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RESEARCH ARTICLE

Development of an evidence-based checklist for the detection of drug related problems in type 2 diabetes

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Abstract *Objective* To develop an evidence-based checklist to identify potential drug related problems (PDRP) in patients with type 2 diabetes. *Setting* The evidence based checklist was applied to records of ambulatory type 2 diabetes patients in New South Wales, Australia. *Method* After comprehensive review of the literature, relevant medication groups and potential drug related problems in type 2 diabetes were identified. All the relevant information was then structured in the form of a checklist. To test the utility of the evidence-based checklist a cross-sectional retrospective study was conducted. The PDRP checklist was applied to the data of 148 patients with established type 2 diabetes and poor glycaemic control. The range and extent of DRPs in this population were identified, which were categorized using the PCNE classification. In addition, the relationship between the total as well as each category of DRPs and several of the patients' clinical parameters was investigated. Main outcome measure: Number and category of DRPs per patient. *Results* The PDRP checklist was successfully developed and consisted of six main sections. 682 potential DRPs were identified using the checklist, an average of 4.6 (SD = 1.7) per patient. Metabolic and blood pressure control in the study subjects was generally poor: with a mean HbA1c of 8.7% (SD = 1.5) and mean blood pressure of 139.8 mmHg (SD = 18.1)/81.7 mmHg (SD = 11.1). The majority of DRPs was recorded in the categories 'therapy failure' ($n = 264$) and 'drug choice problem' ($n = 206$). Potentially non-adherent patients had a significantly higher HbA1c than patients who adhered to therapy (HbA1c of 9.4% vs. 8.5%; $P = 0.01$). *Conclusion* This is the first tool developed specifically to detect potential DRPs in patients with type 2 diabetes. It was used to identify DRPs in a sample of type 2 diabetes patients and demonstrated the high prevalence of DRPs per patient. The checklist may assist pharmacists and other health care professionals to systematically identify issues in therapy and management of their type 2 diabetes patients and enable earlier intervention to improve metabolic control.

Keywords Type 2 diabetes · Drug related problems · Drug therapy · Evidence-based medicine · Evidence-based pharmacy · Diabetes · PCNE DRP classification

Impact of findings on practice

- An evidence-based checklist can be used specifically in patients with type 2 diabetes, to assist pharmacists and other healthcare professionals in systematically identifying DRPs.
- There is a high prevalence of DRPs in the population of patients with type 2 diabetes and poor glycaemic control.
- The most important DRPs in type 2 diabetes patients in New South Wales seem to be therapy failure and drug choice problems.

Introduction

Type 2 diabetes is a chronic metabolic disorder characterised by both defects in insulin secretion and/or tissue

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sensitivity to insulin. The latter is known as insulin resistance and forms part of a cluster of cardiovascular risk factors seen in a high proportion of patients with type 2 diabetes. It is known as the metabolic syndrome and also includes central obesity, hypertension and/or dyslipidaemia. Evidence suggests that a targeted, intensified, multifactorial intervention which includes lifestyle modifications and multiple pharmacotherapy is required to reduce or prevent macrovascular and microvascular complications [1, 2].

The optimal use of medications therefore plays a key role in achieving treatment targets for glucose, blood pressure and lipids. The efficacy of a medication regimen, however, may be limited by a range of drug related problems (DRPs) including adverse drug reactions, interactions, contra-indications and non-adherence [3]. Since patients with type 2 diabetes generally use multiple medications, DRPs are likely to occur in this population and these can negatively influence diabetes control. Research has shown that a substantial proportion of DRPs that exist within the health care system are related to patients with diabetes [4]. Nevertheless, there is currently no specific tool available that can be used by pharmacists or other healthcare professionals to help detect DRPs in patients with type 2 diabetes.

Aim

Our aim was to develop an evidence-based PDRP (potential drug related problems) checklist that may be used to review a patient's clinical status and medication regimen to identify potential DRPs in type 2 diabetes.

Method

Development of the checklist

The development of the PDRP checklist followed a systematic process which is outlined in Fig. 1. Initially, a MEDLINE search of English-language articles published between 1997 and 2007 with the terms 'type 2 diabetes mellitus' and 'drug therapy' was conducted to identify published literature on the subject. The available literature was comprehensively reviewed to provide up to date information on the pharmacological management of type 2 diabetes and the risk management of its related complications. In addition, current standards in the therapeutic management of type 2 diabetes were obtained by reviewing several recently published guidelines [5–8]. According to all guidelines, the current recommended targets for type 2 diabetes for glycaemic control and cardiovascular risk reduction are HbA1c $\leq$7%, blood pressure <130/80 mmHg (125/75 mmHg in case of proteinuria >1 g/day). With respect to lipids, Australian guidelines recommend total cholesterol <4 mmol/l; LDL-C <2.0 mmol/l; HDL-C >1.0 mmol/l; triglycerides <1.5 mmol/l [7]. In the US and Europe the recommended levels for lipids are expressed in mg/dl (LDL-C <100 mg/dL; HDL-C >40 mg/dl; triglycerides <150 mg/dl) [5].

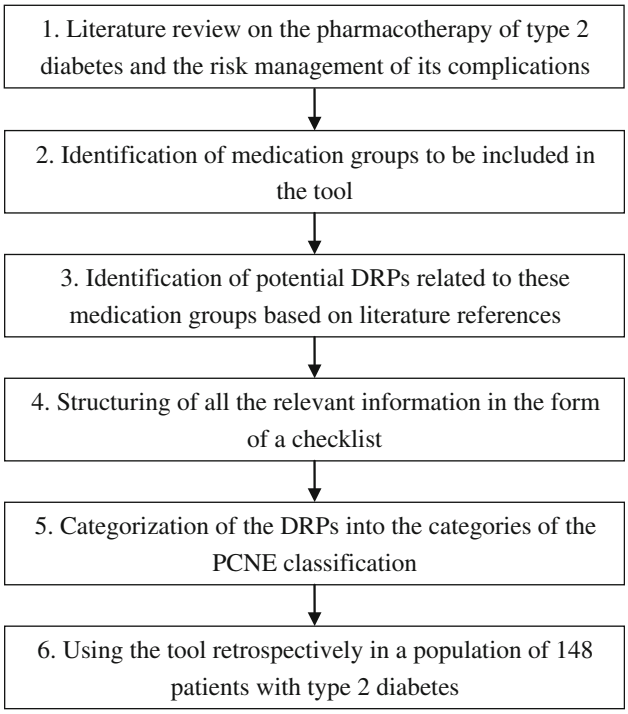

Fig. 1 The development of the PDRP checklist

Based on this, the therapeutic targets and the drug groups to be included in the PDRP checklist were selected (displayed in Table 1) and the potential DRPs related to each group were identified. All the relevant information was then structured in the form of a checklist. To enable easy application in clinical practice, the checklist must be relatively short and concise. Therefore, very rarely used agents (e.g. bile acid binding resins and nicotinic acid for the treatment of dyslipidaemia), were excluded. In addition, only the most common and/or most severe adverse effects, contra-indications and significant interactions were listed [9]. (i.e., drug interactions with a significance rating of 1 or 2 in the Drug Interaction Facts software) [10]. Dosage information for each agent was derived from the Australian Medicines Handbook [9]. After the checklist had initially been developed by the authors, it was extensively reviewed by a panel of experts and corrected hereafter (see Acknowledgements).

Using the PDRP checklist

In the literature, there are several systems available for the classification of DRPs [11]. The characteristics of each

Table 1 Drug groups included in the protocol

Anti-diabetics
Sulphonylureas
Metformin
Thiazolidinediones
Acarbose
Repaglinide
Insulin
Anti-hypertensives
Thiazide diuretics
β-Blockers
ACE inhibitors
Angiotensin II antagonists
Calcium channel blockers
Selective α-blockers
Lipid lowering drugs
Statins
Fibrates
Anti-platelet drugs
Aspirin
Clopidogrel
Dipyridamole

system were examined to select the most suitable for classifying the outcomes of the PDRP checklist. The PCNE classification proved to be the most appropriate one to apply in this study [12]. It is based on a clear definition, has a hierarchical problem classification and its validation has been published [11]. The outcomes of the checklist appeared to be easily categorized into one of the six primary domains of this classification: adverse reactions, drug choice problems, dosing problems, drug use problems, interactions and others. In this study, the primary domain called 'others' was renamed to 'therapy failure' because that is the only type of DRP in this domain that was investigated in this study.

A cross-sectional retrospective study design was used. Study subjects were patients from New South Wales, Australia who participated in the Pharmacy Diabetes Care Program in 2004 [13]. These were all patients with established type 2 diabetes and poor glycaemic control (HbA_{1c} $\geq$7.0%). Full patient medication records and other data collected in the study, including BMI, HbA_{1c}, systolic and diastolic blood pressure, lipid profile and medication adherence were available.. Adherence was assessed using the Brief Medication Questionnaire (BMQ), a validated self-report tool that is used to indicate potential non-adherence [13, 14]. No further data from the patients' perspective were available. The PDRP checklist was used to review each patient's data to determine the prevalence of identified DRPs.

Data analysis

For each type of DRP identified in the review process, the cumulative frequencies and, if relevant, the nature of the problem was reported. All the DRPs were categorized according to their primary domain in the PCNE classification. Next, the relationship between the total number and category of DRPs and several clinical parameters was investigated using either the Spearman's rank correlation coefficients (for continuous or ordinal variables) or the independent-samples Student's *t*-tests for comparing means of two groups. The DRPs in the 'therapy failure' category were not included in this analysis, since the occurrence of a DRP in this category is logically related to poor control of blood glucose levels, blood pressure and/or lipid levels. All the statistical analyses were carried out using SPSS for Windows (version 15.0; SPSS Inc, Chicago, IL, USA).

Results

The PDRP checklist

The checklist (see Appendix) consists of six main sections: lifestyle management, glycaemic control, blood pressure control, lipid control, platelet control and medication adherence. Whilst the main focus of the checklist is on the detection of potential DRPs in the patient's current medications, including missing therapy and the appropriateness of the prescribed agents, lifestyle management issues are also relevant in the overall management of type 2 diabetes and were therefore included.

Sample description

A total of 148 patients with established type 2 diabetes were included in the study. The demographics and clinical parameters of these study subjects are displayed in Table 2. In total, the study subjects were using 599 medications of the four main groups that were included in the checklist. Of these 599 medications, 258 (43.1%) were anti-diabetics, 200 (33.4%) were anti-hypertensives, 80 (13.4%) were lipid lowering drugs and 61 (10.2%) were anti-platelet agents (Table 3).

Distribution of drug related problems

A total of 682 DRPs were identified using the PDRP checklist. This represents an average of 4.6 (SD = 1.7) DRPs per patient. The distribution of the recorded DRPs is presented in Table 4.

Table 2 Demographics and clinical parameters of study subjects

Demographics ($n = 148$)		
Male (%)		50.7%
Age (in years; mean ± SD)		61.4 ± 11.8
Duration of type 2 diabetes (in years; mean ± SD)		9.0 ± 7.5
Clinical parameters	*n*	Mean ± SD
HbA_{1c} (%)	146	8.7 ± 1.5
BMI (kg/m^2)	140	31.9 ± 6.9
Systolic blood pressure (mmHg)	122	139.8 ± 18.1
Diastolic blood pressure (mmHg)	122	81.7 ± 11.1
Total cholesterol (mmol/l)	146	4.8 ± 1.0
HDL cholesterol (mmol/l)	130	1.3 ± 0.7
Triglycerides (mmol/l)	145	2.3 ± 1.3
10 year risk of cardiovascular events[a] (%)	116	16.4 ± 8.8

[a] Estimated with the Framingham risk calculator [26]

Table 3 Use of medications in the study subjects ($n = 148$)

Category	*n*	Percentage of patients
Anti-diabetics	258	
Sulphonylureas	92	63
Metformin	117	79
Thiazolidinediones	9	6
Acarbose	6	4
Insulin	34	23
Proportion of patients using		
1 anti-diabetic	55	37
2 anti-diabetics	74	50
3 anti-diabetics	18	12
Anti-hypertensives	200	
Thiazide diuretics	38	26
β-Blockers	26	18
ACE inhibitors	51	35
Angiotensin II antagonists	45	30
Calcium channel blockers	39	26
Selective α-blockers	1	1
Proportion of patients using		
1 anti-hypertensive	53	36
2 anti-hypertensives	40	27
3 anti-hypertensives	13	9
4 anti-hypertensives	3	2
Lipid lowering drugs	80	
Statins	75	51
Fibrates	5	3
Proportion of patients using		
1 lipid lowering drug	78	53
2 lipid lowering drugs	1	1
Anti-platelet drugs	61	
Aspirin	48	32
Clopidogrel	10	7
Dipyridamole	3	2
Total	599	

Adverse reactions

43 patients (29.1%) reported having experienced at least one episode of hypoglycaemia of any kind in the 1 month period prior to enrollment in the study. All these patients were using a sulphonylurea or insulin, therefore this was considered a potential adverse effect of their drug therapy.

Drug choice problem

This category of DRP was recorded 206 times, resulting in an average of 1.4 drug choice problem per patient. By far the most recorded drug choice problem ($n = 182$) was that of missing therapy despite a clear indication being present. A total of 90 patients (60.8%) were not receiving anti-platelet therapy although they were at increased cardiovascular risk, 71 patients (48.0%) were missing lipid lowering therapy, 20 patients (13.5%) were missing anti-hypertensive therapy and 1 patient (0.7%) was not prescribed any blood glucose lowering therapy at the point of data collection.

Also, drugs that were not the most appropriate treatment option were prescribed in 19 cases. These were all related to the use of a non-preferred agent as monotherapy for the treatment of hypertension: diltiazem or verapamil was recorded 12 times, a non-selective β-blocker was recorded 6 times and 1 patient only used a selective α-antagonist to treat high blood pressure.

Dosing problem

In total, a dosing problem was recorded 40 times. Under-utilization of a drug was recorded when the prescribed dose was below the recommended range or when the dosing regimen was inappropriately infrequent. This was seen 13 times, with the most prevalent being aspirin ($n = 4$) or ACE inhibitors ($n = 4$). Overutilization was recorded 27 times. In 15 of these cases, sulphonylureas were responsible for this type of DRP. ACE inhibitors ($n = 4$) and metformin ($n = 3$) were the next most frequently overutilized drugs.

Drug use problem

Potential non-adherence was categorized as a drug use problem and occurred in 17.6% ($n = 26$) of the study subjects.

Table 4 Drug related problems in the study subjects ($n = 148$)

Type of drug related problem	*n*	Percentage of total DRPs
1. Adverse reaction	43	6.3
2. Drug choice problem	206	30.2
Inappropriate/not most appropriate drug	19	2.8
Duplication of therapeutic group	1	0.1
Contra-indication	4	0.6
No drug prescribed but clear indication	182	26.7
3. Dosing problem	40	5.9
Drug dose too low or regimen not frequent enough	13	1.9
Drug dose too high or regimen too frequent	27	4.0
4. Drug use problem	26	3.8
Potential non-adherence	26	3.8
5. Interactions	103	15.1
6. Therapy failure	264	38.7
Total	682	100.0

Interactions

A total of 103 potential interactions were identified with the use of the checklist. The most recorded type of potential interaction was the combination of an ACE inhibitor with either a sulphonylurea ($n = 32$) or insulin ($n = 14$). The so-called 'triple whammy', defined as the use of a thiazide diuretic and an ACE inhibitor or angiotensin II antagonist in combination with an NSAID, was observed 15 times [15]. Other repeatedly reported potential interactions were the concomitant use of low-dose aspirin and another NSAID ($n = 7$); atorvastatin or simvastatin and a macrolide antibiotic ($n = 6$); a sulphonylurea and an antimalarial drug ($n = 6$); and an ACE inhibitor as well as an angiotensin II antagonist ($n = 6$).

Therapy failure

This was the largest category of DRPs ($n = 264$), accounting for 38.7% of all problems. Therapy failure was assumed to be present when blood glucose levels, blood pressure or lipid levels weren't controlled adequately despite receiving drug therapy to treat these metabolic disorders. The underlying causes of the DRPs in this category are unknown; potential causes are ineffectiveness of medications (e.g. secondary failure of sulphonylureas), missing therapy (e.g. patients requiring more than one antihypertensive to control their blood pressure), incorrect administration of drugs and undetected non-adherence. Therefore, not reaching therapeutic targets while receiving drug therapy was recorded as a separate DRP in this category. Blood glucose levels were above recommended levels in 133 patients (89.9%), blood pressure was elevated in 69 patients (46.6%) and lipid levels failed to reach the treatment goals in 62 patients (41.9%).

To investigate whether there was a relationship between the prevalence of DRPs and the therapeutic status of the patient; Spearman's correlation coefficients were calculated between the number of total DRPs (minus the 'therapy failure' category) and several clinical parameters. A significant correlation was observed between systolic blood pressure and the total number of DRPs minus 'therapy failure' (Spearman's correlatio $n = 0.19$; $P = 0.028$). Potentially non-adherent patients had a significantly higher HbA_{1c} than the other patients (HbA_{1c} of 9.4 vs. 8.5; 95% CI: -1.50 to -0.20).

Discussion

In this study, an evidence-based checklist for the detection of DRPs in type 2 diabetes has successfully been developed. The checklist was used to identify DRPs in a population of patients with type 2 diabetes. A total of 682 DRPs were detected, which were classified in six different categories.

The high average of 4.6 DRPs (SD = 1.7) per patient showed that the early identification and resolution of DRPs is important in the therapeutic management of patients with type 2 diabetes. An earlier study found a comparable average of 4.1 DRPs per patient with type 2 diabetes, albeit using a different method of detecting (by qualitative interviews) and classifying DRPs [16]. Collectively, these findings demonstrated that the prevalence of DRPs in these patients is relatively high. This can partly be explained by the fact that patients with type 2 diabetes generally use many medications, but it also emphasizes the need for adequate medication management in these patients.

One of the major issues identified by the PDRP checklist was the large proportion of patients who were missing therapy for clear indication. This was especially the case for anti-platelet therapy, Approximately 60% of all the patients were not taking aspirin in spite of being at increased cardiovascular risk. Also, nearly half of all the patients were not receiving any lipid lowering drugs although lipid levels were not adequately controlled in these patients. This is a concern, especially since the benefits of anti-platelet and lipid lowering therapy in patients with type 2 diabetes have clearly been established in earlier large randomized clinical trials [17–19].

A high proportion of patients in this study had poor glycaemic control, an expected finding since this was a selection criterion for entry into study [13]. It suggests, however, that pharmacotherapy may need to be intensified for many poorly controlled patients with type 2 diabetes, assuming they have been adherent to their diabetes

management regimen [5]. The findings also highlight the need for self monitoring of blood glucose by all type diabetes patients on medication therapy.

Blood pressure control among this cohort was also suboptimal. Nearly half of the patients had an elevated blood pressure (46.6%) as well as suboptimal lipid control. (41.9%). Thus, notwithstanding the availability of a wide range of pharmacotherapy, achieving metabolic control in type 2 diabetes continues to be a major challenge.

Another notable result was that 16% of all patients in this study on sulphonylurea therapy were prescribed a dose that was higher than recommended. The desirability of this prescribing behaviour is questionable, since it is well known that the risk of hypoglycaemia is enhanced with increased dosages of sulphonylureas [20]. Also, approximately a third of all patients reported having experienced at least one episode of hypoglycaemia of any kind in the month before entry into the study. It is not possible, though, to conclude what proportion of these episodes was directly induced by sulphonylureas from the retrospective patient data. Information on other adverse effects was not available from the patient data, so the number of DRPs collected in this category may have been underestimated. Also, there was no information available from the original data on the patient's renal and hepatic function; so it was not possible to detect possible contra-indications related to these parameters.

Several potential interactions were identified with the use of the PDRP checklist. A large proportion (44.7%) related to the combination of an ACE inhibitor with either a sulphonylurea or insulin. Although the combination of these agents is unavoidable in the therapeutic management of type 2 diabetes for many patients, the increased risk of hypoglycaemia requires careful monitoring [21, 22]. This is also true for the potential impairment in renal function when using the so-called 'triple whammy' combination, which was prescribed in 14.6% of patients. Overall, ACE inhibitors were involved in 63 of all 103 potential interactions (61.2%), suggesting that patients taking these agents should be monitored carefully.

An interesting observation was the significant difference in HbA_{1c} between adherent and potentially non-adherent patients. An earlier observational study demonstrated a significant relationship between adherence to insulin therapy and glycaemic control, but this relationship has not been established previously for other anti-diabetic medications [23]. Since 17.6% of the study subjects were potentially non-adherent, an improvement in medication adherence is highly likely to contribute to improving glycaemic control in type 2 diabetes as has been shown in earlier studies [24, 25]. It should be noted that the PDRP checklist does not detect potential non-adherence, but information on this was available from the patient data. In these data, potential non-adherence had previously been assessed by the use of a self-report tool [13]. Considering the importance of adherence in type 2 diabetes, a tool of that kind should be integrated in the checklist in the future to enable full completion and improve convenience.

The total number of DRPs (minus the 'therapy failure' category) correlated significantly with systolic blood pressure but not with any other clinical parameters. A possible explanation for this is that blood glucose and lipid levels are influenced to a greater extent by non-medication related factors, such as environmental and lifestyle aspects, than is systolic blood pressure.

Certain limitations to this study, however, are due to its retrospective nature. While the statistical analyses showed a relationship between the prevalence of DRPs in a patient and the control of several metabolic parameters, they do not demonstrate causality. Also, it is unsure whether the results of this study are representative for all patients with type 2 diabetes, since nearly all the study subjects had poor glycaemic control.

Another important factor that should be considered is that we studied the prevalence of potential DRPs instead of actual DRPs. Therefore it is unknown whether patients with more potential DRPs actually had worse clinical outcomes during follow-up. As a result, the clinical significance of the detected DRPs cannot be established. This is moreover true because no information on the patients' perspective was included.

The PDRP checklist is the first tool developed specifically to detect potential DRPs in patients with type 2 diabetes and was able to identify DRPs from previously collected patient data. However, the development of an electronic version will be necessary to allow efficient future use. The development of this checklist represents an important first step in developing a tool that can be applied in clinical practice. A broad review on the correctness and completeness by specialists is needed to further determine the contents of the checklist. After this, an additional study on the implementation in practice should be undertaken. For efficient implementation, collaboration between pharmacists and physicians is needed; for example in carrying out the interventions.

The high average of DRPs per patient demonstrates the importance of the early identification and resolution of DRPs in patients with type 2 diabetes. Therapy failure was the most frequently recorded DRP, which suggests that to achieve treatment goals in type 2 diabetes identifying the cause of therapy failure is a critical step. For example if non adherence is the issue, behavioural modification strategies may be needed. If failure of therapy is due to beta cell failure then earlier intensification of therapy is likely to be required [5]. Missing therapy, especially for anti-platelet and lipid lowering medications, was also common which

shows that cardiovascular risk was not adequately addressed in this population.

Conclusion

In conclusion, the wide range of DRPs detected by the checklist shows that optimal medication management in type 2 diabetes remains a major challenge in clinical practice. The use of the PDRP checklist may assist pharmacists and other health care professionals to systematically identify issues in therapy and management of their type 2 diabetes patients and enable earlier intervention to improve metabolic control. Whether this will translate into better health outcomes in the longer term, remains to be proven in the near future.

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Conflicts of interest None.

Appendix

PDRP checklist: medications in type 2 diabetes

This tool is meant to be used by pharmacists in order to detect possible drug related problems and/or potential interventions in patients with type 2 diabetes. It is primarily focused on a patient's medications, and includes the most commonly used agents for the treatment of hyperglycaemia, hypertension, dyslipidaemia and hypercoagulability. Throughout the tool, several footnotes are used. These refer to the following information:

[1] Dietary guidelines for Australian adults are provided by the NHMRC. These can be accessed through http://www.nhmrc.gov.au/publications/synopses/_files/n33.pdf.

[2] The Australian Physical Activity guidelines recommend at least 30 minutes of moderate-intensity physical activity on most, preferably all, days. These can be accessed through http://www.ausport.gov.au/fulltext/1999/feddep/physguide.pdf.

[3] Renal impairment is defined by the creatinine clearance, which is calculated using the Cockroft-Gault formula:

Creatinine clearance = ((140 − age) * weight * constant)/plasma creatinine

Creatinine clearance in ml/min; age in years; weight in kilograms; constant = 1.23 for men and 1.04 for women; plasma creatinine in mg/dl

[1]Creatinine clearance <10 ml/min = severe renal impairment

[2]Creatinine clearance 10–25 ml/min = moderate renal impairment

[3]Creatinine clearance 25–50 ml/min = mild renal impairment

[4]Hepatic impairment is present when transaminase levels are >2.5 times the upper limit of normal

[5]The advised amounts from the NHMRC guidelines are:

For men: an average of no more than 4 standard drinks a day, and no more than 28 standard drinks a week; not more than 6 standard drinks in any one day.

For women: an average of no more than 2 standard drinks a day, and no more than 14 standard drinks a week; not more than 4 standard drinks in any one day.

For both men and women, one or two alcohol free days each week are recommended.

[6]Heart failure is classified as:

NYHA Class I: no limitation is experienced in any activities; there are no symptoms from ordinary activities

NYHA Class II: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion

NYHA Class III: marked limitation of any activity; the patient is comfortable only at rest

NYHA Class IV: any physical activity brings on discomfort and symptoms occur at rest

The Australian Medicines Handbook (AMH Pty Ltd. July, 2007) was used for the information on dosages.

Drug Interaction Facts on disc v1.0 (1999 Facts and Comparisons, Medifor Inc, July 2007 edition) was used for the information on interactions.

Further information was provided by the literature review.

Lifestyle management

1. Is the patient overweight?
   - ⌟ Yes: BMI ≥ 25.0 kg / m^2 → Discuss strategies with the patient to try to lose weight
   - ⌟ No: BMI < 25.0 kg / m2

2. Is the patient following a healthy diet[1]?
   - ⌟ Yes
   - ⌝ No → Discuss strategies with the patient to try to modify his/her diet

3. Is the patient getting regular physical activity[2]?
   - ⌟ Yes
   - ⌝ No → Discuss strategies with the patient to increase the amount of physical activity

4. Is the patient a smoker?
   - ⌟ Yes
   - ⌝ No → Discuss strategies with the patient to try to quit smoking

Glycaemic control

5. What is the patient's current glycaemic control?
   - ⌟ HbA_{1c} ≥ 7.0% → Patient's glycaemic control is good
   - ⌝ HbA_{1c} > 7.0% → Patient's blood glucose is poorly controlled

6. Is the patient using:
   - ⌟ High-dose $beta_2$ agonists
   - ⌝ Antipsychotics
   - ⌟ Glucocorticoids
   - ⌝ Combined oral contraceptives
   - ⌝ Immunomodulators
   - ⌟ Hormone replacement therapy
   - ⌝ Isotrenitoin
   - ⌟ Phenytoin

   → These medications might increase blood glucose concentrations → Check how long these agents have been used and how long blood glucose has been elevated; also monitor changes in therapy

7. Is the patient using:
   - ⌟ A sulphonylurea → Ask patient about the monitoring of side effects: weight gain and hypoglycaemia
   - ⌝ No sulphonylurea → Continue to question 11

8. Check if the patient:
   - □ Has renal impairment[3]
   - □ Has hepatic impairment[4]
   - □ Has irregular eating habits
   - □ Consumes more alcohol than advised[5]
   - □ Is over 65 years of age

   → Patient is at increased risk for hypoglycaemia → Use sulphonylureas with caution

9. Is the daily dose within the recommended range?

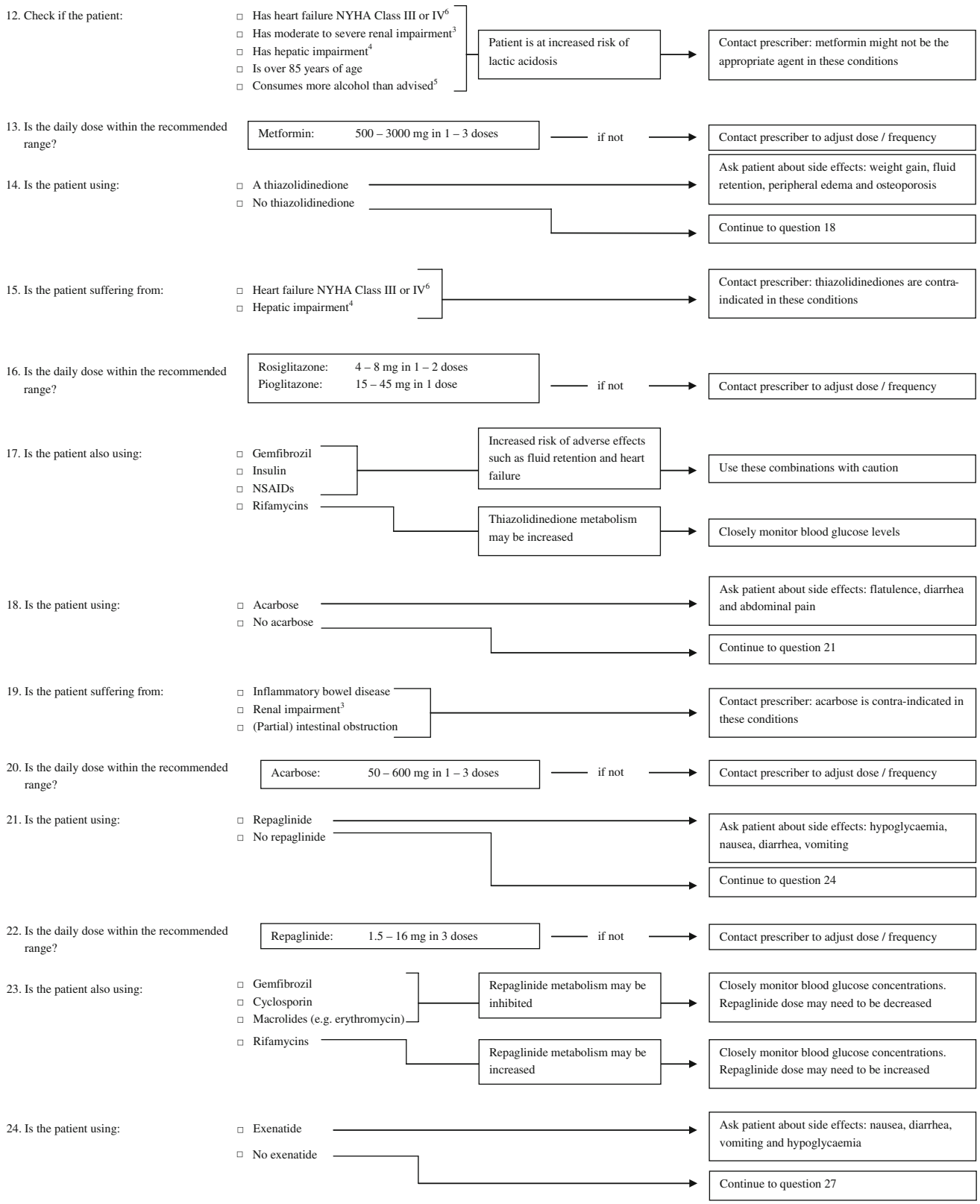
Glibenclamide:	2.5 – 20 mg in 1 – 2 doses
Glimepiride:	1 – 4 mg in 1 dose
Gliclazide:	40 – 320 mg in 1 – 2 doses
(controlled release):	30 – 120 mg in 1 dose
Glipizide:	2.5 – 40 mg in 1 – 3 doses

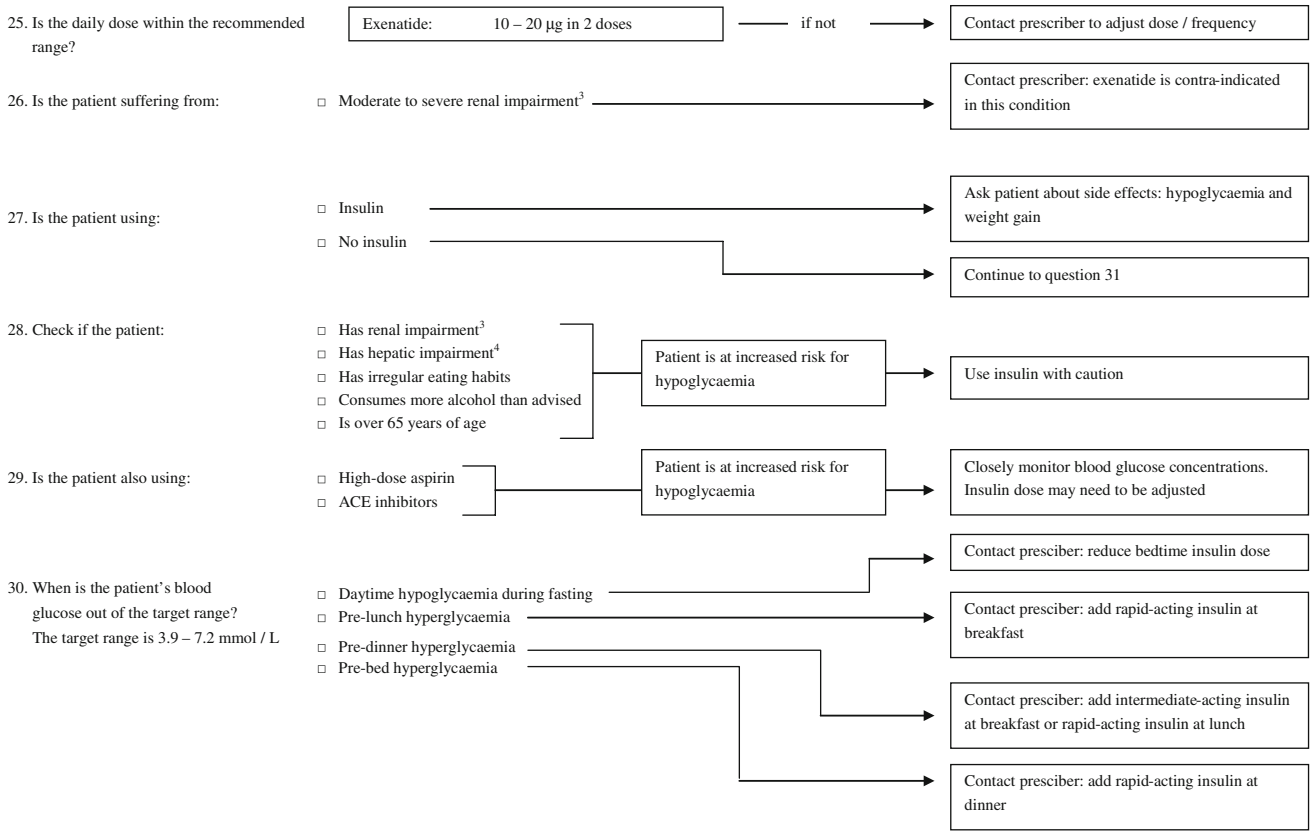
   → if not → Contact prescriber to adjust dose / frequency

10. Is the patient also using:
    - □ Rifamycins → Decrease in sulphonylurea metabolism might lead to hyperglycaemia → Closely monitor blood glucose concentrations. Sulphonylurea dose may need to be increased
    - □ High-dose aspirin
    - □ ACE inhibitors
    - □ Co-trimoxazole

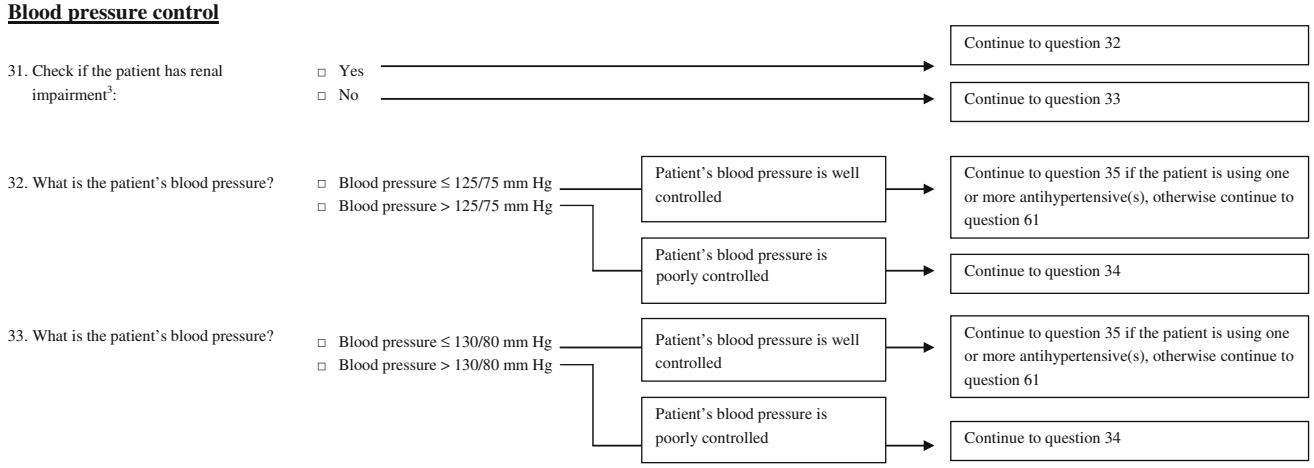
    → Patient is at increased risk for hypoglycaemia → Closely monitor blood glucose concentrations. Sulphonylurea dose may need to be decreased

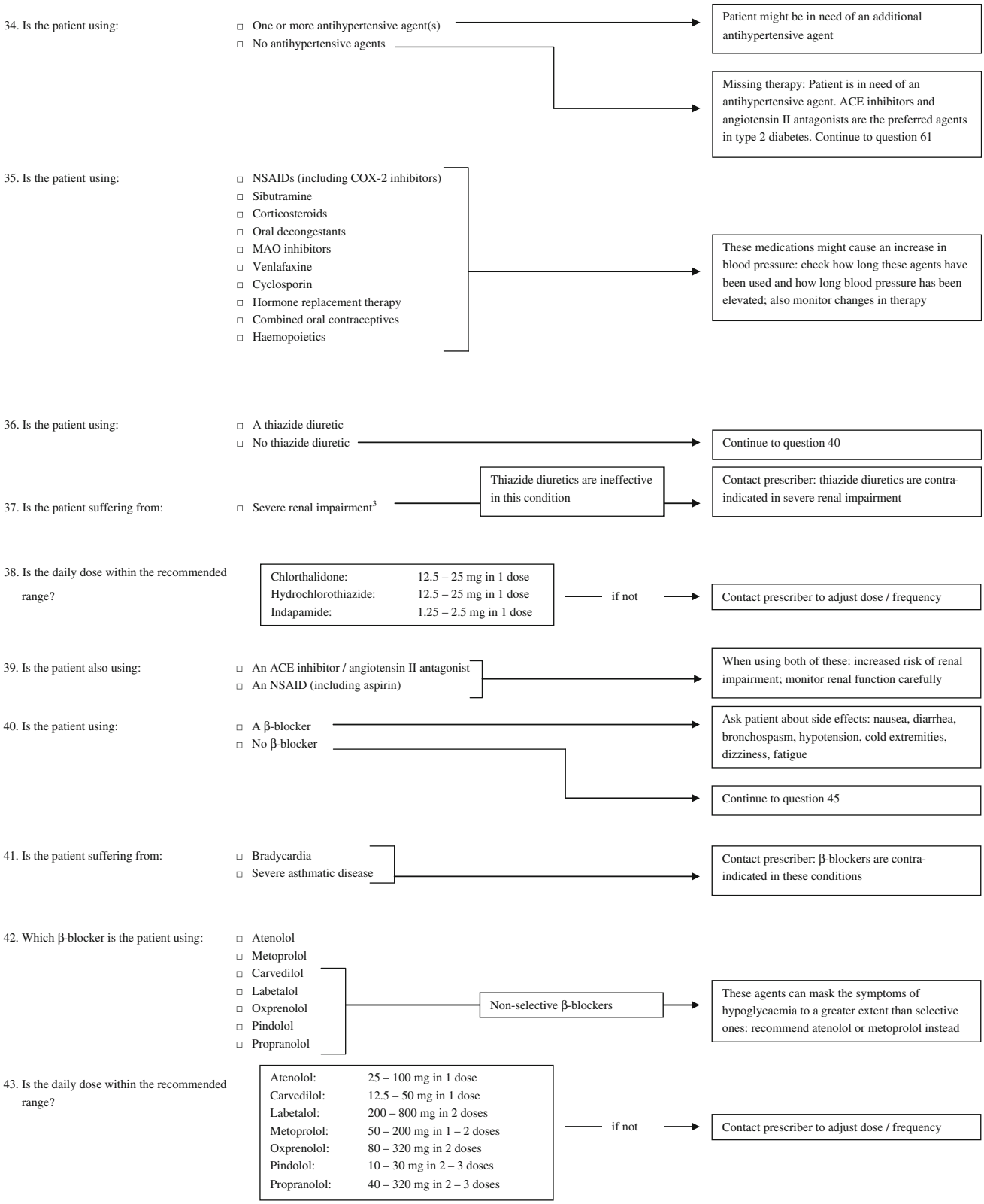
11. Is the patient using:
    - □ Metformin → Ask patient about side effects: nausea, vomiting, abdominal pain and diarrhea. Check for vitamin B_{12} deficiency
    - □ No metformin → Continue to question 14

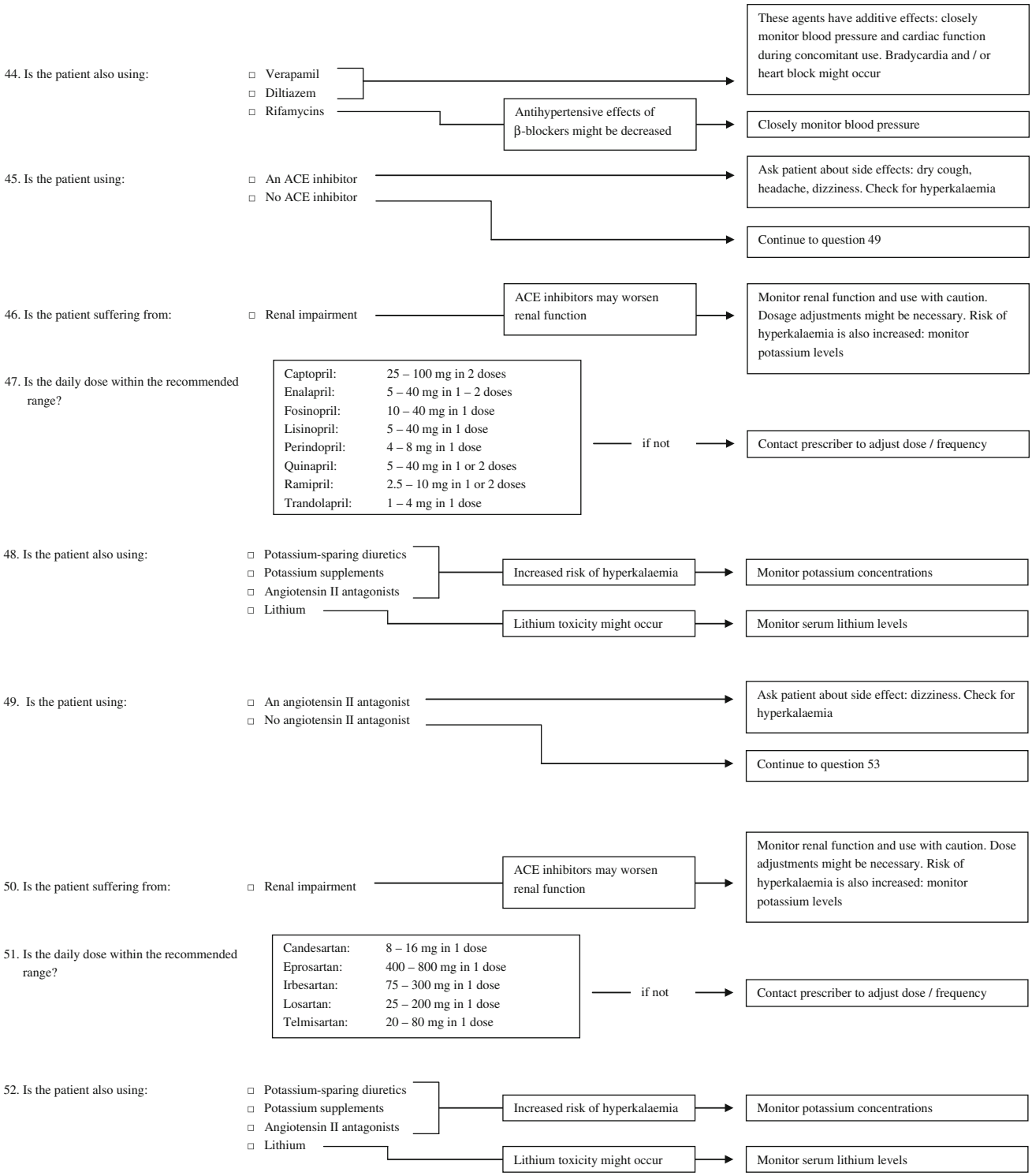

12. Check if the patient:
□ Has heart failure NYHA Class III or IV[6]
□ Has moderate to severe renal impairment[3]
□ Has hepatic impairment[4]
□ Is over 85 years of age
□ Consumes more alcohol than advised[5]
Patient is at increased risk of lactic acidosis
Contact prescriber: metformin might not be the appropriate agent in these conditions
13. Is the daily dose within the recommended range?
Metformin: 500 – 3000 mg in 1 – 3 doses
if not
Contact prescriber to adjust dose / frequency
14. Is the patient using:
□ A thiazolidinedione
□ No thiazolidinedione
Ask patient about side effects: weight gain, fluid retention, peripheral edema and osteoporosis
Continue to question 18
15. Is the patient suffering from:
□ Heart failure NYHA Class III or IV[6]
□ Hepatic impairment[4]
Contact prescriber: thiazolidinediones are contra-indicated in these conditions
16. Is the daily dose within the recommended range?
Rosiglitazone: 4 – 8 mg in 1 – 2 doses
Pioglitazone: 15 – 45 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
17. Is the patient also using:
□ Gemfibrozil
□ Insulin
□ NSAIDs
□ Rifamycins
Increased risk of adverse effects such as fluid retention and heart failure
Use these combinations with caution
Thiazolidinedione metabolism may be increased
Closely monitor blood glucose levels
18. Is the patient using:
□ Acarbose
□ No acarbose
Ask patient about side effects: flatulence, diarrhea and abdominal pain
Continue to question 21
19. Is the patient suffering from:
□ Inflammatory bowel disease
□ Renal impairment[3]
□ (Partial) intestinal obstruction
Contact prescriber: acarbose is contra-indicated in these conditions
20. Is the daily dose within the recommended range?
Acarbose: 50 – 600 mg in 1 – 3 doses
if not
Contact prescriber to adjust dose / frequency
21. Is the patient using:
□ Repaglinide
□ No repaglinide
Ask patient about side effects: hypoglycaemia, nausea, diarrhea, vomiting
Continue to question 24
22. Is the daily dose within the recommended range?
Repaglinide: 1.5 – 16 mg in 3 doses
if not
Contact prescriber to adjust dose / frequency
23. Is the patient also using:
□ Gemfibrozil
□ Cyclosporin
□ Macrolides (e.g. erythromycin)
□ Rifamycins
Repaglinide metabolism may be inhibited
Closely monitor blood glucose concentrations. Repaglinide dose may need to be decreased
Repaglinide metabolism may be increased
Closely monitor blood glucose concentrations. Repaglinide dose may need to be increased
24. Is the patient using:
□ Exenatide
□ No exenatide
Ask patient about side effects: nausea, diarrhea, vomiting and hypoglycaemia
Continue to question 27

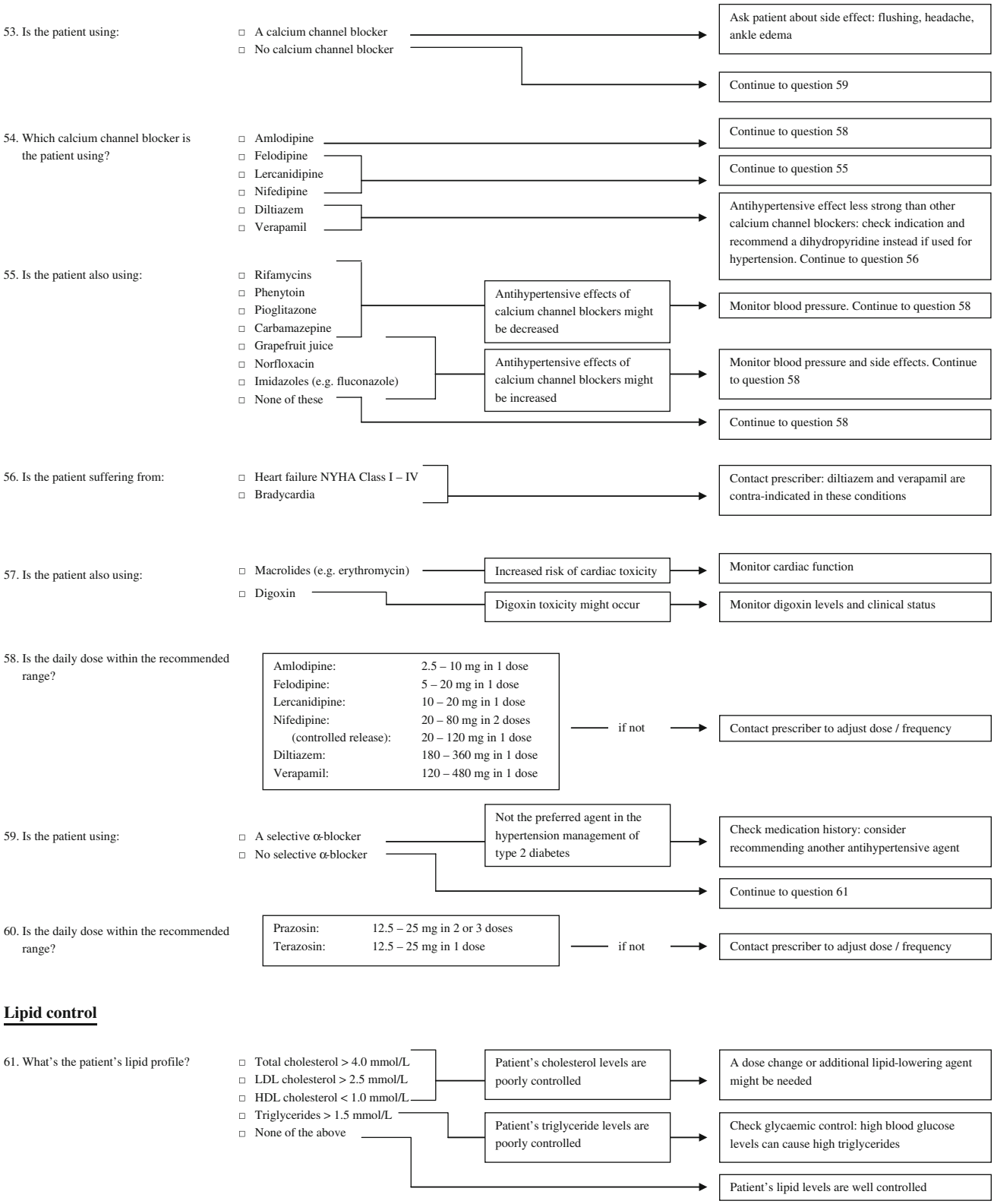


Blood pressure control

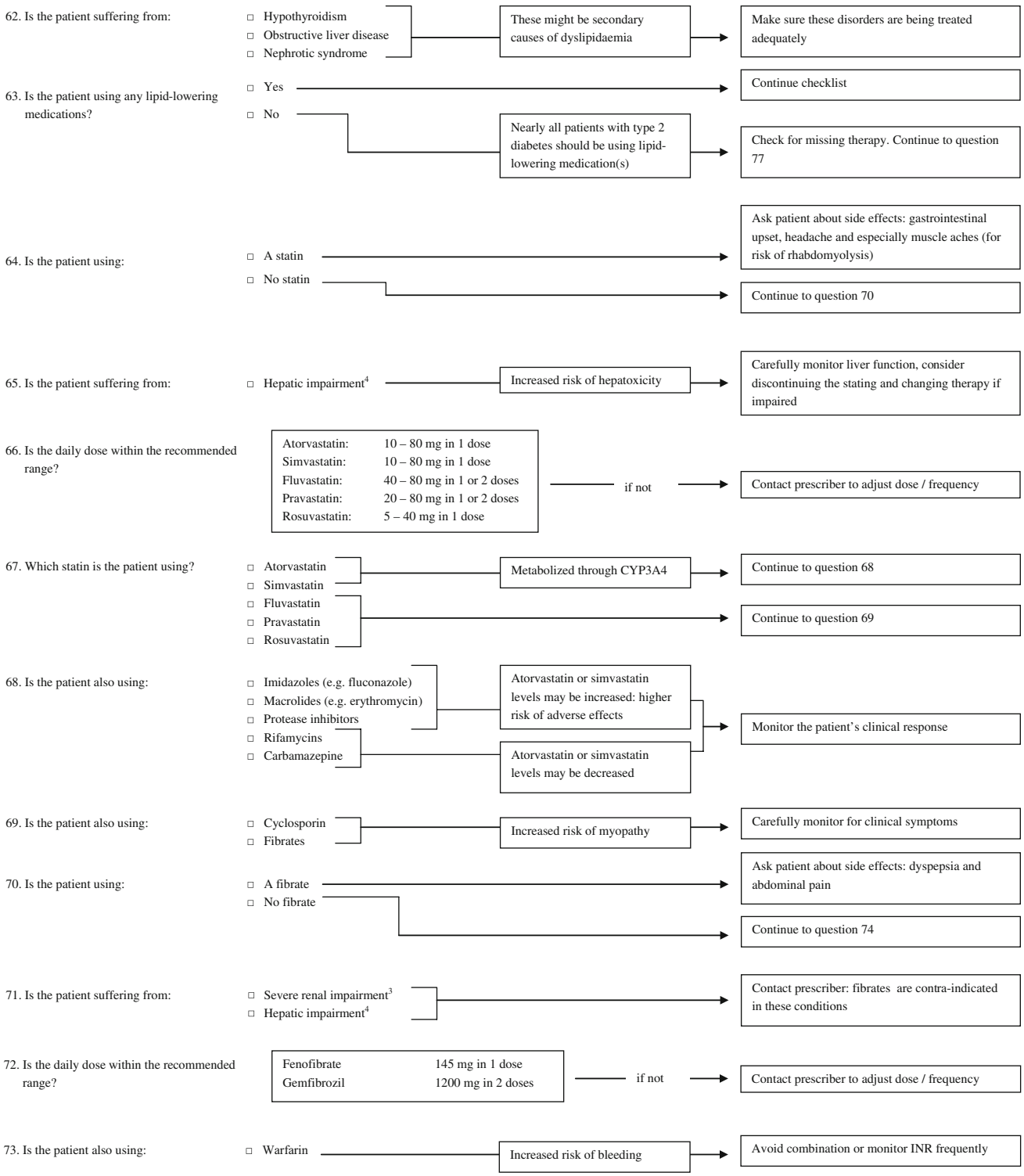


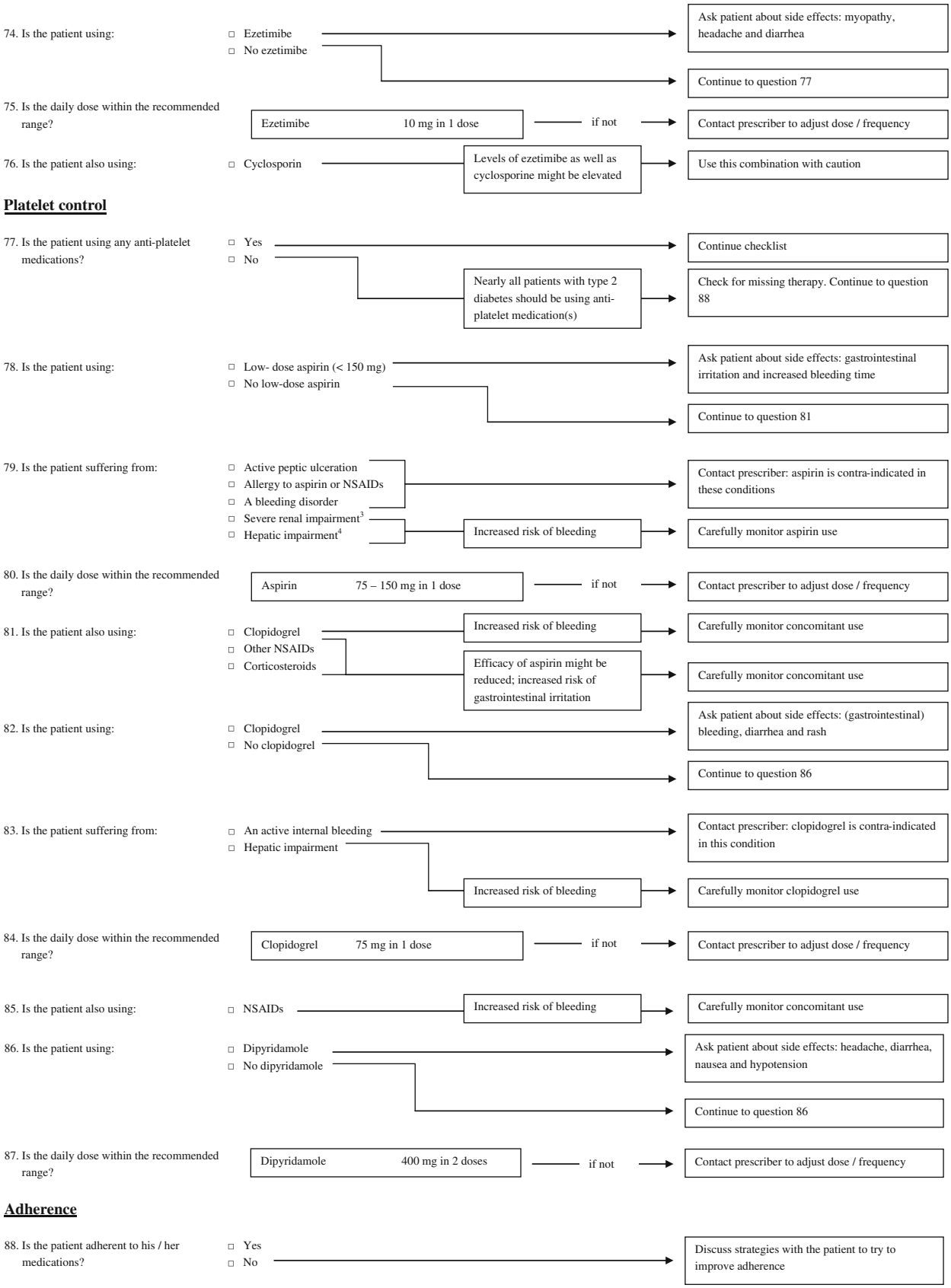

34. Is the patient using:
□ One or more antihypertensive agent(s)
□ No antihypertensive agents
Patient might be in need of an additional antihypertensive agent
Missing therapy: Patient is in need of an antihypertensive agent. ACE inhibitors and angiotensin II antagonists are the preferred agents in type 2 diabetes. Continue to question 61
35. Is the patient using:
□ NSAIDs (including COX-2 inhibitors)
□ Sibutramine
□ Corticosteroids
□ Oral decongestants
□ MAO inhibitors
□ Venlafaxine
□ Cyclosporin
□ Hormone replacement therapy
□ Combined oral contraceptives
□ Haemopoietics
These medications might cause an increase in blood pressure: check how long these agents have been used and how long blood pressure has been elevated; also monitor changes in therapy
36. Is the patient using:
□ A thiazide diuretic
□ No thiazide diuretic
Continue to question 40
37. Is the patient suffering from:
□ Severe renal impairment[3]
Thiazide diuretics are ineffective in this condition
Contact prescriber: thiazide diuretics are contra-indicated in severe renal impairment
38. Is the daily dose within the recommended range?
Chlorthalidone: 12.5 – 25 mg in 1 dose
Hydrochlorothiazide: 12.5 – 25 mg in 1 dose
Indapamide: 1.25 – 2.5 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
39. Is the patient also using:
□ An ACE inhibitor / angiotensin II antagonist
□ An NSAID (including aspirin)
When using both of these: increased risk of renal impairment; monitor renal function carefully
40. Is the patient using:
□ A β-blocker
□ No β-blocker
Ask patient about side effects: nausea, diarrhea, bronchospasm, hypotension, cold extremities, dizziness, fatigue
Continue to question 45
41. Is the patient suffering from:
□ Bradycardia
□ Severe asthmatic disease
Contact prescriber: β-blockers are contra-indicated in these conditions
42. Which β-blocker is the patient using:
□ Atenolol
□ Metoprolol
□ Carvedilol
□ Labetalol
□ Oxprenolol
□ Pindolol
□ Propranolol
Non-selective β-blockers
These agents can mask the symptoms of hypoglycaemia to a greater extent than selective ones: recommend atenolol or metoprolol instead
43. Is the daily dose within the recommended range?
Atenolol: 25 – 100 mg in 1 dose
Carvedilol: 12.5 – 50 mg in 1 dose
Labetalol: 200 – 800 mg in 2 doses
Metoprolol: 50 – 200 mg in 1 – 2 doses
Oxprenolol: 80 – 320 mg in 2 doses
Pindolol: 10 – 30 mg in 2 – 3 doses
Propranolol: 40 – 320 mg in 2 – 3 doses
if not
Contact prescriber to adjust dose / frequency


44. Is the patient also using:
□ Verapamil
□ Diltiazem
□ Rifamycins
These agents have additive effects: closely monitor blood pressure and cardiac function during concomitant use. Bradycardia and / or heart block might occur
Antihypertensive effects of β-blockers might be decreased
Closely monitor blood pressure
45. Is the patient using:
□ An ACE inhibitor
□ No ACE inhibitor
Ask patient about side effects: dry cough, headache, dizziness. Check for hyperkalaemia
Continue to question 49
46. Is the patient suffering from:
□ Renal impairment
ACE inhibitors may worsen renal function
Monitor renal function and use with caution. Dosage adjustments might be necessary. Risk of hyperkalaemia is also increased: monitor potassium levels
47. Is the daily dose within the recommended range?
Captopril: 25 – 100 mg in 2 doses
Enalapril: 5 – 40 mg in 1 – 2 doses
Fosinopril: 10 – 40 mg in 1 dose
Lisinopril: 5 – 40 mg in 1 dose
Perindopril: 4 – 8 mg in 1 dose
Quinapril: 5 – 40 mg in 1 or 2 doses
Ramipril: 2.5 – 10 mg in 1 or 2 doses
Trandolapril: 1 – 4 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
48. Is the patient also using:
□ Potassium-sparing diuretics
□ Potassium supplements
□ Angiotensin II antagonists
□ Lithium
Increased risk of hyperkalaemia
Monitor potassium concentrations
Lithium toxicity might occur
Monitor serum lithium levels
49. Is the patient using:
□ An angiotensin II antagonist
□ No angiotensin II antagonist
Ask patient about side effect: dizziness. Check for hyperkalaemia
Continue to question 53
50. Is the patient suffering from:
□ Renal impairment
ACE inhibitors may worsen renal function
Monitor renal function and use with caution. Dose adjustments might be necessary. Risk of hyperkalaemia is also increased: monitor potassium levels
51. Is the daily dose within the recommended range?
Candesartan: 8 – 16 mg in 1 dose
Eprosartan: 400 – 800 mg in 1 dose
Irbesartan: 75 – 300 mg in 1 dose
Losartan: 25 – 200 mg in 1 dose
Telmisartan: 20 – 80 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
52. Is the patient also using:
□ Potassium-sparing diuretics
□ Potassium supplements
□ Angiotensin II antagonists
□ Lithium
Increased risk of hyperkalaemia
Monitor potassium concentrations
Lithium toxicity might occur
Monitor serum lithium levels



Lipid control


62. Is the patient suffering from:
□ Hypothyroidism
□ Obstructive liver disease
□ Nephrotic syndrome
These might be secondary causes of dyslipidaemia
Make sure these disorders are being treated adequately
63. Is the patient using any lipid-lowering medications?
□ Yes
Continue checklist
□ No
Nearly all patients with type 2 diabetes should be using lipid-lowering medication(s)
Check for missing therapy. Continue to question 77
64. Is the patient using:
□ A statin
Ask patient about side effects: gastrointestinal upset, headache and especially muscle aches (for risk of rhabdomyolysis)
□ No statin
Continue to question 70
65. Is the patient suffering from:
□ Hepatic impairment[4]
Increased risk of hepatoxicity
Carefully monitor liver function, consider discontinuing the stating and changing therapy if impaired
66. Is the daily dose within the recommended range?
Atorvastatin: 10 – 80 mg in 1 dose
Simvastatin: 10 – 80 mg in 1 dose
Fluvastatin: 40 – 80 mg in 1 or 2 doses
Pravastatin: 20 – 80 mg in 1 or 2 doses
Rosuvastatin: 5 – 40 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
67. Which statin is the patient using?
□ Atorvastatin
□ Simvastatin
Metabolized through CYP3A4
Continue to question 68
□ Fluvastatin
□ Pravastatin
□ Rosuvastatin
Continue to question 69
68. Is the patient also using:
□ Imidazoles (e.g. fluconazole)
□ Macrolides (e.g. erythromycin)
□ Protease inhibitors
Atorvastatin or simvastatin levels may be increased: higher risk of adverse effects
□ Rifamycins
□ Carbamazepine
Atorvastatin or simvastatin levels may be decreased
Monitor the patient's clinical response
69. Is the patient also using:
□ Cyclosporin
□ Fibrates
Increased risk of myopathy
Carefully monitor for clinical symptoms
70. Is the patient using:
□ A fibrate
Ask patient about side effects: dyspepsia and abdominal pain
□ No fibrate
Continue to question 74
71. Is the patient suffering from:
□ Severe renal impairment[3]
□ Hepatic impairment[4]
Contact prescriber: fibrates are contra-indicated in these conditions
72. Is the daily dose within the recommended range?
Fenofibrate 145 mg in 1 dose
Gemfibrozil 1200 mg in 2 doses
if not
Contact prescriber to adjust dose / frequency
73. Is the patient also using:
□ Warfarin
Increased risk of bleeding
Avoid combination or monitor INR frequently


74. Is the patient using:
□ Ezetimibe
□ No ezetimibe
Ask patient about side effects: myopathy, headache and diarrhea
Continue to question 77
75. Is the daily dose within the recommended range?
Ezetimibe 10 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
76. Is the patient also using:
□ Cyclosporin
Levels of ezetimibe as well as cyclosporine might be elevated
Use this combination with caution
Platelet control
77. Is the patient using any anti-platelet medications?
□ Yes
□ No
Continue checklist
Nearly all patients with type 2 diabetes should be using anti-platelet medication(s)
Check for missing therapy. Continue to question 88
78. Is the patient using:
□ Low- dose aspirin (< 150 mg)
□ No low-dose aspirin
Ask patient about side effects: gastrointestinal irritation and increased bleeding time
Continue to question 81
79. Is the patient suffering from:
□ Active peptic ulceration
□ Allergy to aspirin or NSAIDs
□ A bleeding disorder
□ Severe renal impairment[3]
□ Hepatic impairment[4]
Contact prescriber: aspirin is contra-indicated in these conditions
Increased risk of bleeding
Carefully monitor aspirin use
80. Is the daily dose within the recommended range?
Aspirin 75 – 150 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
81. Is the patient also using:
□ Clopidogrel
□ Other NSAIDs
□ Corticosteroids
Increased risk of bleeding
Carefully monitor concomitant use
Efficacy of aspirin might be reduced; increased risk of gastrointestinal irritation
Carefully monitor concomitant use
82. Is the patient using:
□ Clopidogrel
□ No clopidogrel
Ask patient about side effects: (gastrointestinal) bleeding, diarrhea and rash
Continue to question 86
83. Is the patient suffering from:
□ An active internal bleeding
□ Hepatic impairment
Contact prescriber: clopidogrel is contra-indicated in this condition
Increased risk of bleeding
Carefully monitor clopidogrel use
84. Is the daily dose within the recommended range?
Clopidogrel 75 mg in 1 dose
if not
Contact prescriber to adjust dose / frequency
85. Is the patient also using:
□ NSAIDs
Increased risk of bleeding
Carefully monitor concomitant use
86. Is the patient using:
□ Dipyridamole
□ No dipyridamole
Ask patient about side effects: headache, diarrhea, nausea and hypotension
Continue to question 86
87. Is the daily dose within the recommended range?
Dipyridamole 400 mg in 2 doses
if not
Contact prescriber to adjust dose / frequency
Adherence
88. Is the patient adherent to his / her medications?
□ Yes
□ No
Discuss strategies with the patient to try to improve adherence
END OF CHECKLIST

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