecting that deaths caused by NCDs will increase to 52 million by 2030. Four major NCDs (i.e., cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes) are responsible for 82% of NCD deaths. In [25], the WHO calculated that 3 out of 17 million of the CVD deaths in 2008 occurred before the age of 60 and could have been prevented. Addressing risk factors such as tobacco use, unhealthy diet, obesity, insufficient physical activity, salt/sodium intake, and/or high blood pressure is crucial to CVD prevention. *Hipertension*: According to the WHO report [26], 16.5% of all deaths can be attributed to high blood pressure. In 2008, worldwide, approximately 40% of adults aged $\geq$25 had been diagnosed with AH. The number of people with the condition rose from 600 million in 1980 to 1 billion in 2008. The global prevalence of raised blood pressure (defined as systolic and/or diastolic blood pressure $\geq$140/90 mmHg) among persons aged $\geq$18 years was around 22% in 2014 [27]. *Heart failure*: With regard to HF [45], approximately 1-2% of the adult population in developed countries has this disease, with the prevalence rising to $\geq$10% among persons $\geq$70 years. *Ischemic heart disease*: The chart book of the National Institutes of Health 2012 [44] reports that the prevalence of IHD in population-based studies increases with age in both sexes, from 5-7% in women aged 45-64 years to 10-12% in women aged 65-84, and from 4-7% in men aged 45-64 years to 12-14% in men aged 65-84. It is not surprising that all the gathered knowledge about how to manage these three important CVDs leaded to the development of CPGs for AH [21, 22], HF [17, 18], and IHD [19, 20].

In order to model medical practice, in [57] we identified 15 clinical questions that are recurrent in the management of chronic CVD patients (see table 1). These questions have to do with the medical processes of diagnosis, treatment, patient evolution, follow-up, and clinical management in general. But it remained unclear whether a single representation formalism could describe the knowledge for a MDSS to be able to help clinicians to answer these questions in a long-term management of CVD patients. An interesting attempt was carried out to represent all these sorts of knowledge with decision tables [55], however it remained unclear whether these structures could be efficiently and automatically derived from health care databases, or able to represent knowledge at different levels of detail.

Beyond this attempt, here we propose an adequate representation mechanism to answer the clinical questions identified in [57]. This mechanism is founded on the timed transition systems (TTSs) [29, 33] that, after our extension, they are able to capture three basic levels of detail for clinical decision making in long-term treatments: therapy strategy, dosage, and intolerances. At the therapy strategy level, we can represent treatment strategies such as recommended lifestyle changes, whether a pharmacological therapy is required or not, changes of drugs, etc. At the dosage level, the constraints on the required drug doses and take frequencies are described. And, at the tolerance level, possible patient intolerances to drugs and their management can be defined. Before proposing this representation mechanism, we analyzed and compared several formal languages for CIG representation from a decision making perspective. We found that several of these formalisms were able to cover

all clinical decision support questions identified in [57]. However, we concluded that these CIG formalisms are complex and they require expert users with special skills in knowledge representation for both, introducing and interpreting the medical knowledge. Besides, they were not adequate to represent multiple levels of detail of procedural knowledge, and their structures are very difficult to machine learn from clinical data.

On the contrary, our proposed formalism resulting from the extension of TTS is intuitive, manageable and efficient for medical knowledge formalization, capable to deal with the three levels of decision making wished for the treatment of chronic CVD, and easy to derive by automatic procedures from clinical data.

Taking into account the WHO reports on CVD [25, 26, 27], we have limited our application to three highly prevalent chronic diseases: arterial hypertension, heart failure, and stable ischemic heart disease. As the WHO emphasizes clinical actions at the primary health care [71], we have focused our work on this primary level, leaving out the secondary and tertiary health care levels.

The rest of the paper is organized as follows. Section 2 is dedicated to the analysis and comparison of formal languages for CIG representation from a decision making perspective. Section 3 deals with our proposal for medical procedures modelling. It begins with a definition of a new representation mechanism to describe medical procedures as extended timed transition diagrams (eTTDs), and continues with a methodological practical application of our structural model to represent the medical procedures of arterial hypertension at three basic levels of detail for long-term treatments. Finally, conclusions and discussion on further research are presented in Section 4.

2. Knowledge Representation for Decision Making in Medical Procedures

There are different studies defending that the quality of health care is directly related to the experience of the physicians involved [8, 34, 37, 43]. The argued rationale is that physicians with experience reason better than physicians with less experience or inexperienced. It means that experienced physicians have a greater ability to combine different sorts of knowledge acquired from several sources and from their own professional education, training, and experience. Consequentially this allows them to make wiser decisions.

Considering knowledge management principles [24, 35] we can differentiate between three levels of knowledge: know-what, know-how, and know-why. Know-what is the lowest knowledge level also known as declarative knowledge. It gathers objects, facts and principles of a specific domain, where facts and principles establish the relationships and restrictions in the objects and among the objects of a domain. They specify which action has to be taken to confront a specific situation. In the medical domain, know-what knowledge refers to diseases, signs and symptoms, interventions, etc.

Know-how is a higher knowledge level, also known as procedural knowledge. It gathers the knowledge on how to decide an appropriate action which has to be taken to confront a specific situation. This knowledge is required when relationships between objects in a specific domain (being the essence of know-what knowledge) are deficient to express a procedure. In the medical domain, know-how knowledge refers to the clinical processes such as diagnosing

or providing a treatment. This knowledge permits a physician to determine the best course of action possible.

Know-why is the highest knowledge level that we consider. It implies a profound understanding of causal relationships, interactive effects and uncertainties which are gathered for a specific domain. In medicine, this knowledge involves physician's understanding of the underlying theory, evidences and experience in the interaction effects, the exceptions, the limitations and the peculiarities of a medical domain. Notice that CPG evidences determine the know-why knowledge of evidence-based medicine.

2.1. Decision Making in Medical Practice

In medical practice, most of the decisions can be classified into decisions about diagnostics, treatments, prognosis, and clinical activities [2, 37, 43, 50]. In [57], we proposed the Medical Practice Model (MPM). It is a general-purpose knowledge-based functional model of clinical practice which combines differential diagnosis, the prescription and integration of treatments, and prognosis, each one organized as a workflow of tasks. It is able to help clinicians answer the 15 decision support questions shown in table 1. These are typical questions that clinicians are faced with in their daily medical practice. For the sake of simplicity, along the paper we will consider these questions grouped into questions about diagnosis (q1-q3), questions about treatment (q4-q9), patient and disease evolution questions (q10-q11), follow-up questions (q12-q13), and clinical management questions (q14-q15).

Using the configuration of tasks in the MPM, we can identify a holistic composition of these 15 questions in the general medical practice plan depicted in figure 1. This plan shows the questions as circles, and it describes the clinical information required for each question to get answered. Answers generate new information that can be required by other questions. For example, differential diagnosis is started with question "which are the diagnostic hypotheses that may explain the patient's condition?" (see q2 in table 1), based on the triggering condition that a diagnosis is required and the information about the health condition of the patient (PC). As a result of the question, a set of diagnostic hypotheses and respective certainty levels is obtained (DH, certainty). All these information elements (PC, DH, certainty) are required by question q3 to be answered. In figure 1, the logical sequence of clinical questions is indicated with dashed arrows, and each question requires specific sorts of clinical knowledge (and input information) to be answered.

2.2. Formal Languages for Know-how Knowledge Representation

In health care, knowledge modelling and computerization is narrowly related to CIG languages. In a span of 15 years, several reviews of CIG modeling languages have been published. These reviews show complementary perspectives. So, [46] presents a control-flow perspective while examining the expressive power of CIG modeling languages and defining the differences between process languages offered by workflow management systems and modeling languages used to design clinical guidelines. In [48], the primary concern was the usage perspective of these languages. There, the entire life-cycle of CIG development was compared, including CIG modeling languages, acquisition and specification methodologies,

Diagnosis	q1	Given a patient condition, is a diagnosis required?
	q2	Given a patient condition, which are the diagnostic hypotheses that may explain that condition?
	q3	Given a patient condition and a set of diagnostic hypotheses, which are the diagnostic tests that further reduce the number of hypotheses?
Treatment	q4	Given a patient condition, is a symptomatic treatment required?
	q5	Given a patient condition, which are the alternative symptomatic treatments?
	q6	Given a patient condition and the prognoses of a set of alternative treatments, is it possible to identify an acceptable treatment?
	q7	Given a patient condition and a previous prognosis based on a past patient condition, do we have to discharge the patient, continue with the treatment, or reconsider it?
	q8	Given a diagnosis, which are the alternative curative treatments?
	q9	Given two treatments, which is the treatment resulting from their combination?
Evolution	q10	Given a patient condition and a diagnosis, what is the expected evolution of the patient condition?
	q11	Given a patient condition, the diagnosis, and a treatment, what is the expected evolution of the patient condition?
Follow-up	q12	Given a patient condition and a prognosis for a diagnosis, is it better to wait or to treat?
	q13	Given a patient condition and a set of diagnostic hypotheses, does one have to study, refine or treat?
Clinical management	q14	Given a set of diagnostic tests, what is their order of application?
	q15	Given a prognosis and a treatment, when will the next encounter be?

Table 1: MPM decision support questions

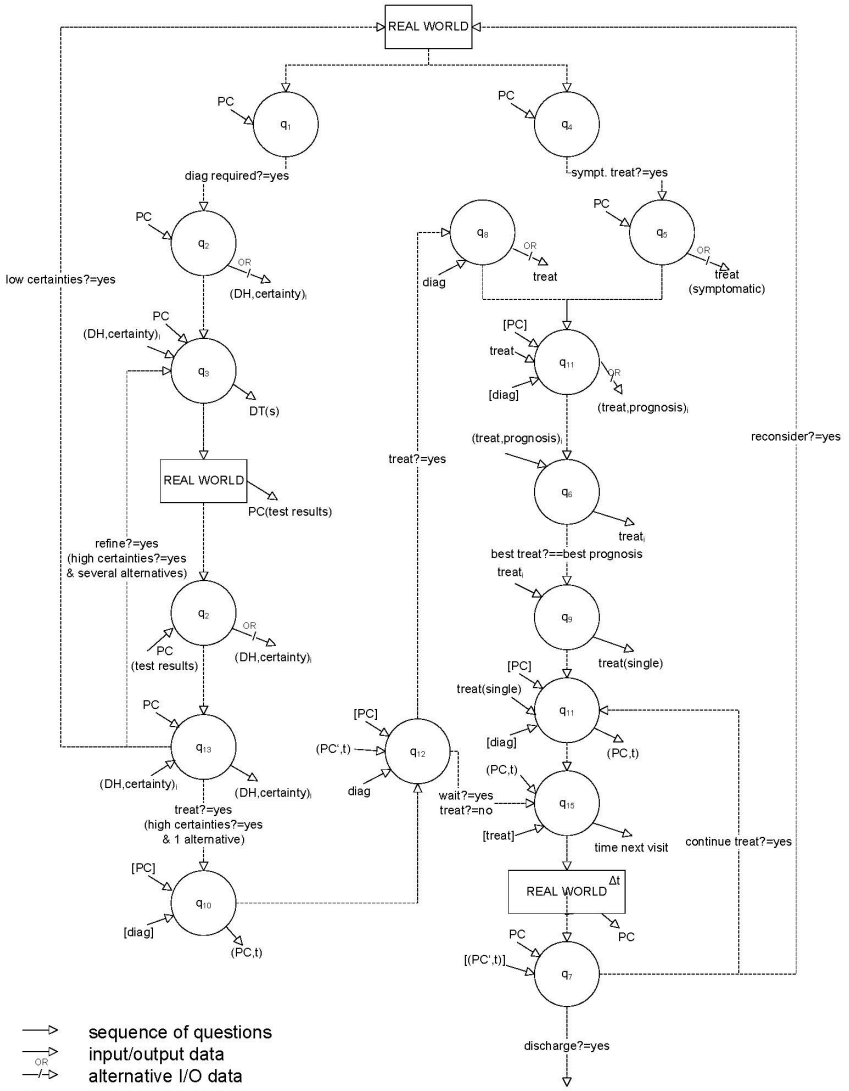

Figure 1: Decision support questions incorporated into general medical practice plan

their integration with electronic health records and organizational workflow, validation and verification, execution engines and supportive tools, exception handling, maintenance and sharing. Also temporal trends in CIG-related researches were examined. In [51], CIG languages are compared from the structural perspective, using eight dimensions of comparison: organization of guideline plans, goals, model of guideline actions, decision model, expression language, data interpretation/abstractions, medical concept model and patient information model.

None of these perspectives to compare CIG languages are decisive to identify the best alternatives to represent the know-how knowledge required to answer clinical questions such as ones shown in table 1. For this reason, we analyzed some of the most frequently used CIG languages from a clinical decision making perspective. The representation languages compared are: Arden Syntax [30], Asbru [41], clinical algorithm (CA) [28], Gaston [12], GLIF [4], GUIDE [53], EON [47], knowledge-experience decision tables (k-e DT) [55], PRODIGY [52], PROFORMA [23], SDA [56] and timed transition diagrams (TTD) [33].

In Appendix A, we provide an overview of each one of these representation formalisms. In the following sections we analyze whether these languages can integrate the know-how knowledge needed to address the decision making requirements to answer the questions in table 1. We organize the discussion according to the five types of questions identified: diagnosis, treatment, patient evolution, follow-up, and clinical management. Conclusions are summarized in table 2.

2.2.1. Diagnosis

Diagnosis questions are mainly based on the management of the clinical concepts *patient condition*, *diagnostic hypotheses*, and *diagnostic tests*. In table 1, these are questions q1-q3. The capacity of each CIG language to answer these questions is indicated in the respective columns q1-q3 of table 2.

All the languages, except TTD, can represent the knowledge to answer all the diagnosis decision support questions. This knowledge must be able to relate patients conditions with diagnostic hypotheses, and these two with useful diagnostic tests. To accomplish this, the Arden Syntax includes units called Medical Logic Modules (MLMs) that make a single medical decision as a production rule that relates a set of input conditions (e.g., patient condition) to a particular set of actions (e.g., suspect of some possible diseases or suggest some diagnostic tests). EON and PRODIGY include the concept of scenario, while GLIF, Gaston, and SDA the concept of state. Both concepts define a particular management context for patients, thus allowing the incorporation of patient conditions in the clinical plan. Asbru, PROforma, and GUIDE use expressions that refer to patient states in decision criteria or preconditions that affect guideline control flow. Clinical algorithm (CA) is able to answer all three diagnosis questions as it offers constructs that represent patient condition, diagnostic hypothesis, and diagnostic tests. SDA is the representation format that is based on the concept of CA [10, 28] but also includes representation primitives such as patient states, decisions, actions [51, 69] which are crucial for representing diagnosis questions. In K-e DT, question q1 is answered with a single loop (i.e., only one of the entries in the decision table is used to provide an answer to the medical question), while questions q2

and q3 are answered with a multiple loop (i.e., all of the entries that are applicable provide their respective conclusions, and these conclusions define a list of alternatives that is the answer to the medical question [55]). TTD is a simple representation formalism which offers knowledge representation to answer q1, but not q2 or q3, because it is able to represent a patient conditions and/or a patient current treatments as states, but it is not meant to describe diagnostic procedures.

2.2.2. Treatment

In the MPM, the treatment questions are q4-q9 (see tables 1 and 2). They are related to medical concepts such as *patient condition*, *diagnosis*, *treatment* (either symptomatic or curative), and *prognosis*. All the languages are able to represent the medical knowledge to answer all these questions, except the Arden Syntax, CA, and TTD.

The Arden Syntax is providing representation for q4 and q7, but it is not considered for long-term treatments representation and it lacks of ability to include more decision questions, especially for treatments, patients and diseases evolutions, and medical reconsiderations. On the contrary, EON, Gaston, GLIF, PRODIGY, and GUIDE can include branch steps, while EON, Gaston, GLIF, and GUIDE also include synchronization steps. Asbru and PROforma implicitly support parallel and sequential execution. Asbru, EON, Gaston, GLIF, GUIDE, and PROforma have explicit constructs to support cyclical and iterative plan execution. Asbru, EON, and GLIF define also fuzzy iteration frequency (e.g., take drug every 5-6 hours). PRODIGY, Gaston, and GLIF specify goals as text strings. EON, GUIDE, and PROforma represent goals formally, while Asbru represents intention as context dependent temporal patterns. Asbru, PROforma, and PRODIGY are not using explicit constructs to represent switching [51], while EON, Gaston, GLIF, and GUIDE have switch constructs that are used for branching. All these are useful components for modeling parallel paths in a guideline plan. Guideline plans are the basic structures to represent the knowledge to answer the questions q4-q8. SDA also includes sequences, concurrences, alternatives, and loops [51, 69], which are crucial for representing decision making process for treatments and prognosis. K-e DT use a single loop to answer questions q4, q7 and q9, while q5 and q6 are answered with a multiple loop. CA is a representation format that may offer representation for q4 and q7 decision support questions as it's constructs are able to capture patient condition and treatment. It is not meant for representation of alternative treatments (q5/q8). Existing CA structure makes possible to apply this feature, but in general CAs are not used for representation of alternative treatments. They normally form part of CPGs, giving the instructions on how to act in certain moment, how to solve a problem for which the diagnosis is already set. The most acceptable treatment is represented in CA but not the alternatives (q6). It does not offer representation of an integrated treatment resulting from the combination of two treatments (q9). TTD offers representation for q7 as current and past patient conditions are represented as states, but it is not convenient to represent therapeutic procedures.

2.2.3. Evolution

Evolution questions are related to a concepts of *patient condition*, *treatment*, and *prognosis*. In table 1, these are questions q10 and q11. All the languages, except the Arden Syntax, can represent the knowledge to answer these evolution decision support questions.

The Arden Syntax is not providing representation for patient and disease evolution. It is not supporting long-term treatments representations, which are crucial to answer q11. MLM constructs make a single medical decision which can relate a patient condition to possible diseases or diagnostic tests, but are not sufficient to represent patient or disease evolutions to answer q10 or q11. Asbru, CA, EON, Gaston, GLIF, GUIDE, Prodigy, PROforma, and SDA provide constructs (presented in section 2.2.2) to represent patient conditions, treatments, and prognoses and therefore they are able to formalize the knowledge required to answer q10 and q11. In K-e DT, evolution questions are answered with a single loop. TTD is able to represent q10 and q11 because it can describe patient conditions and treatments as states, and prognostics as states plus a time delay function which is attached to transitions.

2.2.4. Follow-up

Follow-up is about the control and medical reconsideration of the patient condition or treatment. In the MPM [57], medical reconsideration is represented by questions q12 and q13 (see tables 1 and 2). They are related to a concept of a *patient condition*, *diagnosis* or *diagnostic hypothesis*, and *prognosis*. All the languages, except the Arden Syntax and TTD, can represent the knowledge to answer both these questions.

The Arden Syntax is not providing representation for medical reconsiderations as MLMs are not able to capture prognosis. Asbru, CA, EON, Gaston, GLIF, GUIDE, PROforma, and SDA have explicit constructs to support cyclical and iterative plan execution, while Prodigy is implicitly supporting these components. They offer representation for the two follow-up decision support questions. Again, K-e DT supports a representation of q12 with a single loop, while q13 is answered with a multiple loop. TTD supports representation for q12 using constructs of states and a time delay function assigned to transitions. Question q13 is not supported, as TTD is not able to represent diagnostic procedures.

2.2.5. Clinical management

Clinical management questions are related to the concepts of *diagnostic tests*, *treatment*, and *prognosis*. In table 1, these questions are q14 and q15.

Asbru, EON, Gaston, GLIF, GUIDE, PRODIGY, PROforma, and SDA support the representation of knowledge to answer both clinical management questions. They include constructs presented in section 2.2.1 and 2.2.2 to describe diagnostic tests and their order of application (q14), but also the time constraints needed to determine the next encounter (q15). The Arden Syntax is providing representation for q14 because MLMs are able to represent diagnostic tests, but it fails to represent the sort of knowledge required by q15 since it does not have constructs to indicate when the next encounter will be. K-e DT is able to answer q15 with a single loop, but not q14. CA offers a representation of knowledge for q14 with assigned activities, whereas determining the next encounter in q15 is impossible with this representation format. TTD can answer q15 by representing current conditions

	Diagnosis			Treatment						Evolution		Follow-up		Clinical manag.	
	q1	q2	q3	q4	q5	q6	q7	q8	q9	q10	q11	q12	q13	q14	q15
ARDEN SYNTAX	+	+	+	+	−	−	+	−	−	−	−	−	−	+	−
ASBRU	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CA	+	+	+	+	−	−	+	−	−	+	+	+	+	+	−
EON	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GASTON	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GLIF	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GUIDE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
k-e DT	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
PRODIGY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROFORMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SDA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TTD	+	−	−	−	−	−	+	−	−	+	+	+	−	−	+

Table 2: Decision support questions included by formalisms for medical procedural knowledge representation

and treatments as states where the next encounter is determined with a time delay function assigned to the TTD transitions. Question q14 is not supported because TTD lacks the ability to represent diagnostic tests.

3. Modelling Multi-level Medical Procedures

In this section we define a representation mechanism to formalize medical knowledge as extended timed transition diagrams (eTTDs). They are explained with an example on heart failure. We also show how eTTDs extend TTDs to model the sort of knowledge required to answer all the clinical questions in table 1. Some of these questions require know-what knowledge exclusively (i.e., q1-q4, q7, q9, q10, q12, and q14), but the rest (i.e., q5, q6, q8, q9, q11, q14, and q15) also require know-how knowledge modeling of medical procedures. eTTDs allow this modelling of medical procedures at three levels of detail: treatment strategy, dosage, and tolerance. We used eTTD to represent medical practice for three chronic CVDs at these three levels of detail. However, here we only provide the formalization of medical practice for arterial hypertension and leave the interested reader to confer eTTD of heart failure and stable ischemic heart disease in [32]. Complete modelling of arterial hypertension procedures are contained in Appendix B and Appendix C.

3.1. The extended TTD

Timed Transition System (TTS) was defined in 1992 [29] as quintuples $\langle V, \Sigma, T, l, u\rangle$ where $V=\{v_1,v_2, ..., v_m\}$ is a finite set of variables, $\Sigma=\{\sigma_1, \sigma_2, ..., \sigma_n\}$ is a finite set of states with every state $\sigma_i \in \Sigma$ a subset of variables (i.e., $\Sigma \subseteq 2^V$), T is a finite set of transitions where every transition $t \in T$ is a binary relation on Σ (i.e., $T \subseteq \Sigma^2$), $l : T \rightarrow I\!N$ is the minimal delay

function, and $u : T \rightarrow I\!N \cup \{\infty\}$ is the maximal delay function such that for any $t \in T$, $l(t) \leq u(t)$.

TTS can be naturally represented as timed transition diagrams (TTDs) [29, 33], with Σ the set of vertexes, T the edges that connect these vertexes, and $[l(t), u(t)]$ the label of the edge $t \in T$. TTD is a simple representation formalism which offers an intuitive and understandable representation of the medical knowledge required to answer clinical questions of the sort q1, q7, q10-q12 and q15, as we showed in section 2.2. Notice that TTD states capture the notions of patient condition when Σ is a set of signs and symptoms, and the notion of treatment when Σ is a set of clinical actions. However, TTDs are not good representing diagnostic and therapeutic procedures where different medical concepts such as patient conditions, treatments, and patient tolerances are combined.

An *Extended Timed Transition System* (eTTS) is a nonuple $\langle V_\Sigma, V_C, V_A, \Sigma, T, d, f, l, u \rangle$ where V_Σ is a finite set of state variables, V_C is a finite set of condition variables, V_A is a finite set of activity variables, $\Sigma = \{\sigma_1, \sigma_2, ..., \sigma_m\}$ is a set of states with every state σ_i a different subset of state variables (i.e., $\Sigma \subseteq 2^{V_\Sigma}$), T is a finite set of transitions where every transition $t \in T$ belongs to $\Sigma^2 \times 2^{V_C} \times 2^{V_A}$, $d : V_A \times T \rightarrow I\!N$ and $f : V_A \times T \rightarrow I\!N$ are the dose and the frequency partial functions defined on the set of activity variables and transitions, $l : T \rightarrow I\!N$ and $u : T \rightarrow I\!N \cup \{\infty\}$ are the lower and upper delay functions such that for any $t \in T$, $l(t) \leq u(t)$.

eTTS are represented as extended timed transition diagrams (eTTDs) where eTTS states in Σ are vertexes of the eTTD and transitions in T are eTTD edges connecting pairs of vertexes. An eTTD can contain recursive transitions to describe clinical situations in which a patient remains in the same state after a clinical activity. All the edges are labeled with:

1. A set of conditions in 2^{V_C} describing the patients crossing transition t.
2. A set of activities in 2^{V_A} indicating the treatment of the patients crossing t.
3. A time interval $[l(t), u(t)]$ describing the delay of crossing transition t.

Each activity a in a transition t can have a dose $d(a, t)$ and an intake frequency $f(a, t)$ attached, if the activity corresponds to a pharmacological prescription. The allowed values for a pharmacological prescription dose $d(a, t)$ are expressions of the sort quantity of milligrams (mg) (e.g. $50mg$, $20mg$) of drug a in transition t. Frequency $f(a, t)$ is defined as the frequency of occurrence of variable a in transition t. The allowed values a frequency can take are expressions of the sort quantity of hours, such as $4h$, $8h$, $24h$, representing every 4 hours (6 times a day), every 8 hours (3 times a day), every 24 hours (once a day), respectively. These two constructs (dose d and frequency f) in eTTD are represented together as $[D]$ where D represents a dosage (i.e., a dose and a take frequency, together). In the eTTD, the allowed values of D are expressions of the form *initial*, *increment*, *target* representing initial dosage, dosage increment (modification) and target prescribed dosage, respectively.

For example, the eTTD in figure 2 represents part of the knowledge required for the correct treatment of heart failure according to the CPG [18]. Only two states and the corresponding state transitions with their temporal components are shown.

This diagram captures the know-how knowledge of a HF patient evolving between a 2-drug and a 3-drug treatment. It describes two possible states: the CLASS II HF stage[1] (i.e, slight limitation of physical activity) with the patient taking two drugs and one possible diuretic to relieve the signs and symptoms of congestion, and a CLASS III-IV HF stage (i.e., less than ordinary physical activity limited by dyspnea because it could not be controlled with lifestyle modifications and pharmacological therapy with two drugs) with the patient taking three drugs and an optional diuretic. Patients in the first state must complement a healthy lifestyle with a pharmacological therapy (e.g., ACE-inhibitor or beta blocker), starting with an [initial] dosage. Diuretic is optional, also at an [initial] dosage. Then, after 2 to 4 weeks if the patient is not controlled in the CLASS II HF stage, the dosage must be incremented (see transitions with dosage values [increment]). The process can be repeated every 2-4 weeks till the [target] dosage is reached (i.e., the appropriate dosage to keep the patient stable and controlled). At this time, if the patient remains in CLASS II HF stage, he must continue taking drugs at the target dosage and follow-up is fixed to be between 3 to 6 months. But, if the patient evolves to CLASS III-IV HF stage, then the treatment must be complemented with additional drug (e.g., MRA), starting with an [initial] dosage. Then, after 2 to 4 weeks if the patient is not controlled in CLASS III-IV HF stage, the dosage is incremented. The process can be repeated every 2-4 weeks till the [target] dosage is reached. At that time, if the patient remains in CLASS III-IV HF stage, he continues taking drugs at the target dosage and follow-up is fixed to be between 3 to 6 months. The patient can also evolve from CLASS III-IV HF to CLASS II HF stage, this representing an improvement in patient condition, with a reconsideration of the prescribed drugs.

[1]The NYHA (New York Heart Association) Classification of HF stages.

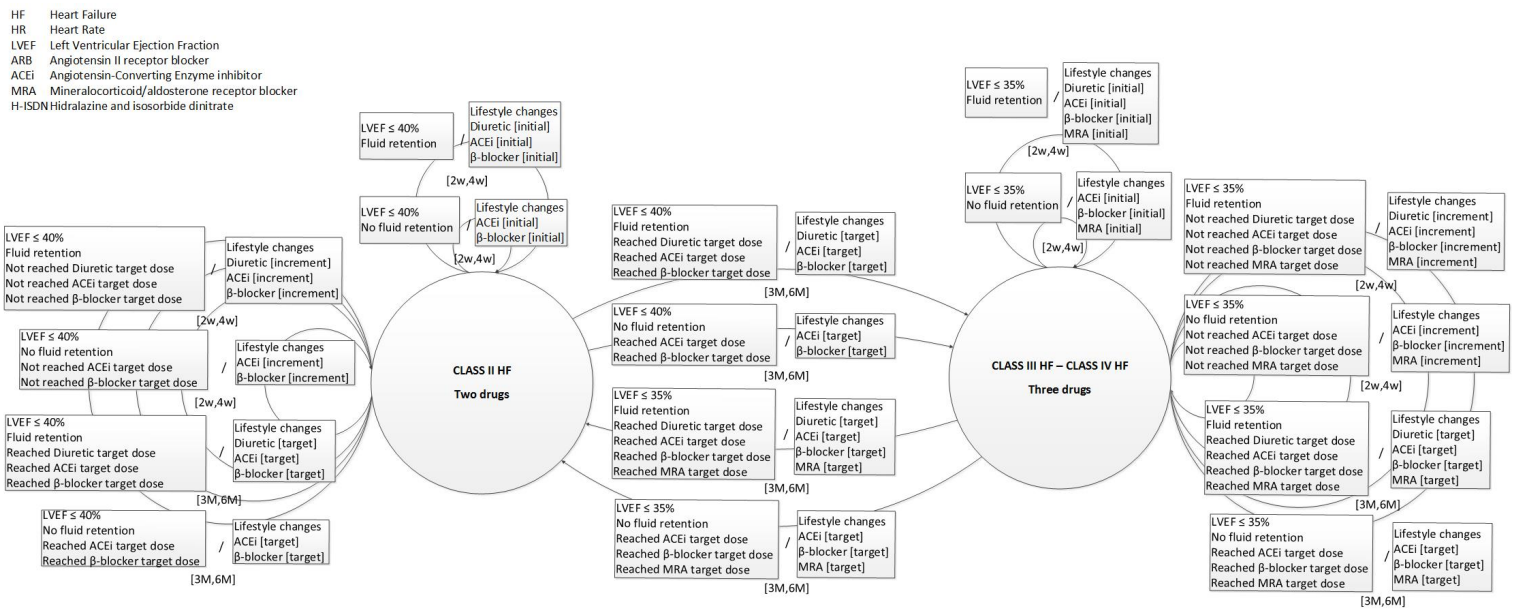

Figure 2: Partial eTTD for Heart Failure treatment

	q1	q2	q3	q4	q5	q6	q7	q8	q9	q10	q11	q12	q13	q14	q15
TTD	+	−	−	−	−	−	+	−	−	+	+	+	−	−	+
eTTD	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table 3: TTD and eTTD comparison considering covered decision support questions

With respect to the descriptive capacity of the eTTDs, these allow formalizing the type of knowledge required to answer all the clinical questions listed in table 1. Specifically, as extensions of TTDs, eTTDs can help answer all the questions that TTDs are able to answer (see table 3). In addition, eTTS include a set of conditions and a set of activities that allow eTTDs to relate patients conditions with possible diseases (q2) and useful diagnostic tests (q3). With an eTTD we can also represent the knowledge needed to answer the treatment questions q4-q9. In particular, the set of conditions 2^{V_C} and set of activities 2^{V_A} allow representing symptomatic (q4, q5) or curative (q8) treatments, while transitions in T can be used to represent alternative treatments (q5). A time delay $[l(t), u(t)]$ of transition t offers a prognosis of evolution that allows the identification of acceptable treatments (q6). With the given eTTD structure it is also possible to represent the combination of two given treatments (q9). Moreover, eTTDs are also able to cover medical assessments (q12, q13) since TTD already supported q12, and q13 is supported by eTTD if patient conditions are related with the possible diagnostic hypotheses using a set of conditions in 2^{V_C}. eTTDs also support the clinical management question q14 using a set of activities in 2^{V_A}.

In table 3, we summarize the capability of eTTD to represent all sorts of knowledge required to answer the medical questions in table 1, in comparison with the limited capability of the TTD model. For questions involving medical procedures (i.e., q5-q9, q11, q14, and q15) eTTDs are also able to provide answers at three levels of detail.

3.2. Three-level Therapy Modelling for Chronic Diseases

Medical treatment process can be detailed at three different levels: treatment strategy, dosage, and tolerance. At the treatment strategy level therapy plans are represented. Therapies can be pharmacological or non pharmacological. Pharmacological therapies involve the use of drugs. Contrarily, non pharmacological therapies do not include medications but clinical activities such as analyses, radiographies, and lifestyle changes (e.g., diet actions, control of smoking and drinking alcohol, exercise, etc.). Chronic diseases combine pharmacological and non pharmacological therapies to provide a long-term treatment and therefore, their treatment defines an order in which pharmacological and non pharmacological actions should take place. Moreover, treatment is also defined at the level of the number of drugs to be taken at each particular moment of the treatment. All these indications define the strategy level of a treatment.

At the more detailed dosage level, drug dosages are defined. A regular procedure for the management of drugs is to start with a minimal dosage (or the appropriate dosage to the current patient condition) and increase it to a limit while the treatment is not having the expected results. Upon reaching the dosage limit, or sometimes before that, the physician may decide to change the drug or either complement the current drug with a new one. For chronic patients, the process is continued till the patient condition reaches a controlled stage.

The tolerance level represents a third level of detail of therapies. It describes drug intolerances and their management. Usually, the drug that a patient is intolerant to should be replaced with another one having the same or similar curative, palliative, or symptomatic effect.

We have analyzed all these three levels of detail for three chronic CVDs and their respective CPGs [32]: arterial hypertension [21, 22], heart failure [17, 18], and stable ischemic heart disease [19, 20]. For all of them, we represented the knowledge available in these CPGs, published by the European Society of Cardiology and the European Society of Hypertension. The resulting models were detailed in [32] once they were validated by two senior physicians. In this paper we show the results corresponding to the modelling for arterial hypertension.

3.2.1. Modelling Therapy Strategy (level 1) for Arterial Hypertension

In this section, we propose a methodology for the modelling of medical knowledge at the therapy strategy level. It was validated after the application to three CVDs: arterial hypertension, heart failure, and stable ischemic heart disease. The methodology is structured in the following steps:

1. Identify the disease stage categories.
2. Identify the disease risk factors.
3. Cross stage categories and risk factors in a management table.
4. Model the therapy strategy I: number of drugs.
5. Identify possible combination of drugs.
6. Model the therapy strategy II: drug preferences.

The application of this methodology to the management of arterial hypertension follows. Arterial hypertension (AH) is defined as having high values of systolic blood pressure (SBP) and/or diastolic blood pressure (DBP). Normal values are agreed to be below 140 mmHg for SBP, and below 90 mmHg for DBP. Deviations from these values define different categories of AH stages [22], as table 4 shows.

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 4: Blood Pressure Classification of AH patients [22]

The decision on when to initiate a pharmacological treatment depends not only on the blood pressure levels but also on the patient disease history and the risk factors (RFs) associated to that specific patient. Risk factors influencing the initiation of a pharmacological treatment are gathered in table 5 [21].

Systolic and diastolic BP levels
Levels of pulse pressure (in the elderly)
Age

- Man $>$ 55 years
- Woman $>$ 65 years

Smoking
Dyslipidaemia

- TC $>$ 5.0 mmol/l (190 mg/dl) or
- LDL-C $>$ 3.0 mmol/l (115 mg/dl) or
- HDL-C: Man $<$ 1.0 mmol/l (40 mg/dl), Woman $<$ 1.2 mmol/l (46 mg/dl) or
- TG $>$ 1.7 mmol/l (150 mg/dl)

Fasting plasma glucose 5.66.9 mmol/L (102125 mg/dl)
Abnormal glucose tolerance test
Abdominal obesity

- Waist circumference $>$ 102 cm (Man)
- Waist circumference $>$ 88 cm (Woman)

Family history of premature CV disease

- Man at age $<$ 55 years
- Woman at age $<$ 65 years

Table 5: Risk factors and gender differential values for AH patients [21]

The management of hypertension should be related to the quantification of total number of cardiovascular risks. This premise is based on the fact that the majority of hypertensive population has not only elevated BP but also additional cardiovascular RFs [22]. Table 6 represents the importance of risk factors in combination to BP levels for the management of hypertension [22]. For example, we can observe the combinations that require immediate pharmacological therapy (e.g., all patients having Grade 3 hypertension should immediately be prescribed with drugs) or the cases that begin with a non pharmacological therapy (i.e., lifestyle changes) and continue introducing a drug treatment if BP levels do not improve after some time. The cells of this management table also describe alternative disease levels of severity HT1, HT2, and HT3 (between parenthesis) as a combination of the disease stage, the risk factors, and other comorbid diseases and conditions. This table concludes the third step of our proposed methodology to model the therapy strategy level.

Pharmacological therapy for chronic diseases can be interpreted considering changes in the number of prescribed drugs and also in the order in which drugs have to be applied. This provides a double description of the treatment at the treatment strategy level. Considering the decisions that physicians are faced with to offer an optimal treatment with regard to the number of drugs to be applied along a long-term treatment of AH, we concluded with the model depicted in figure 3. It identifies four treatment situations: initial which represents the patient's first visit, and the rest representing whether the patient is currently taking zero, one, or two drugs. Edges represent transitions which are conditioned to the severity of the disease identified in the management table (i.e., HT1, HT2, and HT3 values in table 6). Edges can also contain a combination of non pharmacological therapies (e.g., lifestyle changes or LSC) with the optional prescription of one- or two-drug treatment (i.e., 1D or 2D).

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal	Grade 1 HT	Grade 2 HT	Grade 3 HT
No other RF	No BP intervention (HT1)	Lifestyle changes for several months then add BP drugs targeting $< 140/90$ (HT1)	Lifestyle changes for several weeks then add BP drugs targeting $< 140/90$ (HT1)	Lifestyle changes Immediate BP drugs targeting $< 140/90$ (HT2) (HT3)
1-2 RF	Lifestyle changes No BP intervention (HT1)	Lifestyle changes for several weeks then add BP drugs targeting $< 140/90$ (HT1)	Lifestyle changes for several weeks then add BP drugs targeting $< 140/90$ (HT1)	Lifestyle changes Immediate BP drugs targeting $< 140/90$ (HT2) (HT3)
≥ 3 RF	Lifestyle changes No BP intervention (HT1)	Lifestyle changes for several weeks then add BP drugs targeting $< 140/90$ (HT1)	Lifestyle changes BP drugs targeting $< 140/90$ (HT2)	Lifestyle changes Immediate BP drugs targeting $< 140/90$ (HT2) (HT3)
OD CKD stage 3 DM	Lifestyle changes No BP intervention (HT1)	Lifestyle changes BP drugs targeting $< 140/90$ (HT2)	Lifestyle changes BP drugs targeting $< 140/90$ (HT2)	Lifestyle changes Immediate BP drugs targeting $< 140/90$ (HT2) (HT3)
Symptomatic CVD CKD stage ≥ 4 DM with OD/RF	Lifestyle changes No BP intervention (HT1)	Lifestyle changes BP drugs targeting $< 140/90$ (HT2)	Lifestyle changes BP drugs targeting $< 140/90$ (HT2)	Lifestyle changes Immediate BP drugs targeting $< 140/90$ (HT2) (HT3)

CKD: Chronic Kidney Disease, DM: Diabetes Mellitus, OD: Organ Damage, RF: Risk Factor

Table 6: Management of AH considering blood pressure levels and risk factors [22]

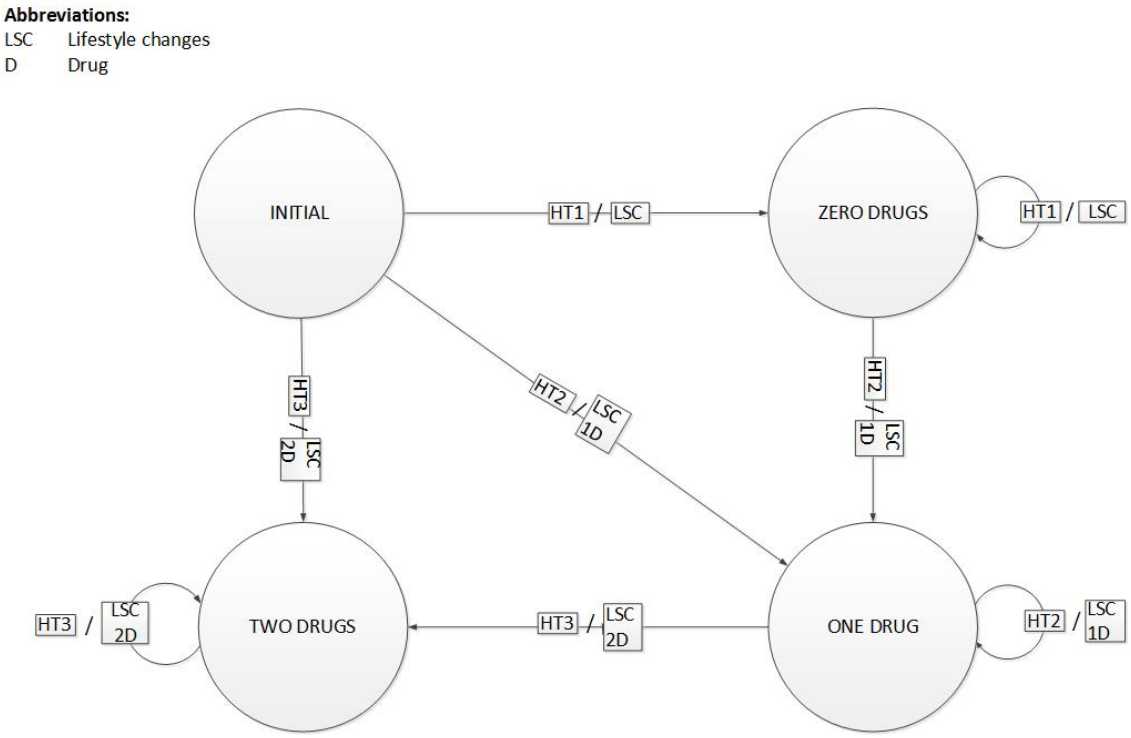

Figure 3: Structural model of therapeutic strategy for AH patients

Besides the number of drugs, physicians take yet other important decisions in order to efficiently treat a chronic CVD. When the decision to initiate a drug therapy is taken, they have to determine which drug to prescribe. The knowledge required to make this decision is the one captured in the fifth and sixth steps of our proposed methodology.

CPG for the management of AH [22] states that diuretics, beta-blockers, CCB, ACEi, and ARB are all suitable drugs for the initiation and maintenance of an antihypertensive treatment, either to be used as monotherapy or in combination with each other. For some specific conditions (e.g., isolated systolic hypertension, organ damage, or diabetes mellitus) preferred drugs are ACEi and ARB. It is recommended to use statin therapy at moderate to high CV risk [22]. Pharmacological therapy in AH can be interpreted as a drug increment where each further stage of the disease involves including an additional drug to the existing therapy. Table 7 summarizes the information provided in CPG [22], considering possible combinations of classes of antihypertensive drugs and the indication if the combination is preferred, useful, possible, or not recommended. We can observe that preferred combinations are diuretic with ARB, CCB or ACEi; also CCB with ARB or ACEi. Not recommended combination is ARB with ACEi. Useful combination is beta blocker with diuretic, but it has some limitations; e.g., in many trials this combination was as effective as other ones, but it appears to provoke more cases of new-onset diabetes in susceptible patients. Combinations of beta blocker with ARB, CCB or ACEi are possible, but not as well-tested as the other ones.

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 7: Possible combinations of classes of antihypertensive drugs

The last step of the methodology is to provide more detail on the edges of the structural model obtained after the forth step (see figure 3 for AH). On the one hand, the severities of the disease contained in the edges can be made more specific with the values in the first column of the management table (see table 6 for AH). On the other hand, we can replace pharmacological therapies of the sort 1D, 2D, etc. in the edges by preferred, useful, and possible drugs and drug combinations (see table 7 for AH). This will conclude with a model of the treatment strategy level at the detail of drugs. For AH, the complete information about this level can be found in [32], but here we describe part of this model as an example.

The possible alternatives of introducing a first drug in an AH treatment are summarized in table 8. In figure 3, this transition is labeled HT2/LSC, 1D. The introduction of drugs implies that this transition is replaced with the ones described in the rows of table 8. In this table, the initial transition (column ID), the state the transition starts at (column State OUT), and the state the transition ends at (column State IN) are fixed. Column Option identifies the new transitions substituting the initial one. Each new transition has a patient condition (column Condition) and a detailed therapy (column Activity). For example, Option b_3 describes a transition of a patient who has not received pharmacological treatment so far, has BP levels in the Grade 1 HT to Grade 2 HT category of table 4 and has two or less risk factors of table 5. Under such circumstances, a physician should recommend lifestyle changes and prescribe ACEi. Consequently, the patient is now in state "taking one drug". Notice that for this same condition five alternative acceptable treatments (options b_1, b_2, b_3, b_4 and b_5 in the table) could have been prescribed. All these options in table 8 are directly represented as transitions of the eTTD in figure 4.

ID	State OUT	State IN	Option	Condition	Activity
5	Zero drugs	One drug	a_1	IS Grade 1 HT − IS Grade 2 HT	Lifestyle changes Diuretic
			a_2		Lifestyle changes CCB
			b_1	Grade 1 HT − Grade 2 HT ≤ 2 risk factors	Lifestyle changes Diuretic
			b_2		Lifestyle changes β-blocker
			b_3		Lifestyle changes ACEi
			b_4		Lifestyle changes ARB
			b_5		Lifestyle changes CCB
			c_1	Grade 1 HT ≥ 3 risk factors	Lifestyle changes Diuretic
			c_2		Lifestyle changes β-blocker
			c_3		Lifestyle changes ACEi
			c_4		Lifestyle changes ARB
			c_5		Lifestyle changes CCB

Table 8: Example of partial treatment of AH

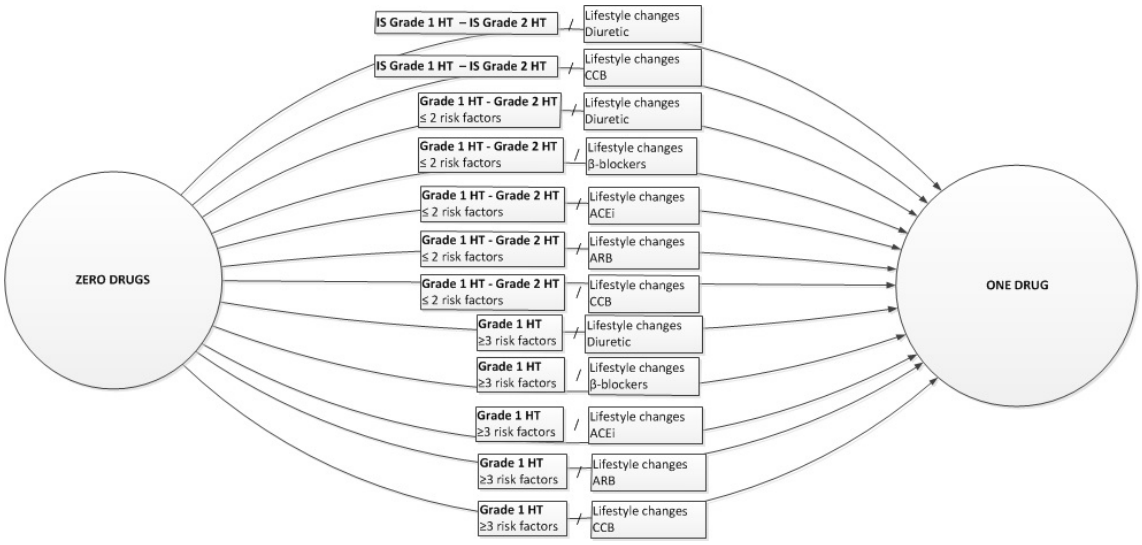

Figure 4: Example of partial treatment of AH

3.2.2. Modelling Drug Dosage Prescription (level 2) for Arterial Hypertension

Dosage is defined as "the determination and regulation of the size, frequency and number of doses" [42]. For each drug prescribed in a pharmacological therapy, the drug dose and the intake frequency should be provided. Drug dose is presented in milligrams (mg), while frequency is presented as abbreviations of the sort o.d., b.i.d., t.i.d., or q.i.d., standing for 'once a day', 'twice a day', 'three times a day', or 'four times a day', respectively.

Our proposed methodology to model drug dosage prescription is composed of two steps:

1. Model the drug titration procedure.
2. Define the initial, maximal, and incremental drug dosages.

For chronic diseases, a typical pharmacological therapy starts with a drug prescription at an initial dosage. This dosage is usually determined by the stage of the disease, the specific patient condition, and some facts such as the patient's gender, age, or weight. During the treatment, the dosage is titrated. Titration is defined as the "increment in drug dosage to a level that provides the optimal therapeutic effect" [1]. When the optimal therapeutic effect is achieved for a specific patient, we reach the target dosage. If we reach the maximal dosage of the drug, then a change in the therapy should be considered (e.g., change or complement that drug with other drugs). Figure 5 shows the structural model of drug titration for AH.

Figure 5: Structural model of drug titration for AH patients

This information is complemented with the initial, maximal, and incremental dosages of all the drugs involved in the treatment of the target disease. Table 9 shows the usual initial and maximal dosages of drugs in the pharmacological therapy of AH. It was compiled using the information provided by the CPGs [21] and [22], and consulting the data available in Drug Registry of Republic of Slovenia [15]. For AH, double dosage increments are recommended for ACEi [64] and beta blockers [65], but not for other drugs whose dosage increment is left to the physicians judgement.

3.2.3. Modelling Drug Intolerances (level 3) for Arterial Hypertension

Drug intolerance refers to "the state of reacting to the normal pharmacological doses of a drug with the symptoms of overdosage" [42]. A drug D_1 that a patient is intolerant to should be replaced with another one D_2 having the same or similar curative effect. A pharmacological treatment should start considering the information provided in basic model of the specific disease. Then, the treatment must be dynamically modified in order to detect and solve drug intolerances. An appropriate treatment is reached when the patient is tolerant to all the drugs involved.

We propose a methodology to capture the basic medical knowledge required to manage intolerances in CVDs. This methodology defines three steps:

1. Model drug intolerance behaviours for 1, 2, 3, ... drug treatments.
2. Define a table of intolerant drug replacements.
3. Model the final disease treatment in case of drug intolerances.

In figure 3, the structural model of the therapeutic strategy for AH shows that pharmacological therapies exist for one or two drugs. Consequently, we have to provide models for the AH treatment that contemplate considering 1-drug treatment intolerances, and 2-drug treatment intolerances. These models are shown in figure 6, respecting the information on drug intolerances and recommended replacements of the CPGs [21] and [22].

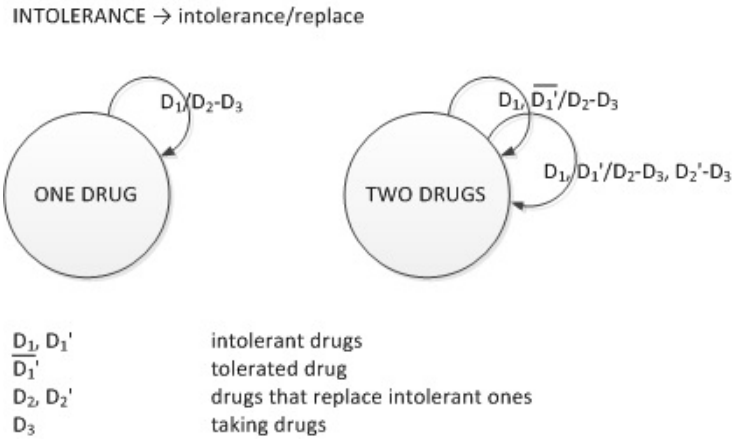

Figure 6: Structural model of drug intolerance for Arterial Hypertension

Drug	Initial dose (mg)	Maximal dose (mg)
ACEi		
Captopril	12.5 o.d.	100 t.i.d. - 150 t.i.d.
Enalapril	5 o.d.	10 - 20 o.d.
Lisinopril	10 o.d.	80 o.d.
Ramipril	2.5 o.d.	10 o.d.
Trandolapril	0.5 o.d.	4 o.d.
ARB		
Candesartan	8 o.d.	32 o.d.
Valsartan	80 o.d.	160 o.d.
Telmisartan	40 o.d.	80 o.d.
Losartan	50 o.d.	100 o.d.
β-Blocker		
Bisoprolol	5 o.d.	20 o.d.
Carvedilol	12.5 - 25 o.d.	50 o.d.
Metoprolol succinate	100 o.d. or 50 b.i.d.	400 o.d.
Nebivolol	2.5 o.d.	5 o.d.
Atenolol	50 o.d.	100 o.d.
CCB		
Verapamil	40 t.i.d	120 t.i.d. or 240 b.i.d.
Nifedipine	20 o.d.	120 o.d.
Diltiazem	120 b.i.d or 80 t.i.d	120 t.i.d. or 180 b.i.d.
Amlodipin	5 o.d.	10 o.d.
Lerkanidipin	10 o.d.	20 o.d.
Lacidipin	2 o.d.	6 o.d.
Thiazide diuretic		
Clortalidone	25 o.d.	50 o.d.
Hidroclorotiazide	12.5 o.d.	25 o.d.
Indapamide	1.5 o.d.	2.5 o.d.
Statin		
Simvastatin	10 o.d.	80 o.d.
Pravastatin	10 o.d.	40 o.d.
Atorvastatin	10 o.d.	80 o.d.
Rosuvastatin	5 o.d.	40 o.d.
Fluvastatin	40 o.d.	80 o.d. or 40 b.i.d.

Table 9: Drug dosages recommended in the therapies of AH patients

If one drug D_1 is prescribed and a patient is intolerant to that drug, it should be replaced with other drug D_2 from the AH drugs list having the same or similar curative effect. D_3 is used to indicate that D_2 cannot be one of the drugs the patient is already taking, i.e., $D_2 \neq D_3 = D_1$. This behavior is represented with the model on the left-hand side of figure 6.

In the case of a 2-drug treatment there are two possibilities: intolerance to one or intolerance to both prescribed drugs. In the first case, just one drug D_1 should be replaced with a drug D_2 from the AH drugs list excluding the ones the patient is already taking, i.e., D_3. In the second case, both drugs D_1 and D_1' should be replaced with drugs from the AH drugs list, except the D_3 drugs, i.e., D_1 and D_1'. The idea is presented on the right-hand side of figure 6.

In more detail, CPGs [21] and [22] provide only one suggestion considering drug intolerances that affect the ACEi group of drugs: non tolerated ACEi drugs should be replaced with drugs from the ARB drug group, see table 9. This defines a reduced table of replacements in the second step of the proposed methodology. Considering that suggestion, however, we obtain a model for AH treatment in the cases of drug intolerances which is fully described in [32]. Here, a subset of this eTTD model is presented in figure 7.

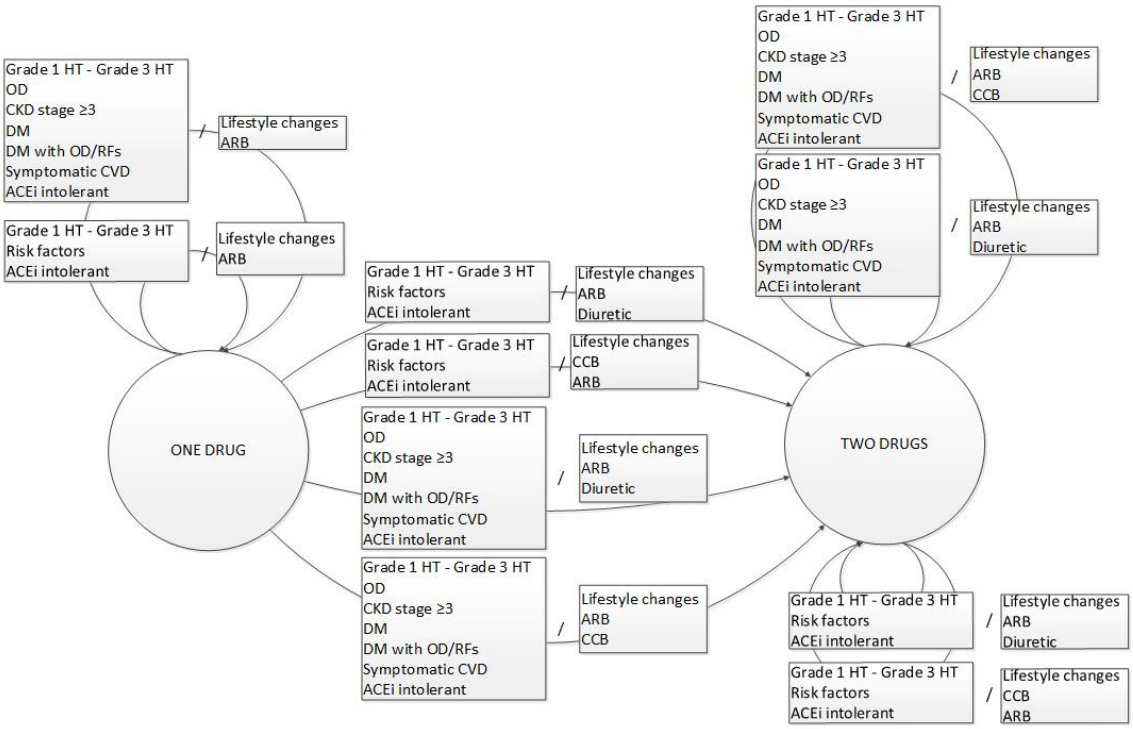

Figure 7: Reduced model for AH treatment with drug intolerances

There, 1-drug treatments with detected ACEi drug intolerance are replaced by 1-drug treatments with ARB drug. Four cases of second drug introduction, reflecting ACEi drug intolerance and replacement, are also included. The eTTD also reflects equivalent replacements of ACEi when the patient is treated with two drugs, one of them being ACEi.

3.2.4. Three-level Modelling to Help Decision Making in Medical Procedures

Reconsidering the MPM questions presented in section 2.1 and summarized in table 1, the general medical practice plan incorporating these questions in figure 1, and the structural models resulting from the application of the proposed methologies (i.e., one model for the therapeutic strategy, one model for dosages, and one model for drug intolerances), we provide a knowledge-based framework to help physicians to deal with patients with CVDs. In the next lines, we discuss whether this framework offers a good representation of the knowledge required to answer the 15 clinical questions of the MPM [57].

As shown in table 3, eTTD modelling supports representation of all sorts of knowledge required to answer the medical decision support questions from table 1. Moreover three-level therapy modelling (i.e., models of therapeutic strategy, drug dosages, and drug intolerances) supports all medical questions related to treatment procedures (i.e., q5, q6, q8, q9, q11 and q15).

The provided analysis and the obtained results suggest that we have successfully defined a formalism, that is efficient in medical procedural knowledge formalization and that includes three levels of detail involved in the treatment of chronic CVDs.

4. Conclusion

In medical practice, procedural knowledge permits a physician to determine the best course of action possible. Physicians use their medical knowledge to make diagnostic and therapeutic decisions. Decision making processes depend on whether they can find, understand, and use a huge amount of medical knowledge and information [43, 50].

In the line of the MPM model [57], here we have summarized a general framework to help medical practice which is based on its capability to answer 15 decision support questions. From this medical utility perspective (i.e., medical questions), we have compared several of the most relevant formal languages to represent computer-interpretable guidelines. In spite that some of these languages are able to answer all the decision support questions identified, we noticed that, to some extent, they are complex languages that require their users to be not only expert practitioners, but also to have knowledge representation skills. Moreover, they show some complications when it comes to representing relevant levels of detail of medical therapy, such as the treatment strategy, the dosage titration, and the management of intolerances.

Noticing this technological gap, we have proposed a new structural model based on timed-transition systems (TTSs). This extended representation mechanism is called the extended timed transition diagram (eTTD). In a simple and intuitive way, eTTDs are suitable to answer all the medical questions of the MPM model [57], and they are also able to capture three levels of detail involved in the therapies of CVDs. Here, we have also proposed a methodology to capture in eTTDs the different sorts of procedural knowledge required to answer clinical questions about medical treatments. The methodology and the eTTDs were tested with three chronic CVDs: arterial hypertension (AH), heart failure (HF) and stable ischemic heart disease (SIHD) [32].

In this paper we have presented the results of modeling these three levels of detail for AH, after the application of the proposed methodology. The results were a therapeutic strategy model presented in section 3.2.1, a structural model of drug titration presented in section 3.2.2, and structural model of drug intolerances presented in section 3.2.3. A complete description of the knowledge models for AH, HF, and SIHD is found in [32]. For the sake of completeness about AH procedures, the models for AH are also presented in Appendix B and Appendix C. All the models and their application have been validated by two senior GPs and their comments and improvements incorporated in the final eTTD versions of the knowledge presented here and in [32].

These validated eTTDs can be used as the knowledge base of new MDSSs that can be used to transfer knowledge about the management of patients with CVDs, so helping young, less experienced physicians in their training about decision making processes, but also as a reminder to more experienced physicians for verification of their treatment decisions. These eTTDs also represent a starting point of a future study in which two groups of physicians will be involved, one group using these models to face clinical cases and compare their medical practice results to the other control group not using them.

One of the main limitations of this model is that it lacks of a temporal level. Not considering this level implies that all the clinical decisions have to be interpreted instantaneous. However, long-term planning in medicine requires a temporal dimension to restrict the times when certain processes have to be applied. Patient features and measurements hold during time points or time periods. Clinical interventions occur at one or more time points or over periods [59]. This time dimension is not always incorporated or just partially considered in CPGs. Some CPGs can include certain recommendations considering time (such as, time that should pass between two consecutive encounters while dosage titration), but very often these times are unspecified and, consequently, physicians have to decide them based on their own knowledge and experience. But physicians may have serious difficulties, or they are reluctant, to define general time constraints for some diseases. To our knowledge, currently there is no a mechanism to help physicians obtain medical evidences about temporal constraints in CPGs. But health care centres have medical records and information systems that register medical processes and patients' data, including information about times of the encounters, prescriptions, and other clinical actions. Consequently medical records and health care information systems are a promising source of data to calculate temporal medical knowledge and evidences about times in medicine. Based on these data sources, computer programs can be developed to find out time models that could offer an explicit representation of the time dimension of past medical procedures and use these models to complement the knowledge contained in the CPGs, and also to complement our eTTD model, thus allowing timed MDSS development and reasoning.

Time dimension of medical practice and its incorporation to the eTTD model is left for future research and discussion.

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Acknowledgements

The authors acknowledge financial support from the Slovenian Research Agency (Research Core Funding No. P2-0057), and the RETOS P-BreasTreat project (DPI2016-77415-R) of the Spanish *Ministerio de Economia y Competitividad*.

Appendix A. Summary of CIG languages

The *Arden Syntax* is a HL7 standard for encoding medical knowledge. It encodes medical knowledge as independent units called Medical Logic Modules (MLMs) [30]. Each guideline is modeled as a MLM that makes a single medical decision (a production rule that relates a set of input conditions to a particular set of actions, e.g. a single step if-then rule). Each MLM contains slots grouped into three categories: maintenance, library and knowledge. MLMs are executed serially as a sequence of instructions [14]. They have been used to generate clinical alerts and reminders, interpretations, diagnoses, screening for clinical research studies, quality assurance functions, and administrative support [30]. They are intended to execute in a data-driven manner when relevant and thus are not suitable for representing a long-term treatment. They do not support application of guidelines over extended periods of time; consequently they are not useful for representing chronic diseases guidelines [9].

Asbru is a guideline representation formalism developed within the Asgaard project [60] which focuses on the application and critiquing of time-oriented clinical guidelines. Asbru is a plan representation language that implements clinical guidelines as time-oriented skeletal plans, where prescribed actions are introduced. In order to manage these (often complex) plans, Asbru enables definition and representation of high-level goals (intentions), temporal patterns and time annotations, and the development of user interfaces to visualize the developed plans [41]. Asbru plans consist of a collection of subplans. Plans can be executed sequentially or in parallel. Plans that have been started can be suspended, aborted, or completed (based on the plans conditions). When a plan is completed, the next plan in the sequence (if any) is executed [14]. Asbru can be used to combine diagnosis and treatment plans. Treatment plans are modeled as a hierarchy of plans. Diagnosis can either be modeled as a part of conditions under which treatment plans are taken, or it can be modeled as separate plans [48].

EON is a component-based architecture used to build decision support systems that reason about guideline directed care [47]. It includes reusable problem-solving components that have specific functions (e.g., planning, classification of time-oriented clinical data) [9]. These components facilitate the acquisition and execution of clinical guidelines. EON is a non-closed guideline model, which consists of a standard set of primitives (scenarios, decisions, actions and goals) that can be extended with task-specific submodels. It is possible to model additional sets of primitives related to the knowledge requirements of different guidelines. Guidelines are represented in EON by temporally sequenced graphs (flowcharts) of instantiated classes [14], [66], [67].

The *Gaston* model is a frame-based representation, which uses ontologies as an underlying mechanism to represent guidelines in terms of Problem-Solving Methods (PSMs) and primitives. Frames are used to represent knowledge related to the application domain modeling concepts of entities, attributes and relations (domain ontologies) and to represent knowledge related to the guidelines control structure (method ontologies). Primitives are used to describe single guideline steps and to describe the internal structure of PSMs. Action, decision, branching, and synchronization primitives are used to describe guidelines. Action primitives specify clinical actions, decision primitives model decision points in a guideline, branching

primitives direct the guideline flow to multiple (parallel) paths and synchronization primitives combine paths that diverged because of branching primitive. The formalism supports the use of subguidelines in order to solve multiple tasks. Ontologies can be extended to capture new guideline characteristics [12], [13].

The *Guideline Interchange Format* (GLIF) version 2 was designed to model guidelines in the context of a flowchart that consists of structured (synchronization) steps (patient-state determination step), action (intervention step), branch (decision step), case (multiple branching step), and synchronization step), representing clinical actions and decisions [4], [9], [14], [49]. GLIF3 is a version designed to support computer-based execution. It was built upon the GLIF2 version. It enables guideline specification at three levels: the conceptual level (a top-level graphical representation as a flowchart), the computable level (which can be verified for logical consistency and completeness), and the implementable level (a bottom-level representation which is customized to the local needs) [4], [49].

The *GUIDE* project [53] is part of a guideline modeling and execution framework, developed for modeling and applying clinical guidelines in the broader context of general medical care. It focuses on the integration of modeled guidelines into organizational workflows, supporting the usage of decision analytical models (e.g. decision trees and influence diagrams) in addition to standard procedural models and simulation of guideline implementation in terms of Petri nets [5]. Petri nets are used for modeling concurrent (clinical) processes and for supporting the representation of sequential, parallel, and iterative control structures. GUIDE has extended Petri nets to support improved modeling of time, data, and plan hierarchies. It has adopted a multi-level representation where lower level representation includes describing concepts expressed in the higher level. Medical processes specified in the GUIDE method consist of a sequence of blocks, on different levels, each having a precise medical meaning or a precise flow management function. The graphical GUIDE authoring tool enables designers to interactively create a guideline flowchart as a Petri net. Computational tools enable simulation of the resulting guideline using the Petri net semantics [6], [7], [53].

The *PRODIGY* Project [52] was created to model guidelines for chronic disease management. It focuses on primary-care management of major chronic diseases, such as hypertension, coronary heart disease, diabetes, and asthma. It supports modeling a series of decisions that a general practitioner may face with during different patient encounters. A key knowledge structure in the PRODIGY framework is the scenario, which defines a particular clinical context (current treatment and patients condition) or patient state. Scenarios support creation of multiple, explicit entry points into the guideline, especially when patients might return in the future in a different state, or might enter the guidelines flow of control at various points. Scenarios can lead to specific actions or whole sub-guidelines. Actions might lead to additional scenarios [31].

PROforma is a knowledge composition language supported by acquisition and execution tools with the goal of supporting guideline dissemination. It aims at the development of reliable expert systems that assist patient care through active decision support and workflow management [23]. PROforma represents guideline as a directed graph in which nodes are instances of a closed set of classes, called the PROforma task ontology. It defines four task classes (decisions, actions, enquiries, and plans), each with their own attributes. Each

guideline in PROforma is modeled as a plan that consists of a sequence of tasks that can be composed into networks representing plans or procedures carried out over time, representing the high level structure of a guideline, and logical constructs (pre- and post-conditions) which allow the details of each task and inter-relationships between tasks to be defined using the task-specific templates. PROforma contains temporal and scheduling constraints [9], [23].

SDA model stands for State-Decision-Action model. It is based on the concept of flowchart and extended with several elements which ease medical procedural knowledge representation. Such elements are the concept of state as starting point (which allows the execution of the chart from different points) or the time constraint (which allows the introduction of time restrictions in medical procedures) [3], [56]. The SDA model is based on the concept of term, which can be state, decision, or action terms. Terms that represent the signs and symptoms of a particular patient at the moment of making an observation are called state terms. Decision terms are building decision criteria which lead the treatment in a specific direction considering the patient's current signs and symptoms, while action terms represent healthcare activities which should be performed as a result of an earlier analysis of the healthcare context. These terms are used to construct three sorts of elements: states, decisions and actions. Once these elements are connected (using connectors) they describe the medical procedure. The model allows representation of sequences, concurrences and loops of medical procedures. Also it is possible to represent non-determinism (e.g. representing alternative paths or alternative evolutions).

Knowledge-experience Decision Tables (k-e DT) are decision tables [61], [62] able to store medical knowledge and past experiences [55]. Decision table is a matrix that relates a set of decision input variables with a set of output actions. It is divided into four areas: the condition stub, the action stub, the condition entry, and the action entry. The condition stub contains the decision input variables as a column. Action stub describes a list of the feasible output single actions. Condition entry is a subset of decision input variables. Action entry is a subset of the output actions. A decision rule or k-e DT column provides the relation between the condition and the action entries [55].

Clinical Algorithms (CAs) are schematic models of the clinical decision pathway described in CPGs. They use CPG's knowledge to represent medical procedures to assist patients suffering from one or several diseases. Decision points are represented with yes/no nodes, and the clinical characteristics, test characteristics, or treatment options are also simplified into their basic components. They are more reduced and simplified structures than CPGs. CAs can be executable [10], [28].

Timed Transition System (TTS) consists of five components: a finite set of variables, a set of states, a finite set of transitions and two categories of time constraints, lower-bound and upper-bound requirements. Every state is defined as a subset of variables. Every transition is a binary relation on set of states. Lower-bound and upper-bound are defined for every transition, representing the minimal delay function and the maximal delay function, respectively [29]. They are useful for representing a patient condition and/or a patient current treatment. They are not meant for representing diagnostic and therapeutic procedures.

Appendix B. Model for AH treatment

Abbreviations:

BP	Blood Pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
HT	Hypertension
DM	Diabetes Mellitus
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disea
OD	Organ Damage
RF	Risk Factor
ARB	Angiotensin II Receptor Blocker
ACEi	Angiotensin-Converting Enzyme inhibitor
CCB	Calcium Channel Blocker

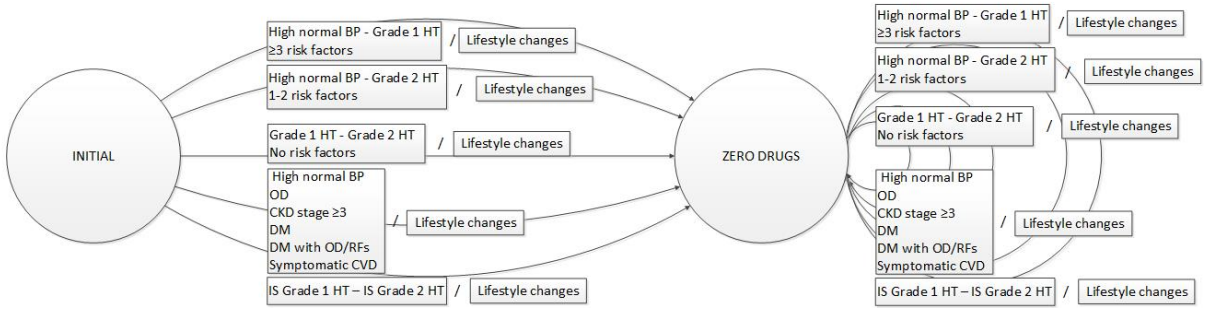

Figure B.8: Partial model of AH treatment - part A

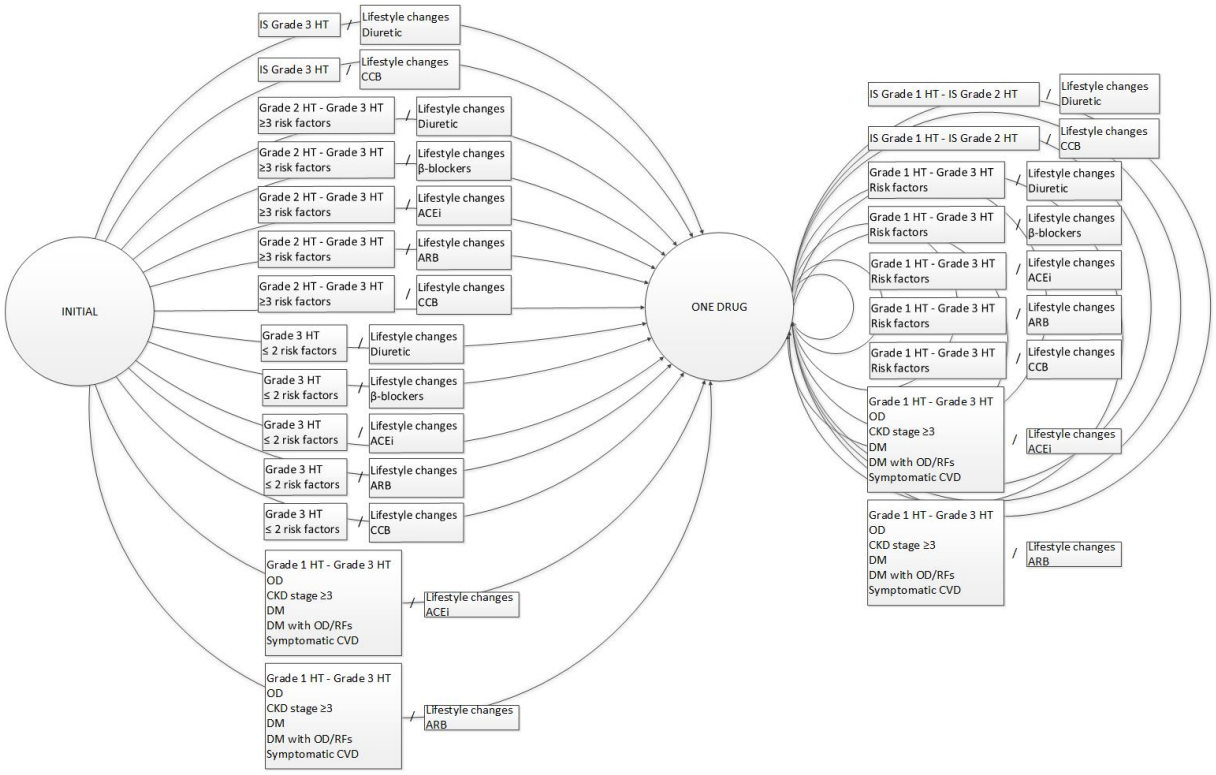

Figure B.9: Partial model of AH treatment - part B

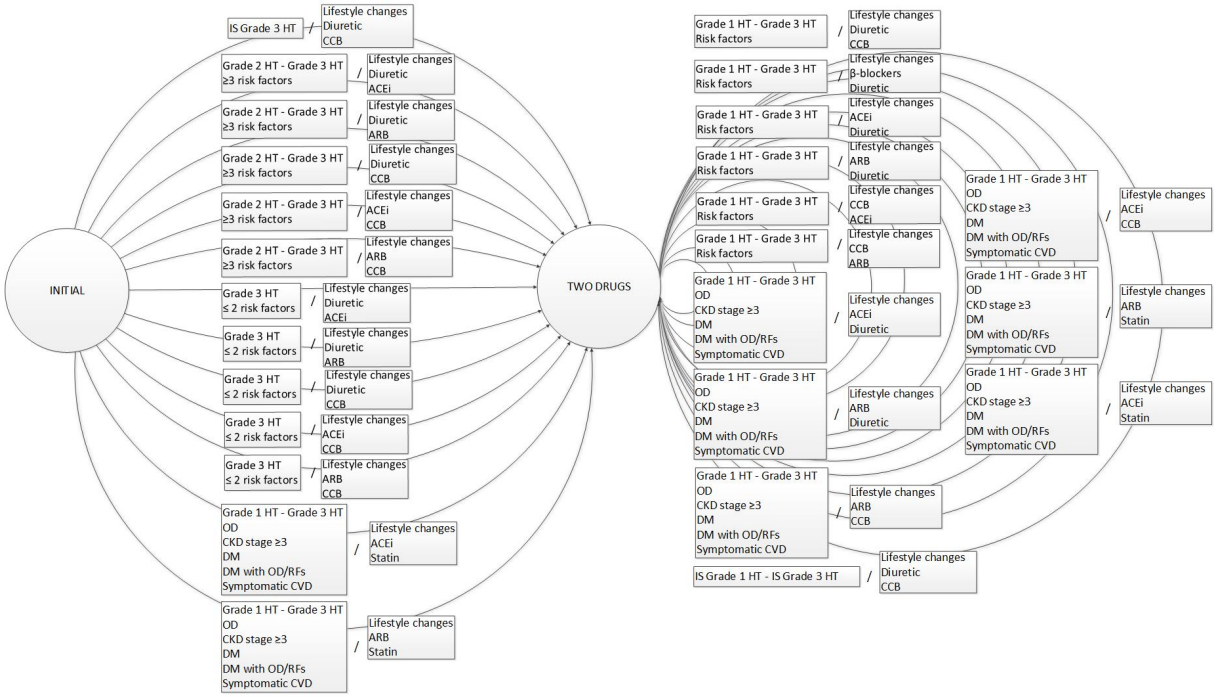

Figure B.10: Partial model of AH treatment - part C

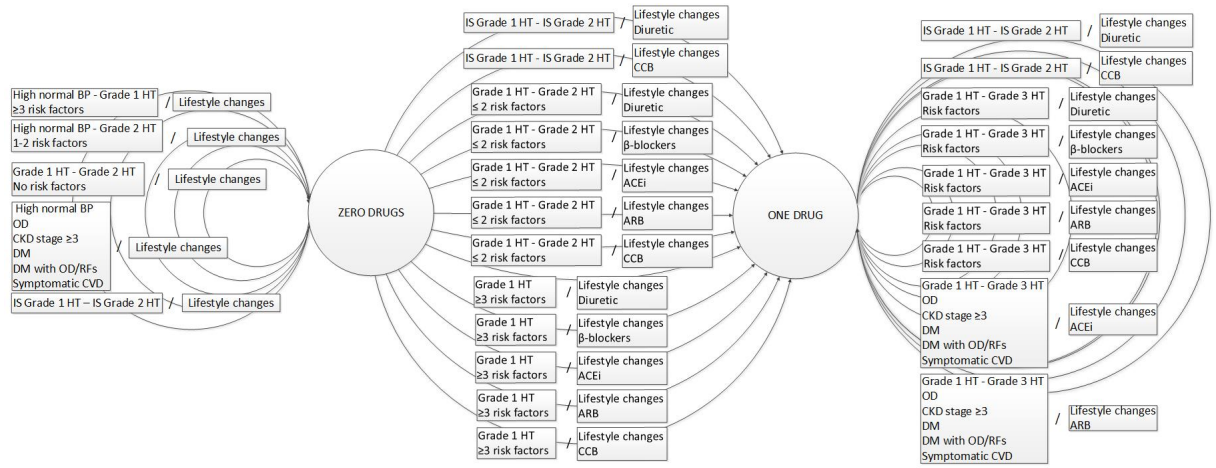

Figure B.11: Partial model of AH treatment - part D

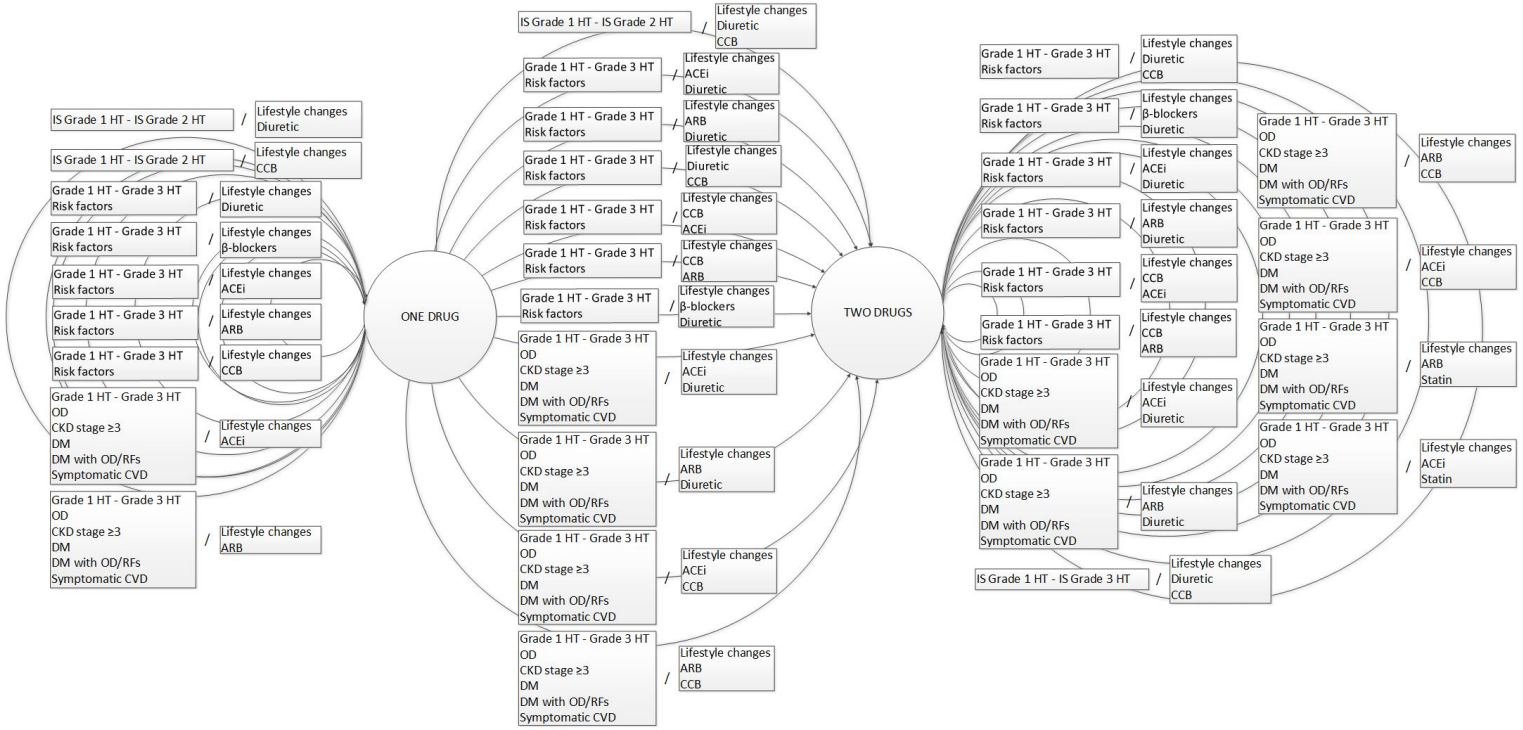

Figure B.12: Partial model of AH treatment - part E

Appendix C. Model for AH treatment with drug intolerances

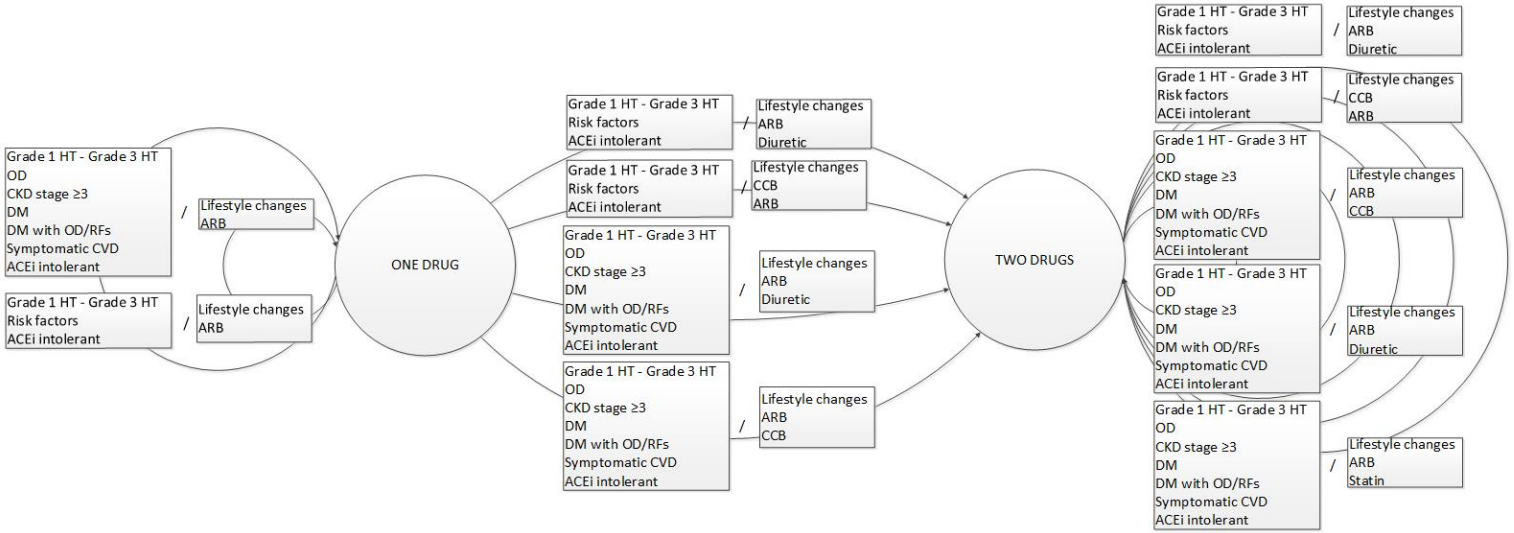

Figure C.13: Model for AH treatment with intolerances

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