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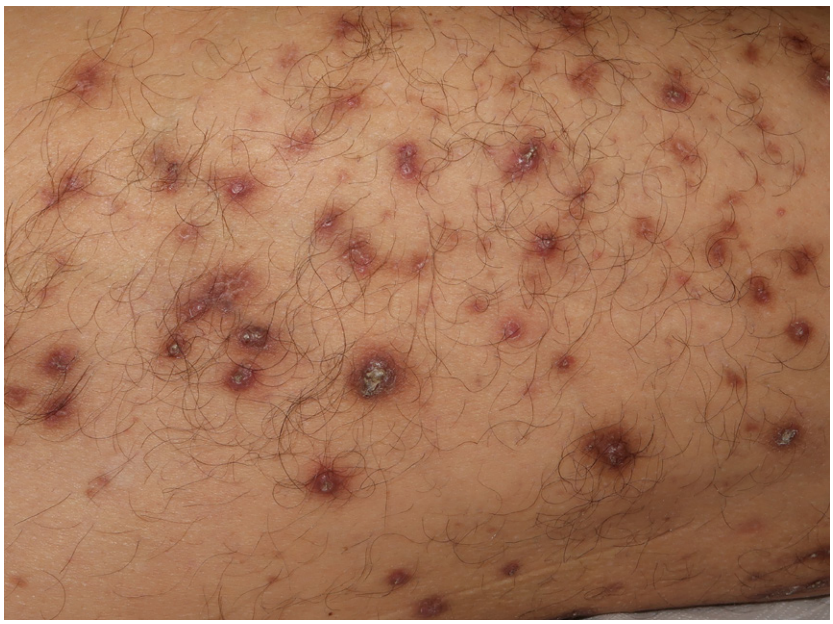

Skin lesions in a diabetic patient: what is your diagnosis?

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EDITORIAL

Primary G-CSF prophylaxis following docetaxel treatment

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Febrile neutropenia is a frequently occurring complication following chemotherapy. It causes significant short-term morbidity, mortality, and is costly. It may also affect subsequent chemotherapy dosing, which in turn, could lead to inferior long-term survival.[1] To reduce the incidence of febrile neutropenia and its complications, primary granulocyte-colony stimulating factor (G-CSF) prophylaxis is recommended by international guidelines when the risk of febrile neutropenia is 20% or higher.[2] In daily practice, febrile neutropenia rates are based on data from randomised controlled trials, but observational studies consistently report higher incidences of febrile neutropenia.[3]

In this issue of the Netherlands Journal of Medicine, van Dooijeweert et al.[4] describe that in a retrospective cohort of 181 breast cancer patients, the rate of febrile neutropenia following three cycles of 5-fluorouracil, epirubicin, cyclophosphamide (FEC) and three cycles of docetaxel (D) is significantly higher (31.5%) than the commonly assumed rate (10-20%) described in the European Organisation for Research and Treatment of Cancer guideline.[5] The occurrence of febrile neutropenia was highest after the first docetaxel cycle (20.9%). The authors conclude that this high percentage of febrile neutropenia following docetaxel treatment justifies starting primary G-CSF prophylaxis during the first docetaxel cycle.

This conclusion adds to the existing literature on the incidence of febrile neutropenia after FEC-D and its prevention by primary G-CSF treatment, as the authors rightly mention. A recent systematic review, also cited by van Dooijeweert et al., summarizes 11 mostly retrospective studies on the rate of febrile neutropenia after FEC-D with and without primary G-CSF prophylaxis. This review concludes that patients who received FEC-D with and without primary prophylaxis, presented median febrile neutropenia rates of 10.1% and 23.9%, respectively.[6]

Although G-CSF clearly reduces the rate of febrile neutropenia after FEC-D, a remaining question is whether primary G-CSF prophylaxis after FEC-D is cost-effective, and whether preventing febrile neutropenia reduces long-term mortality. These studies are difficult to conduct, and will most likely not be performed anymore because FEC-D is less frequently used. Nonetheless, as is concluded by van Dooijeweert et al., the febrile neutropenia rate of more than 20% justifies, according to international guidelines, the use of primary G-CSF prophylaxis when FEC-D is given, in breast cancer patients in adjuvant and neo-adjuvant settings.

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SPECIAL REPORT

Serious gaming in internal medicine education: do we know best or do we know last?

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KEYWORDS

Education, internal medicine, serious games

ABSTRACT

The use of digital tools is indispensable in our daily lives. The medical world keeps up with this progress by implementing digital tools to facilitate and improve patient care, such as eConsults and self-care apps. Serious games are also becoming increasingly popular in healthcare education, particularly in surgical residency training and nursing education. However, gaming and digitisation of education have not been widely integrated in internal medicine residency education yet. Therefore, these programs are not yet modernised to meet the demands of the 21th century physician. In this article, we will explicate our view on digitisation of the internal medical education programme with special attention to serious gaming. We will discuss pros and cons of digitisation, describe challenges of development and implementation of games, and offer some examples of digital educational tools for practical use.

INTRODUCTION

Digital serious games in healthcare education are becoming increasingly popular.[1,2] A serious game is an information technology (IT)-based modality designed to teach knowledge, skills, and behaviour, while integrating a score element, challenging goals, and appealing design.[3,4] Serious games appear in many shapes and forms. More sophisticated forms of serious games often involve high-tech IT solutions to generate two-dimensional (2D) computer games or three-dimensional (3D) virtual patients.[2,5] A serious game enables standardised repeated practice to enhance knowledge and skills without interaction with real patients, and allow for trial-and-error learning without compromising patient safety.

In particular, surgical residency training and nursing education already widely use serious games to simulate realistic situations.[1,2,6] By practicing skills in a simulated environment, surgical residents are exposed to many hours of rehearsing specific situations and a diversity of possible scenarios to help them train essential techniques. Although the learning potential of gaming in surgical education is not yet fully investigated, a recent trial shows that adding a serious game to an existing curriculum can help residents to improve their problem-solving abilities in the operating room.[7] This trial demonstrates that technical skills can be acquired by this form of education and cautiously suggests that behavioural changes may also be promoted. Gamification, the use of gaming elements for educational purposes, is also more customary in nursing educational programs, as reported by numerous articles, which describe a broad range of effects, varying from knowledge acquisition to reducing anxiety in stressful situations.[8-11]

Internal medicine is the largest hospital-based specialty and a rapidly developing and broad field of expertise. We would expect that gaming and digitisation of education are important components for internal medicine, including its subspecialties. Residents in internal medicine must obtain a variety of diagnostic skills, train in therapeutic decision making, and gain knowledge about rare diseases not often encountered in daily patient care; therefore, online games may be a good approach. Surprisingly, gaming has not been widely integrated into internal medicine residency education.

An overview generated in 2016 on serious games in healthcare identified 42 serious games in 14 fields of medical expertise. Only two games, *InsuOnline* and a blood pressure management game, contained training in specific internal medicine topics, and teach players

about the management of diabetes and hypertension, respectively.[2] Remarkably, even these two games were designed to train primary care physicians and not internal medicine specialists. Although games from different medical specialties can benefit internal medicine residents, serious games developed specifically for internal medicine education are lacking. Based on a review by Gentry et al.[6] in 2019, we can conclude that this is still the case. We believe that internal medicine residents could benefit from a game-enhanced curriculum and would like to challenge our colleagues to take a critical look at their own curricula.

DIGITAL EVOLUTION OF INTERNAL MEDICINE

Knowledge and skills required of an internist

Specialists in internal medicine, internists, are classically thought of as doctors with endless knowledge attained from books.[12-14] However, in a rapidly developing digital age, this traditional method of attaining knowledge is severely inefficient since it is virtually impossible to keep up with rapid medical developments in the different aspects of internal medicine. As a result, digital medical magazines and search platforms, such as UpToDate and PubMed, are frequently used to quickly find contemporary answers to clinical questions. Over time, skills such as patient counselling, management, and communication skills, have become increasingly important in residency education.[15] Addition of new roles to that of the clinical physician require supplementary skills. Creative thinking, computational thinking (problem solving with vast amounts of information, variables, and computing power) and basic information and communications technology (ICT) skills, so called 21st century skills, are necessary to fulfil all the roles demanded of the modern internist. Surprisingly, internal medicine resident education has not transformed to meet the needs of our new generations of internists.

Internists readily advocate patient digital tools

Remarkably, internists do urge their patients to use new technical solutions to increase their wellbeing. The strategic plan of the Netherlands Internists Association (NIV, Nederlandse Internisten Vereniging), a document describing the vision and ambitions of internists, encourages internists to inform their patients about new digital options in health education and to motivate patients to use apps for digital support in patient healthcare.[16]

Another example is the Dutch Society of Internal Medicine Innovation Platform that gives healthcare professionals an overview of digital medical applications.[17] The launch of this platform of medical innovations and the existence of an E-health week underscores the importance of digitisation for our professional group.

Digital tools and use of, are lacking in internal medicine education

Internists are progressive when it comes to digitisation of patient care and educators are inclined to use digital tools for medical students; thus, it remains unclear why the use of digital tools in internal medicine education is limited. One reason may be the restricted access to some of these digital tools. From our own experiences, internal medicine residency program directors are reluctant to adapt new digital tools into their curricula, which may be explained by a reluctance to adopt unknown elements. As stated by three medical information science professors, there is too little education on digitisation in the current medical curricula, and doctors are usually not actively involved in the process of developing new educational tools.[18] As a result, using new technology becomes difficult due to the lack of technical training and support from the medical world to implement these tools. In contrast to other, more technically supported medical specialties such as surgery or intensive care medicine, most internists do not regularly work with technical equipment. This unfamiliarity with extensive technical equipment may also contribute to hesitation in implementing digital educational tools. Lastly, in patient care, internists are trained to think about all possible solutions for a problem, explore them thoroughly before making a well-considered, preferably evidence-based, choice. Since there is no unambiguous evidence on the working mechanisms of gaming, an evidence-based decision is difficult to make in this context.

SERIOUS GAMING IN INTERNAL MEDICINE EDUCATION

Current state of education technology

Despite the lack of games, a few apps are available that enable internal medicine residents to practice clinical cases. The app *Prognosis*[19] offers players short cases in all medical fields. With a limited number of choice options and a large quantity of text explaining what (should have) happened to the patient, this app can be used to gain more background information on specific illnesses. Players can choose which specialty they want to practice, thus making this app suitable for all physicians. The *Clinical Sense*[20] app offers predominantly the same features. Both apps are the result of an international collaboration and are freely accessible. Unfortunately, reports on the goals and the effect the apps have on achieving these goals are lacking.

In the Netherlands, a few internal medicine residents have developed podcasts and apps to educate their colleagues. Examples include *Medische Snippers*[21], which offers 10-minute audio fragments containing background information on a topic to be discussed later that week in an analogue group meeting; and the *Internal Medicine Knowledge Test App*[22], which presents the player with numerous knowledge questions in preparation for the annual mandatory knowledge test for internal medicine residents in the Netherlands. Two serious games were developed in collaboration with Dutch internists, the *abcdeSim*[23] and *Geriatrix*[24]. Although internists played an important role in developing these games, again, its content is not primarily aimed at internists. The *abcdeSim* app trains the player to stabilise patients in the emergency department in a specific, structured way, the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) method.[23] This method is universally accepted as a valid approach to address acutely ill patients, but is not confined to internal medicine alone. A study on the effectiveness of the *abcdeSim* app showed that game-playing residents scored higher on objectively-measured and self-assessed clinical competencies.[25] The *Geriatrix* app was developed by an internist specialising in geriatric medicine and aims to teach the player about desirable treatment options in older patients with multiple medical problems; it also teaches students about cost effectiveness. A randomised controlled trial on the effectiveness of the game demonstrated higher self-perceived competence in medical students on all described learning goals.[26]

Advantages of serious gaming

While the medical world is rapidly evolving, financial cutbacks have mandated the shortening of training for Dutch internists and other specialists.[27] As a result, residents are expected to obtain more knowledge in less time, while simultaneously gaining insights into new developments. Digital forms of education may be a solution. With digital education, residency program directors can offer their residents exposure to every disease without having to wait for the right patient to visit the emergency room or outpatient clinic. All residents can therefore acquire the same level of knowledge independent of their particular practical training or internship. Moreover, digital forms of education can be used for testing purposes, to keep track of a resident's progress, or used as a self-assessment tool for residents to monitor their own knowledge or skills.

Digital forms of education can also ensure uniform acquisition of basic skills for residents in all sub-areas in internal medicine, and can be customised for individual learning needs. As stated in a policy document in 2016 by the Royal Dutch Medical Association, every resident in the Netherlands should be able to receive a personalised curriculum.[28] Though reasonably difficult to realise such demands when using analogue education, digital education can be adapted to every personal need. Depending on the design and content of the educational tool, residents would be able to train in various skills in a more compact and efficient way. Ultimately, residents can be exposed to much more repetition using digital forms of education in comparison with traditional forms of education. Repetition is associated with improved knowledge retention.[29] Luckily, the modality in which repetition is offered to residents seems to make no difference on learning potential,[30] serious gaming and other forms of digital education appear to be an acceptable alternative form of education.

Serious games stimulate active learning, which is encouraged more and more in medical curricula[31], and games promote this by offering challenging tasks and a story. Games also allow for flexible learning, which helps residents better incorporate learning tasks into their very busy schedules. Although promising in its possibilities, games are not likely to take over a complete curriculum. More research is needed to determine in what context and in what form a game should be used in current resident education.

Working mechanisms of serious gaming

Although the exact mechanisms of learning through playing games in medical residency education are not yet fully understood, there is increasing evidence on elements contributing to learning through gaming. A few key features in learning through gaming include application of knowledge, usability, the extent to which players accept the game, and learning by exploration.[32] Application of knowledge means that players have to apply previously acquired knowledge into the game, thus testing themselves on previously acquired knowledge and skills. Usability relates to the way players feel about becoming familiar with the game: If players feel like they are mastering a game, they become more involved and more motivated. They then continue to use the game and therefore learn from it. Exploration relates to the feasibility to investigate the possibilities within the game, make mistakes, and learn from them by trying again. This implicates that a game should be easy to use and relate to daily practice when used for training purposes.

Apart from these three principles, game design is important. There is no unambiguous evidence which design principles best promote learning. For example, one issue in designing games is the fidelity of the game, how the game situation resembles real life. Fidelity can be subdivided into two forms: structural fidelity, which describes to what extent the game and personas in the game look like real surroundings and people; and functional fidelity, which describes to what extent a functional task within the game resembles real life.

For example, the popular video game *Assassins Creed®*, in which an historical figure is sent on a mission to slay opponents, has high structural fidelity (buildings look like everyday structures and characters are lifelike), but low functional fidelity given that most of us are not murderers. In contrast to what one might think, high structural fidelity games do not necessary lead to increased learning. Although earlier reports questioned the relationship between fidelity and learning potential,[33] recent literature describes that high functional fidelity, rather than high structural fidelity, facilitated learning in simulation-based education.[34] However, medical students who engaged in a game with high-level structural and functional fidelity cases, did not demonstrate better procedural skills than students who used an online program with low-fidelity cases.[35] This study suggests that the efficacy of fidelity is dependent on the level of expertise of the player. In inexperienced players, high structural fidelity can create cognitive overload and thus diminish learning effects.[35] From this, we conclude that functional fidelity should be aligned to the intended user's expert level of using digital tools, or at least offer an excellent tutorial, and that structural fidelity should resemble daily functional tasks.

Challenges to developing and implementing serious games

The main challenges of creating and implementing games are to generate financial support and to continuously engage a multidisciplinary team with medical, educational, and IT experts during the development process. Although digital games are often more expensive to develop than traditional, analogue methods of education, the enhanced learning potential and amplification of skills beyond knowledge[6] is too valuable to ignore. Serious games have the potential to deliver highly-qualified doctors with a well-rounded education.

In order to implement a serious game into the curriculum, it is crucial to connect it to the learning goals and assessments, or other educational tools that may already exist. Unfortunately, even well-designed serious games are underused after delivery due to a lack of urgency among the target group to play. In addition, serious games require more support than traditional educational methods. A serious game requires continuous IT support to host and maintain a well-functioning game, including regular updates. Providing expertise for updating medical content regularly might even be more challenging. Medical professionals have to gain experience with the functionality of the game and keep up with new developments, including new guidelines, to regularly adjust the content of the game. Lastly, support and research from an educational perspective is required to provide the latest educational insights on serious gaming.

Dutch Society of Simulation in Healthcare

It is understandable that residency program directors may find it difficult to know where to start when thinking of using a game in their curriculum or to develop a game themselves. Recently, the Dutch Society of Simulation in Healthcare (DSSH) launched a quality assessment to evaluate the validity of serious games in healthcare.[36] Developers of serious games can submit their projects for evaluation at the DSSH quality committee of volunteer experts. The committee will review the submitted game with special attention to nine characteristics. Safe storage of data, gaming elements, collaboration with relevant experts, and validation of working mechanisms are some of the criteria which will be assessed. Evaluated games will receive one to five stars, with five stars being the maximum rating for games with validated working mechanisms. These criteria can also be used as guideline for future game development.

CONCLUSION

In summary, internal medicine is a rapidly developing field of medical expertise, with increasing emphasis on 21st century skills. Resident medical education can, and must be, adjusted to facilitate these learning demands. Serious games would be a way to improve current curricula to meet these demands. The DSSH could be a good reference for more information on how to develop a game, or as a contact to experienced development teams for advice. Other medical disciplines, such as surgery and nursing educational programs, have already made attempts to improve their curricula through gamification. We urge the internal medicine specialty to offer its residents a game-enhanced curriculum to promote active learning and create flexibility. By investigating these digital interventions on their effectiveness, design principles, gaming elements, and learning capacities, we can advance from knowing last to knowing best.

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ORIGINAL ARTICLE

Chemotherapy-induced febrile neutropenia: primary G-CSF prophylaxis indicated during docetaxel cycles

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ABSTRACT

Background: Chemotherapy-induced febrile neutropaenia (FN) is a common and life-threatening adverse event, which can be largely prevented by the use of granulocyte colony-stimulating factor (G-CSF); G-CSF, however is expensive and not without side effects. Although primary G-CSF prophylaxis is recommended when the risk of FN is ≥ 20%, it is unclear during which cycles it should be administered. This study assessed and compared the FN incidence in the neo-adjuvant or adjuvant administration of two chemotherapy regimens that are widely used in breast cancer care to provide clinically useful recommendations for G-CSF use.

Methods: 221 breast cancer patients were included in this retrospective single-centre study. In total, 181 patients received three cycles of 5-flourouracil, epirubicin, cyclophosphamide (FEC) followed by three cycles of docetaxel (3F-3D) (81.9%); 40 patients received four cycles of doxorubicin, cyclophosphamide (AC) followed by twelve cycles of paclitaxel (4AC-12P) (18.1%). The episodes of FN, extracted from the electronic patient files, were analysed and compared.

Results: Overall, FN was identified in 27.8% of patients and occurred significantly more in patients receiving 3F-3D compared to patients receiving 4AC-12P (31.5% versus 10.0%, OR 4.14, 95% CI: 1.14-12.18). Comparison of FN occurrence after first exposure to FEC (6.1%), AC (5.0%), docetaxel (20.9%), or paclitaxel (0%) showed a significantly higher risk in patients receiving docetaxel than following administration of the other three agents.

Conclusions: In breast cancer treatment, compared to other frequently-used agents, monotherapy with docetaxel (100 mg/m^2) renders a substantial risk of FN (20.9%), thereby justifying the use of primary G-CSF according to international guidelines.

KEYWORDS

Breast cancer, chemotherapy-induced febrile neutropenia, docetaxel, granulocyte colony-stimulating factor, G-CSF

INTRODUCTION

Febrile neutropaenia (FN) is a common and potentially life-threatening complication of chemotherapy, with a reported overall mortality of up to 10%.[1-4] Furthermore, FN is associated with substantial morbidity and costs,[4-6] often resulting in treatment delays, dose reductions, and even cessation of treatment;[7] all result in poorer outcomes.[8-10] Therefore, preventing febrile neutropaenia is of high clinical relevance, especially in the curative setting.

A well-known supportive care intervention is the use of granulocyte colony-stimulating factor (G-CSF), which stimulates the proliferation of neutrophils and thereby minimises the incidence of FN and its associated morbidity and costs.[11-14] However, the use of G-CSF itself is relatively expensive (approximately € 1,000 per injection)[15] and it is associated with side effects such as thrombocytopaenia and muscle-, joint-, and back pain (1-10%).[11,15] Both European and American guidelines recommend the use of primary G-CSF prophylaxis in cases of FN risk ≥ 20%.[16-20]

As FN rates in randomised clinical trials (RCTs) are significantly lower than in observational studies,[21] it is important to study the incidence of FN after specific chemotherapy cycles in daily clinical practice to provide clinicians with clinically applicable recommendations for G-CSF use. However, despite the global and widespread use of chemotherapy, high quality literature on the incidence of FN during specific chemotherapy regimens in daily clinical practice in various cancer types, for example, breast cancer, is scarce.[22] In addition, guidelines usually

lack advice when to administer G-CSF. Thus, although the 20% cut-off may be clear, it remains unclear when to use primary G-CSF prophylaxis in daily clinical practice.

In our experience, a substantial number of breast cancer patients treated with docetaxel (100 mg/m²) experienced FN during these chemotherapy cycles, which was in concordance with the experience of four regional cancer centres in Ontario, Canada.[23] Two systematic reviews also reported median FN rates of 23.9%[22] and 30.6%[24] in a specific regimen, containing three cycles of FEC (5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m²) every three weeks followed by three cycles of docetaxel (100 mg/m²) (3F-3D) every three weeks, yet they did not specify in which specific cycles the risk of FN was highest.

In contrast, another widely used regimen consisting of four cycles of AC (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²) every three weeks, followed by 12 weekly cycles of paclitaxel (80 mg/m²)(4AC-12P) seems to cause FN in substantially fewer patients, with FN rates during AC cycles ranging from 2.5%[25] to 16.1%,[26] although literature is scarce.

Recently, Aagaard et al. developed a risk score for febrile neutropenia after chemotherapy (FENCE score), both for the first cycle of chemotherapy[27] and for cycles 2-6 in patients with solid cancers.[28] This risk score[27] is easily available online and requires various patient and chemotherapy characteristics. Although the FENCE score may be a helpful tool, it does not discriminate between different taxane regimens while, in our experience, other taxane regimens such as weekly paclitaxel, almost never cause FN. Thus, simply following the FENCE score may lead to unnecessary administration of G-CSF. Therefore, the question remained whether the use of primary G-CSF prophylaxis would be justified during all or a specific cycle of docetaxel for breast cancer patients. The primary aim of this study was to provide clinical recommendations for the use of primary G-CSF prophylaxis in breast cancer patients by assessing data from daily clinical practice. We assessed and compared the incidence of chemotherapy-induced FN in breast cancer patients receiving either the 3F-3D or 4AC-12P regimens, both of which are widely used in primary breast cancer care.[29,30]

MATERIALS AND METHODS

Study population

This study was assessed by the Research Assessment Committee and approved by the board of directors of the Meander Medical Centre.

All breast cancer patients receiving neo-adjuvant or adjuvant chemotherapy with either 3F-3D or 4AC-12P in the Meander Medical Centre between January 1st, 2014 and December 31st, 2015 were identified. Patients receiving alternative chemotherapy regimens were excluded.

For each patient, data on gender, age, tumour characteristics, and type of chemotherapy regimen were obtained from the electronic patient files. Episodes of FN, any subsequent dose delays, and any emergency department visits were identified and analysed, as was the use of G-CSF.

In general, hormone-positive, human epidermal growth factor receptor 2 (HER2)-negative patients were given 3F-3D and triple negative or HER2-positive patients were given 4AC-12P. For HER2-positive patients, the 12 paclitaxel cycles were combined with administration of the monoclonal antibody trastuzumab, which was continued as weekly monotherapy up to a total treatment duration of one year. However, the choice of chemotherapy regimen was determined by the attending medical oncologist, in consultation with the patient; when necessary, in the expert opinion of the medical oncologist, choice of chemotherapy regimen could differ from regional policy. FEC (5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m²), AC (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²), docetaxel (100 mg/m²), and paclitaxel (80 mg/m²) were all administered in protocolled doses.

Neutrophil counts were measured one day in advance, or on the day of the planned chemotherapy cycle. Chemotherapy cycles were delayed when neutrophil count was below 1000 cells/mm³. In addition to the protocolled measurements, neutrophil count was only monitored when patients experienced fever during their chemotherapy.

FN was defined as any fever ≥ 38.5°C, reported by the patient or measured in the hospital, in combination with an absolute neutrophil count of < 500 cells/mm³. Patients were instructed to contact and visit the emergency department in any case of fever. When patients visited the emergency department for a possible FN episode, a full physical examination was performed, followed by the collection of blood samples, urine samples, and a chest X-ray to identify a focus of the fever. If patients did indeed experience an FN episode, they were admitted and treated with intravenous antibiotics, according to hospital protocol.

Overall, the incidences of FN in patients undergoing 3F-3D and 4AC-12P were compared. Since trastuzumab is not kwown to cause myelotoxicity, the HER2-positive patients who received 4AC-12P with trastuzumab during the paclitaxel cycles were included in this group in our analyses. Finally, to evaluate the risk of FN during specific chemotherapy cycles, all first administered cycles of AC, FEC, docetaxel, and paclitaxel were compared and odds ratios with a 95% confidence interval were calculated.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Advanced version 22. Two-sided p-values less than 0.05 were considered statistically significant. Distributions of categorical variables were compared using the Chi-square test, and odds ratios with 95% confidence interval were calculated. Means of continuous variables were compared using the Two-sample t-test.

RESULTS

Patients and tumour characteristics

In total, 227 patients breast cancer patients who received chemotherapy between January 1st, 2014 and December 31st, 2015 were identified. Six patients were excluded for receiving an alternative chemotherapy regimen. These patients received their specific chemotherapy regimen because of comorbidity or previous chemotherapy cycles for prior malignancies. Therefore, a total of 221 patients, all receiving the 3F-3D or 4AC-12P-regimen, were included in the data analyses.

All patients were female with a mean age of 52.9 years (SD ± 9.7 years) (table 1) and no distant metastases were present upon diagnosis, except for one patient who had an oligometastasis in her ileum for which an ileocecal resection was successfully performed.

The 3F-3D-regimen was administered in 181 patients (81.9%). The 4AC-12P-regimen was administered in 40 patients (18.1%); of these 40 patients, 21 received their paclitaxel cycles in combination with trastuzumab. A total

Table 1. *Baseline characteristics for all breast cancer patients receiving neo-adjuvant or adjuvant systemic chemotherapy cycles of the 3F-3D- or 4AC-12P treatment regimen in the Meander Medical Centre (n=221)*

Study characteristics	Total (n = 221)	3F-3D (n = 181)	4AC-12P (n = 40)
Mean age (years)[a]	52.9 ± 9.7	52.9 ± 9.4	53.0 ± 11.2
Age > 60 years	59 (26.7%)	48 (26.5%)	11 (27.5%)
Setting			
Adjuvant	201 (91.0%)	166 (91.7%)	35 (77.5%)
Neo-adjuvant	20 (9.0%)	15 (8.3%)	5 (12.5%)
ER status			
Positive	170 (76.9%)	151 (83.4%)	19 (47.5%)
Negative	51 (23.1%)	30 (16.6%)	21 (52.5%)
PR status			
Positive	141 (63.8%)	126 (69.6%)	15 (37.5%)
Negative	80 (36.2%)	55 (30.4%)	25 (62.5%)
Her2 status			
Positive	23 (10.4%)	0 (0%)	23 (57.5%)
Negative	198 (89.6%)	181 (100%)	17 (42.5%)
Triple-negative status	42 (19.0%)	30 (16.6%)	12 (30.0%)
Finished all cycles	**169(76.5%)**	**141 (77.9%)**	**28 (70.0%)**
Histology [b]			
Ductal carcinoma	173 (78.3%)	143 (79.0%)	30 (75.0%)
Lobular carcinoma	35 (15.8%)	30 (16.6%)	5 (12.5%)
Medullary carcinoma	10 (4.5%)	7 (3.9%)	3 (7.5%)
Remaining	8 (3.6%)	5 (2.8%)	3 (7.5%)

[a]Expressed as mean, ± SD
[b]In total, 254 carcinoma were identified in 221 patients
3F-3D = 3 x FEC (5-fluorouracil 500 mg/m², epirubicin 100 mg/m²; cyclophosphamide 500 mg/m²) and 3 x docetaxel (100mg/m²); 4AC-12P = 4 x AC (doxorubicin 60mg/m², cyclophosphamide 600 mg/m²) and 12 x paclitaxel (80mg/m²); ER = estrogen receptor; PR = progesterone receptor; Her2 = human epidermal growth factor receptor 2

Table 2. *Risk of febrile neutropaenia in breast cancer patients receiving neo-adjuvant or adjuvant systemic chemotherapy cycles of the 3F-3D or 4AC-12P regimens*

Event	Number of events (total cycles = 1657)	Number of patients (total = 221)	3F-3D (n = 181)	4AC-12P (n = 40)	OR (95%CI) [a]
Febrile neutropaenia	66 (4.0%)	61 (27.6%)	57 (31.5%)	4 (10.0%)	4.14 (1.41-12.18)

[a]3F-3D versus 4AC-12P
3F-3D = 3 x FEC (5-fluorouracil 500 mg/m², epirubicin 100 mg/m²; cyclophosphamide 500 mg/m²) and 3 x docetaxel (100 mg/m²); 4AC-12P = 4 x AC (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²) and 12 x paclitaxel (80 mg/m²); OR = odds ratio; CI = confidence interval

of 181 patients were exposed to FEC, whereas 40 patients in total were exposed to AC. All patients within the 4AC-12P group continued with paclitaxel cycles;, resulting in 40 patients who were exposed to paclitaxel. Within the first three cycles of FEC, four patients ceased treatment and thus 177 of 181 patients of the 3F-3D-group were exposed to docetaxel.

Febrile neutropaenia

FN was identified in 61 patients (27.6%) who developed a total of 66 FN episodes. Patients receiving 3F-3D developed significantly more FN episodes during any of their cycles than patients receiving 4AC-12P (31.5% versus 10.0%, OR 4.14, 95% CI: 1.41-12.18) (table 2). Three patients experienced two FN episodes and one patient experienced three episodes, all within the same type of cycles in the 3F-3D group and without G-CSF prophylaxis after their first FN episode. There were no repeated episodes of FN in the 4AC-12P regimen and paclitaxel never caused FN.

First exposure of patients to docetaxel rendered a significantly higher risk of developing FN (20.9%) than first exposure to AC (5.0%; OR 5.02, 95% CI: 1.16-21.78),

Figure 1. *Risk of febrile neutropaenia in breast cancer patients after first exposure to the specific chemotherapy agents of the 3F-3D and 4AC-12P regimens. AC = doxorubicin 60mg/m², cyclophosphamide 600mg/m2; FEC = 5-fluorouracil 500 mg/m², epirubicin 100 mg/m²; cyclophosphamide 500 mg/m²; docetaxel (100 mg/m²); paclitaxel (80 mg/m²)*

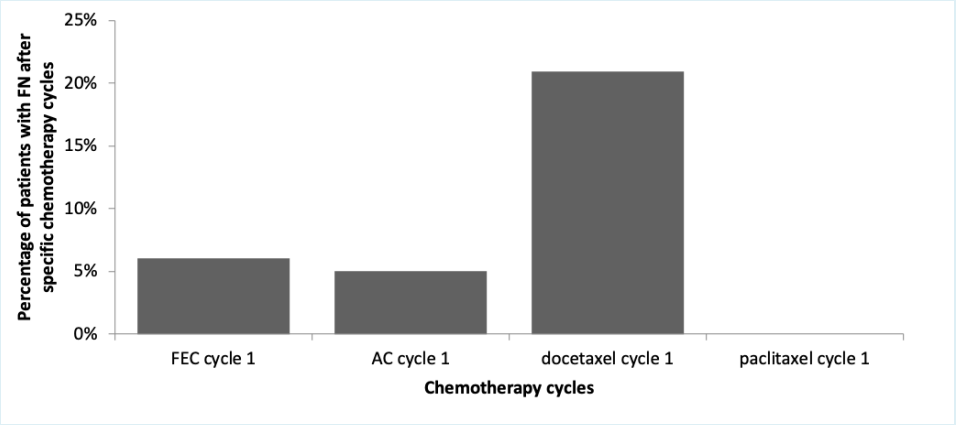

Table 3. *Risk of febrile neutropaenia in patients after first exposure to specific chemotherapy agents of the 3F-3D and 4AC-12P regimens*

Type of event	AC (n=40)	FEC (n=181)	D (n=177)	P (n=40)	p-value	OR (95% CI)	
Febrile neutropaenia	2 (5.0%)	11 (6.1%)	37 (20.9%)	-	0.000[a]	D vs. AC D vs. FEC D vs. P	5.02 (1.16-21.78) 4.08 (2.01-8.30) 21.62 (1.30-359.84)

[a]Calculated with Chi-square test
AC = doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²; FEC = 5-fluorouracil 500 mg/m², epirubicin 100 mg/m²; cyclophosphamide 500 mg/m²; OR = odds ratio; CI = confidence interval; D = docetaxel (100 mg/m²); P = paclitaxel (80 mg/m²)

FEC (6.1%; OR 4.08, 95% CI: 2.01-8.30), or paclitaxel (0.0%; OR 21.62, 95% CI: 1.30-359.84) (table 3, figure 1).

G-CSF use

G-CSF was administered in 8.1% of all chemotherapy cycles (135/1657) in 50 patients in total (22.6%). Both pegfilgrastim and lipefilgrastim were used as a G-CSF analogue. The use of G-CSF was not protocolled yet, when prescribed, it was mostly as a secondary prophylaxis with the next cycle of chemotherapy after an FN episode. Four patients (8.0%) received G-CSF as primary prophylaxis due to their age (> 60 years) in combination with a fragile condition. Two episodes of neutropaenia occurred while patients received G-CSF to prevent neutropaenia. However, these two episodes were both not complicated by fever or cycle delay due to neutropaenia and in both cases, neutropaenia was not profound (< 500 cells/mm^3).

Focus of infection

The respiratory tract was the most common focus of infection, affecting 13.6% (9/66) of patients; this was a clinical diagnosis without confirmation by a positive culture in all cases. Urinary tract infections and mucositis both occurred separately in 10.6% of FN episodes (both 7/66). Various other foci were identified in 25.8% of FN episodes, for example pneumonia, sinusitis, and ileocolitis. In 39.4% of FN episodes, a focus was not identified (26/66). Overall, pathogens were only isolated in 9.1% of FN episodes (6/66), of which 50.0% (3/6) involved *Escherichia coli*. FN patients spent a median of five days in the hospital (range: 2-31 days).

Age and central venous catheters

Central venous catheters were identified in a total of 39 patients (17.6%), of whom 20 received 3F-3D and 19 received 4AC-12P. Among patients with a central venous catheter (in both chemotherapy regimens), FN was identified in 28.2%, whereas among patients without a central venous catheter, FN was identified in 27.5% (OR 1.04, 95% CI: 0.480-2.239). The numbers in this study are however, too low to draw any conclusion on whether a central venous catheter increases the risk of FN.

The mean age of patients with and without FN was 52.9 years in both groups (p = 0.988). Of all patients older than 60 years, 27.1% developed FN, whereas 27.8% of patients younger than 61 years developed FN (OR 0.97, 95% CI: 0.50-1.88).

DISCUSSION

As FN rates from RCTs are significantly lower than FN rates from observational studies, it is extremely important to provide FN incidence rates derived from daily clinical practice to provide clinically useful recommendations. These daily clinical practice data are, however, scarce. Therefore, we assessed and compared the incidence of FN in two chemotherapy regimens that are widely used in primary breast cancer care.

We show a high overall incidence (27.6%) for FN in breast cancer patients receiving chemotherapy in our hospital. FN occurred significantly more in patients in the 3F-3D group (31.5%) than in the 4AC-12P group (10.0%) (OR 4.14, 95% CI: 1.41-12.18). This difference seems to be primarily caused by docetaxel (100 mg/m^2) within the 3F-3D regimen, as first exposure to docetaxel rendered a significantly higher risk of FN (20.4%) than first exposure to FEC (6.1%), AC (5.0%), or paclitaxel, which never caused FN. This shows that docetaxel poses a high enough risk to justify the use of primary G-CSF, independent of age or World Health Organization (WHO) performance status. In addition, not all taxanes should be considered equally potent in causing FN, considering the absence of FN following paclitaxel administration. This is highly clinically relevant as docetaxel is not only used in breast cancer treatment, but also in other cancer types including in prostate cancer, lung cancer, gastric cancer, and head and neck cancer, although not always as regimen of first choice.[15,31]

The results of this study raise the question why the 3F-3D treatment regimen, and especially docetaxel within this regimen, would lead to more FN. A possible explanation might be that docetaxel is a more potent cause of neutropaenia. In both treatment regimens, patients received previous cycles of chemotherapy (3 x FEC or 4 x AC), which seemed to be similarly potent causes of FN (6.1% for FEC versus 5.0% for AC) and the first cycles of docetaxel and paclitaxel were only administered when the patient's bone marrow was sufficiently recovered after the previous chemotherapy cycle, i.e., with a neutrophil count of 1000 cells/mm^3 or higher. Another explanation might be that mucositis is a frequently seen side effect of docetaxel cycles. Mucositis causes a potential port d'entrée for bacteria and thus might contribute to a higher FN incidence.

Literature on the incidence of FN in daily clinical practice for different chemotherapy regimens in breast cancer treatment is limited. Bennett et al[32] developed a risk stratification of FN for different types of tumours and chemotherapy regimens by using National Comprehensive Cancer Network data. They found that FEC plus sequential docetaxel contributes to an intermediate risk of developing FN (10-20%) in neo-adjuvant or adjuvant systemic chemotherapy treatment of breast cancer patients, which is notably lower than the 31.5% risk of FN that was found in this study.[32] As previously described, two large systematic reviews described the incidence of FN without primary prophylactic G-CSF during 3F-3D and found median

FN rates of 23.9%[22] and 30.6%,[24] which resembles the mean FN rate of 31.5% found in this study. Despite these systematic reviews, high-quality evidence remains scarce and to our knowledge, primary G-CSF prophylaxis during 3F-3D is not yet recommended, although national and international guidelines justify this, since the risk of FN is higher than 20%.[11-14] This is mostly due to a lack of evidence on the optimal timing of primary G-CSF prophylaxis, either during all cycles of 3F-3D or only during specific cycles. We believe our study addresses this issue by comparing the first exposure to AC, FEC, paclitaxel, and docetaxel and thereby identifying docetaxel as the most potent agent in causing FN.

In addition, literature on FN incidence during 4AC-12P is both insufficient and divergent with FN rates during AC cycles ranging from 2.5%[25] to 16.1%.[26] Interestingly the 16.1% rate of FN during AC was found by Kim et al, [26] who studied the incidence of FN in Korean breast cancer patients receiving four cycles of neoadjuvant and adjuvant AC followed by four cycles of docetaxel. In contrast to our study, they found that 16.1% of patients experienced FN after the first AC cycle and remarkably, only 2.0% of patients experienced FN after the first docetaxel cycle in their treatment regimen.[26] It should be noted however, that these data were derived from Asian breast cancer patients and may therefore not be applicable to the Dutch or Western populations of breast cancer patients.

Aagaard et al. recently published a proposed FN risk stratification[27,28] which should be welcomed, however, a major limitation is that while this score incorporates certain types of agents (platinums, non-platinum alkylating agents, taxanes, topoisomerase inhibitors, antimetabolites, vinca alkaloids, and other), it does not discriminate between, for example, different types and doses of taxanes. This would result in the same risk score for both a docetaxel and paclitaxel-containing regimen, underscoring our findings that the risk of FN is significantly higher in a docetaxel regimen compared to a paclitaxel regimen, where the risk of FN was zero. Thus, simply following the FENCE score, would result in unnecessary administration of G-CSF, and would subsequently expose patients to unnecessary side effects, in addition to increasing health costs.

This study has several limitations, including its retrospective design, a relatively small sample size, especially for the 4AC-12P group, and single institution focus. However, all hospitals in this region follow the same guidelines and chemotherapy treatment of breast cancer patients is generally analogous in the Netherlands. Moreover, these data reflect the actual situation in daily clinical practice, where the patient population may differ from patient populations in RCTs.[21]

We are aware that 3F-3D is currently not as widely used as in 2014-2015, while 4AC-12P is increasingly used. Consequently, the unbalanced distribution of both treatment regimens (81.9% 3F-3D vs. 18.1% 4AC-12P) is a major limitation of this study. However, both regimens are still used in clinical practice. We therefore believe that our data remain relevant and address the lack of evidence in optimal timing of primary G-CSF prophylaxis during 3F-3D, which may still benefit patients with breast cancer and possibly other types of cancers.

Finally, we would like to make a remark about the use of primary G-CSF prophylaxis in this study with regard to the observed FN rates. The primary G-CSF prophylaxis in older patients could have masked the incidence of FN, however, this was only the case for four patients. In addition, the incidence of FN could have also been masked by the use of secondary G-CSF prophylaxis during the docetaxel cycles in 11 patients who developed febrile neutropaenia after one of their FEC cycles. Therefore, without both forms of G-CSF prophylaxis, the actual incidence of FN may be even higher.

CONCLUSION

In conclusion, this study with data based on regular clinical practice shows that incorporating docetaxel monotherapy (100 mg/m^2) in a neo-adjuvant or adjuvant chemotherapy regimen in the treatment of breast cancer patients renders a high risk of FN compared to a weekly paclitaxel-containing regimen, 31.5% versus 10.0%, (OR 4.14, 95% CI: 1.41-12.18). Our analysis of the docetaxel monotherapy section of the treatment regimen demonstrates that the risk of FN (20.9%) clearly surpasses FN risk following paclitaxel monotherapy (0%), and it is also considerably higher than the FN risk of the anthracycline section in both regimens (~ 5%). It can therefore be concluded that, according to international guidelines, the nearly 21% risk of FN justifies the use of primary G-CSF following docetaxel monotherapy.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

This study was assessed by the Research Assessment Committee and approved by the board of directors of the Meander Medical Centre.

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ORIGINAL ARTICLE

Trends in mortality, cardiovascular complications, and risk factors in type 2 diabetes

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ABSTRACT

Background: Quality of diabetes care in the Netherlands ranked second in the Euro Diabetes Index 2014, but data on outcomes are lacking. We assessed trends in cardiovascular disease and mortality among type 2 diabetes (T2DM) patients in the context of risk factor control.
Methods: Annual cohorts of adult T2DM patients were constructed from the PHARMO Database Network. Age-standardised mortality rates and incidence rates (IR) of hospitalisations for acute myocardial infarction (AMI), stroke, and congestive heart failure (CHF) were compared with a diabetes-free population matched on age, sex, and general practitioner. Life years lost (LYL) to T2DM or cardiovascular disease were determined by comparing life expectancy between matched groups. Proportions attaining glycated haemoglobin (HbA1c), blood pressure (BP), and low-density lipoprotein cholesterol (LDL-C) goals were assessed annually.
Results: Among 53,602 T2DM patients, slight increases in IR between 2008 and 2016 were proportional to those in diabetes-free controls; on average T2DM increased the risk of mortality by 86%, hospitalisation for AMI 69%, stroke 57%, and CHF 185%. At age 55, LYL to T2DM averaged 3.5 years and established CVD added 1.8 years, irrespective of sex. HbA1c goal attainment increased from 58% to 65%, LDL-C from 56% to 65%, and systolic BP from 57% to 72%.
Conclusion: Despite highly organised diabetes care, excess incident cardiovascular events and mortality due to T2DM did not decrease over the study period. Life expectancy of T2DM patients is significantly reduced and risk factor control is suboptimal. This suggests there is considerable room for improvement of diabetes care in the Netherlands.

KEYWORDS

Cardiovascular events, glucose-lowering drugs, mortality, risk factor control, type 2 diabetes

INTRODUCTION

The quality of T2DM care in the Netherlands ranked second in the Euro Diabetes Index 2014,[1] due to its highly organised primary care programs that involve regular check-ups in a multidisciplinary team of general practitioners (GPs), assistants, dieticians, podologists, and ophthalmologists. GPs are the primary treating physicians of T2DM patients in the Netherlands. Quality indicators used by healthcare insurance companies to incentivise GPs to optimise diabetes care focus on procedural aspects of care, such as the intervals between check-ups and adherence to guidelines with respect to risk factor control and treatment. The Euro Diabetes Index 2014[1] stated that the main criticism of Dutch diabetes care is the lack of data on short- and long-term cardiovascular outcomes.
T2DM is associated with increased risk of microvascular complications, cardiovascular morbidity, and mortality,[2,3] which is generally more pronounced among women.[4] The aim of T2DM treatment guidelines is stated as the prevention and treatment of micro- and macrovascular complications.[5-7] Lifestyle advice includes a healthy diet, smoking cessation, increased exercise, and weight loss. Treatment targets are set for the three pharmacologically treatable risk factors low-density lipoprotein cholesterol (LDL-C), blood pressure (BP), and glycated haemoglobin (HbA1c). The relationship between LDL-C and BP and

major cardiovascular events is well established.[8,9] For HbA1c, there is a well-established relationship with microvascular complications[10,11] and to a lesser extent with macrovascular complications.[12,13] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that intensive glucose-lowering treatment to reach HbA1c < 42 mmol/mol (< 6%) decreased the risk of microvascular events and myocardial infarctions, but increased the risk of mortality and severe hypoglycaemic events.[13,14] Re-evaluation of the benefits and risks of treatment in specific age groups led to the introduction of individualised targets in the 2013 revision of the Dutch treatment guideline for T2DM.[5]

No new BP and cholesterol-lowering drugs were introduced in the study period, except for pro-protein convertase subtillsin/kexin type 9 (PCSK-9) inhibitors for very high-risk patients in 2015.[15] Glucose-lowering treatment options changed considerably, with new additions in the classes of dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors,[16] and withdrawal of rosiglitazone. Nevertheless, the stepwise treatment algorithm to obtain glycaemic control (start with metformin and if necessary, add sulfonylureas (SU) and ultimately basal insulin) was only revised with regard to the mention of gliclazide as preferred SU in 2013.[5] This was due to its low risk of cardiovascular mortality and hypoglycaemia in comparison to other SUs, and the fact that no dose adjustment is deemed necessary for renal impairment.[17]

In Sweden, a country with good quality and accessibility of health care, incidence rates of cardiovascular disease remained high despite changing diabetes care. However, improvements in the number of life years lost to diabetes were observed in a T2DM population relative to a diabetes-free population from 2006 to 2013, with the excess mortality among women slowly declining over time.[18] So far, it is unclear what changes have occurred in diabetes care and outcomes in the Netherlands. We therefore investigated trends in excess cardiovascular incidence and mortality in the T2DM population relative to the diabetes-free population between 2008 and 2016, goal attainment of pharmacologically-treated risk factors, and changing glucose-lowering treatment, in view of changing guidelines.

MATERIALS AND METHODS

Setting and patient selection

Health care data were obtained from the PHARMO Database Network, which links out-patient pharmacy drug dispensings, laboratory test results from both primary and secondary care, primary care GP records, secondary care hospitalisations, and mortality records. In order to be able to accurately capture cardiovascular event dates, we used hospitalisation data from the Dutch Hospital Data Foundation.[19] The source population for this study was limited to the overlapping geographical areas in which these data were collected. Mandatory health insurance and required registration with a GP makes the GP Database representative of the general Dutch population. The out-patient Pharmacy Database is representative of the general population that has picked up prescription drugs or has registered with a pharmacy. Therefore, the diabetes population represented in the PHARMO Database Network has been shown to be representative of the pharmacologically-treated Dutch diabetes population.[20]

Within this source population, we identified annual cohorts of patients with T2DM with index dates of January 1st of each year in the period 2008-2016. Patients with less than a year of recorded history prior to index date (i.e., start of data collection < 365 days before index date) were excluded from the annual cohort. Patients were identified based on at least two glucose-lowering drug (GLD) dispensings within the year prior to index date. Inclusion was restricted to patients aged 18 or older at index date, without type 1 diabetes, gestational diabetes, or polycystic ovary syndrome. Matched cohorts of patients without diabetes were created separately for each annual cohort based on age (i.e., matched 1:1 with birth year), sex, and treating GP, to control for possible differences in recording of morbidity and data collection periods between GPs.

Patient characteristics

Prevalent cardiovascular morbidity and cancer at index date were extracted from GP and hospitalisation records in all available history. Antihypertensive medication use, statin use, and platelet aggregation inhibitor use were determined in the year prior to index date. In the year prior to index date, the last recorded body mass index (BMI) and BP were extracted from GP records; HbA1c and LDL-C from GP records were supplemented with available clinical laboratory results.

Cardiovascular events and mortality

Annual age-standardised mortality rates and incidence rates of hospitalisations for acute myocardial infarction (AMI), congestive heart failure (CHF), and stroke were determined in the year after index date. Patients with T2DM were compared to matched controls without diabetes using rate ratios (RR).

The number of life years lost to T2DM, cardiovascular disease (CVD; including AMI, angina pectoris, CHF, stroke, and peripheral artery disease) or both T2DM and CVD were determined by subtracting life expectancy in patients with the condition to those without it.

Unmatched patients with T2DM were excluded from analyses of cardiovascular events and mortality.

Risk factor control

HbA1c goal attainment was assessed per age group according to the guidelines in use. From 2008-2012 the HbA1c target was 53 mmol/mol (7.0%) for all age groups. After the revision of the Dutch GP guidelines in 2013, the HbA1c target of 53 mmol/mol (7.0%) remained unchanged for patients aged < 70 and for elderly patients who were managed with lifestyle advice or treated with metformin only. For patients over 70 years treated with other GLD, the target was set to 58 mmol/mol (7.5%) if they were diagnosed up to 10 years ago, or 64 mmol/mol (8.0%) if they were diagnosed more than 10 years ago. For LDL-C and systolic blood pressure (SBP), the corresponding targets were set at ≤ 2.5 mmol/l and ≤ 140 mmHg, respectively. For patients over 80 the SBP target was raised to 160 mmHg in 2013.

GLD use

The type of GLD treatment was determined using drug classes based on level 3 Anatomical Therapeutic Chemical coding for non-insulin GLD, and insulin was considered as one class. In addition, gliclazide was analysed separately from other SUs. The proportion of patients in each annual cohort using specific GLD classes at some time during the year was determined. Furthermore, per annual cohort, we recorded which new class of GLD was initiated as second-line GLD after at least six months of first-line metformin monotherapy, either as add-on or switch. First-line therapy was defined as the first GLD dispensing after at least six months of recorded medication history without GLD. Simultaneous initiation of more than one GLD class was classified as 'other' GLD in this analysis.

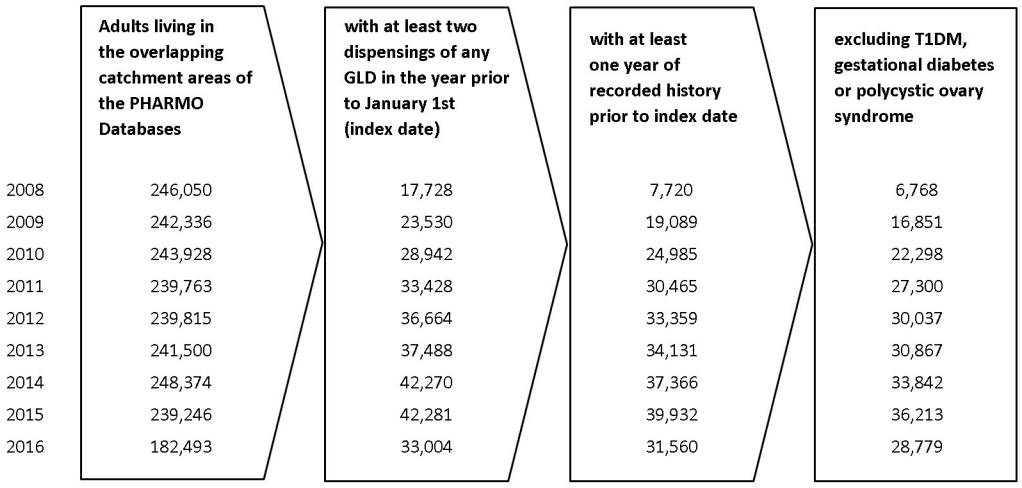
Statistical analyses

Confidence intervals around annual incidence rates (excluding patients with a history of the event investigated) were based on Byar's approximation of the Poisson distribution. Trends over time were tested using Poisson regression at P-value < 0.05. Age standardisation of incidence rates was performed by direct standardisation where the Dutch population on January 1st of the calendar year (according to data from the Dutch Central Bureau for Statistics) was used as the standard population.[21]

Sullivan's life table analysis was applied for calculating life expectancy at the specific reference age using 2-year age strata. The Sullivan method combines information on morbidity and mortality to estimate years lived with and without a specific disease, i.e., T2DM, CVD, or both.[22] Sex differences were explored for all outcomes. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Figure 1. *Flow chart of patient selection per annual cohort*



GLD = glucose-lowering drugs; T1DM = type 1 diabetes mellitus

Table 1. *Characteristics of T2DM patients per annual cohort*

	2008 n = 6,768	2009 n = 16,851	2010 n = 22,298	2011 n = 27,300	2012 n = 30,037	2013 n = 30,867	2014 n = 33,842	2015 n = 36,213	2016 n = 28,779	p for trend
Male, n (%)	3,425 (51)	8,795 (52)	11,713 (53)	14,365 (53)	15,876 (53)	16,312 (53)	18,101 (53)	19,642 (54)	15,795 (55)	< .0001
Age, mean ± SD	66 ± 12	66 ± 12	67 ± 12	67 ± 11	68 ± 11	68 ± 12	68 ± 11	69 ± 11	69 ± 11	< .0001
Morbidity[a], n (%)										
Any CVD	1,561 (23)	4,138 (25)	5,924 (27)	7,774 (28)	9,094 (30)	9,695 (31)	11,071 (33)	12,594 (35)	10,600 (37)	< .0001
AMI	405 (6)	1,138 (7)	1,606 (7)	2,120 (8)	2,537 (8)	2,708 (9)	3,153 (9)	3,752 (10)	3,228 (11)	< .0001
AP	739 (11)	1,958 (12)	2,792 (13)	3,611 (13)	4,259 (14)	4,482 (15)	5,107 (15)	5,707 (16)	4,693 (16)	< .0001
CHF	202 (3)	545 (3)	860 (4)	1,178 (4)	1,412 (5)	1,622 (5)	1,908 (6)	2,274 (6)	1,899 (7)	< .0001
Ischaemic stroke	293 (4)	1,016 (6)	1,445 (6)	2,051 (8)	2,448 (8)	2,569 (8)	2,887 (9)	3,491 (10)	3,070 (11)	< .0001
PAD	481 (7)	1,099 (7)	1,574 (7)	2,077 (8)	2,453 (8)	2,823 (9)	3,308 (10)	3,715 (10)	3,243 (11)	< .0001
Cancer	365 (5)	1,068 (6)	1,725 (8)	2,385 (9)	2,989 (10)	3,567 (12)	4,305 (13)	5,051 (14)	4,395 (15)	< .0001
Co-medication										
Antihypertensives	4,659 (69)	12,051 (72)	15,975 (72)	19,832 (73)	22,150 (74)	22,752 (74)	25,055 (74)	26,750 (74)	21,204 (74)	< .0001
Statins	4,081 (60)	10,357 (61)	14,219 (64)	17,991 (66)	20,228 (67)	21,066 (68)	23,204 (69)	24,912 (69)	19,658 (68)	< .0001
Platelet aggregation Inhibitors	2,025 (30)	5,147 (31)	6,801 (31)	8,397 (31)	9,377 (31)	9,552 (31)	10,472 (31)	11,093 (31)	8,958 (31)	0.6324
BMI[b]										
Recorded, n (%)	3,377 (50)	9,540 (57)	14,476 (65)	18,347 (67)	20,961 (70)	22,351 (72)	26,062 (77)	29,209 (81)	23,538 (82)	<.0001
Mean kg/m2 ± SD	30 ± 5	30 ± 5	30 ± 5	30 ± 5	30 ± 5	30 ± 5	30 ± 5	30 ± 5	30 ± 5	0.0363
HbA1c[b]										
Recorded, n (%)	4,221 (62)	11,493 (68)	16,111 (72)	22,037 (81)	24,681 (82)	25,100 (81)	28,314 (84)	31,461 (87)	25,245 (88)	<.0001
Mean mmol/mol ± SD	52 ± 11	53 ± 11	52 ± 11	52 ± 11	52 ± 11	53 ± 11	53 ± 11	54 ± 11	54 ± 12	<.0001
LDL-C[b]										
Recorded, n (%)	4,246 (63)	11,601 (69)	15,776 (71)	20,696 (76)	23,033 (77)	23,509 (76)	26,554 (78)	29,905 (83)	24,423 (85)	<.0001
Mean mmol/l ± SD	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.4 ± 0.9	2.4 ± 0.9	2.4 ± 0.9	2.4 ± 0.9	2.3 ± 0.9	<.0001
Systolic BP[b]										
Recorded, n (%)	3,954 (58)	10,265 (61)	15,640 (70)	20,231 (74)	22,835 (76)	23,541 (76)	27,189 (80)	30,396 (84)	24,430 (85)	<.0001
Mean mmHg ± SD	141 ± 17	141 ± 17	140 ± 17	139 ± 17	138 ± 16	138 ± 16	137 ± 16	137 ± 16	137 ± 16	<.0001
Diastolic BP[b]										
Recorded, n (%)	3,923 (58)	10,199 (61)	15,583 (70)	20,122 (74)	22,845 (76)	23,521 (76)	27,143 (80)	30,366 (84)	24,370 (85)	<.0001
Mean mmHg ± SD	79 ± 9	79 ± 9	79 ± 9	78 ± 9	78 ± 9	78 ± 9	77 ± 9	77 ± 9	77 ± 9	<.0001

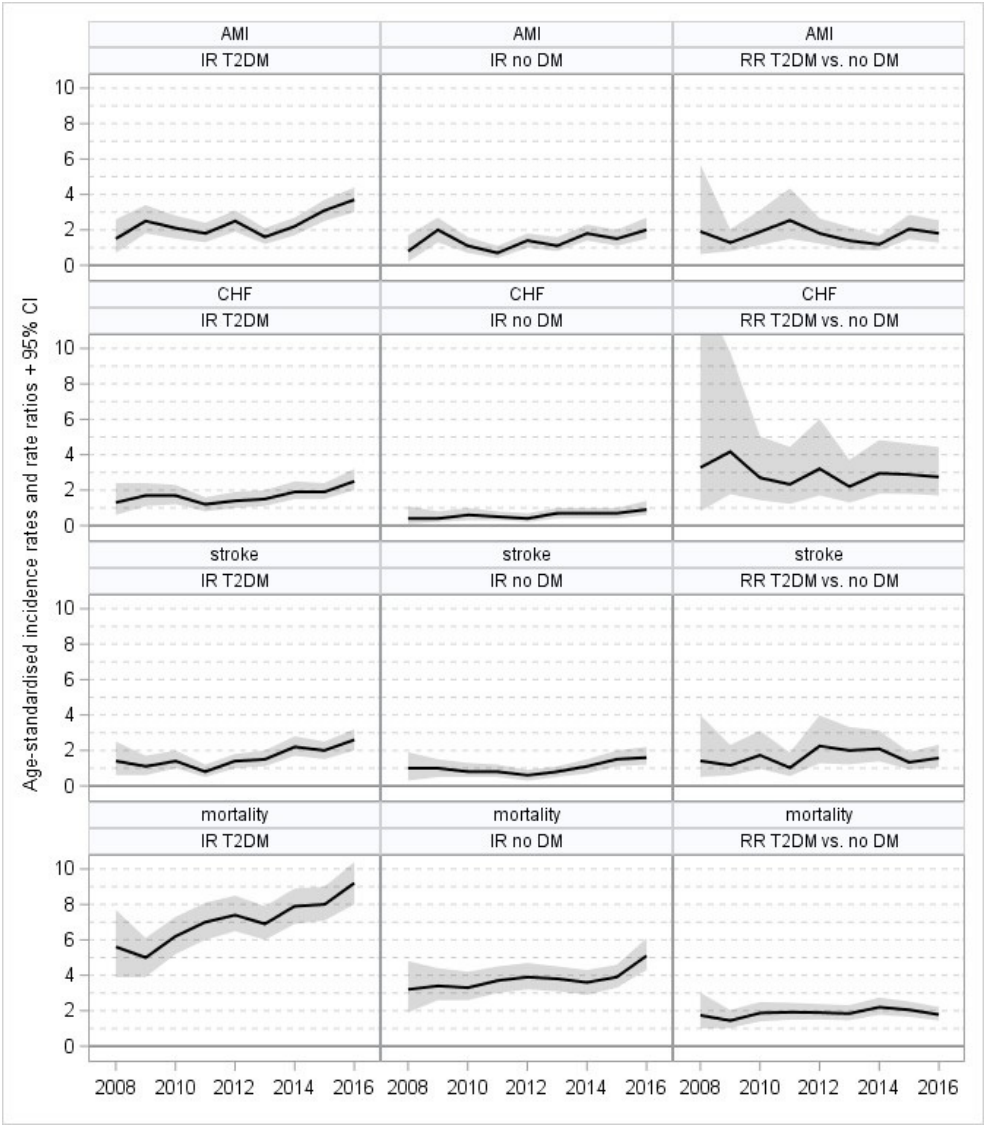
[a]Recorded in all available history; [b]Last recorded in the year prior to index date; [c]According to the general practioner guidelines, applicable at that time in the Netherlands and relative to known values only.
AMI = acute myocardial infarction; AP = angina pectoris; BMI = body mass index; BP = blood pressure; CHF = congestive heart failure; CVD = cerebrovascular disease; HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral artery disease; SD = standard deviation

Patient selection, characteristics

In total, 53,602 T2DM patients were included in annual cohorts (figure 1). Fewer than 4% could not be matched to diabetes-free patients because age- and sex-matched controls were not available in some general practices. The proportion of men increased from 51% to 55% between 2008 and 2016 and the overall mean age from 66 to 69 years (table 1), with women being slightly older (68 to 71 years) than men (64 to 68 years). The proportion with cardiovascular morbidity increased from 23% to 37% and cancer from 5% to 15%. Antihypertensive drug use increased from 69% to 74% and statin use from 60% to 68%; platelet aggregation inhibitor use was stable over time at 31% (not included in table 1).

The proportion of patients with recorded assessments of LDL-C, BP, HbA1c, and BMI increased over time (table 1). Mean levels of LDL-C, BP, and HbA1c decreased slightly over the study period. Mean BMI was 30 kg/m^2 (SD 5 kg/m^2) over the entire study period and comparable between sexes. Characteristics of matched cohorts of patients without diabetes are presented in *Supplemental table 1*.

Figure 2. *Age-standardised IR and RR of major cardiovascular events and mortality, T2DM vs. no DM*



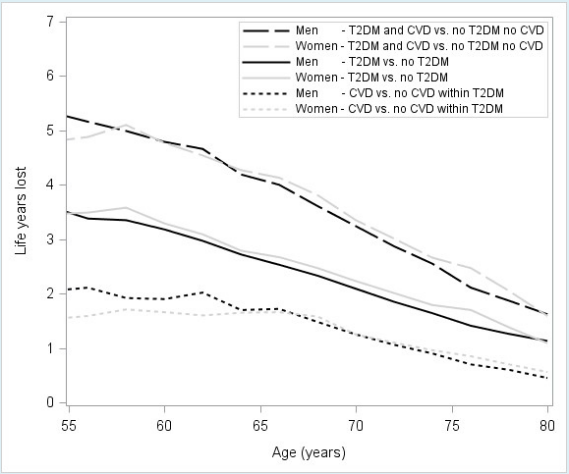
AMI = acute myocardial infarction; CHF = congestive heart failure; CI = confidence interval; DM = diabetes mellitus; IR = incidence rates; RR = rate ratio; T2DM = type 2 diabetes mellitus

Cardiovascular events and mortality

Age-standardised incidence rates of hospitalisations for cardiovascular (CV) events (AMI, CHF, and stroke), and mortality rates were higher among T2DM patients compared to diabetes-free patients (figure 2). On average, T2DM increased the risk of mortality by 86% without a clear trend over the study period. Slowly increasing trends were observed for age-standardised incidence rates for CV events (p for $trend_{T2DM}$ = 0.0153 for AMI; < .0001 for CHF and stroke) and mortality (p for $trend_{T2DM}$ < .0001), but RRs did not show clear trends, indicating the increase was proportional in diabetes patients and non-diabetes patients. On average, T2DM increased the risk of AMI by 69%, CHF by 185%, and stroke by 57%. Incidence rates for AMI and mortality were considerably higher for males compared to females, but RRs were similar between sexes (*Supplemental figure 1*).

Life years lost to T2DM decreased from 3.5 years at age 55 to just over 1 year at age 80 (figure 3). No clear differences were observed between the sexes. Below the age of 55 the power was insufficient for both sexes to reliably calculate the life years lost to T2DM. The number of life years lost to the combination of T2DM with CVD ranged from about 5 years at age 55, and just below 2 years at age 80. CVD combined with T2DM thus caused an additional loss of 1.5 years at age 55 and 0.7 years at age 80 compared to T2DM alone. Comparing patients with and without CVD within a T2DM population resulted in about 1.8 life years lost to CVD at age 55 (higher for men) and 0.7 years at age 80 in both sexes.

Figure 3. *Life years lost to T2DM, to T2DM with CVD, and to CVD within T2DM*

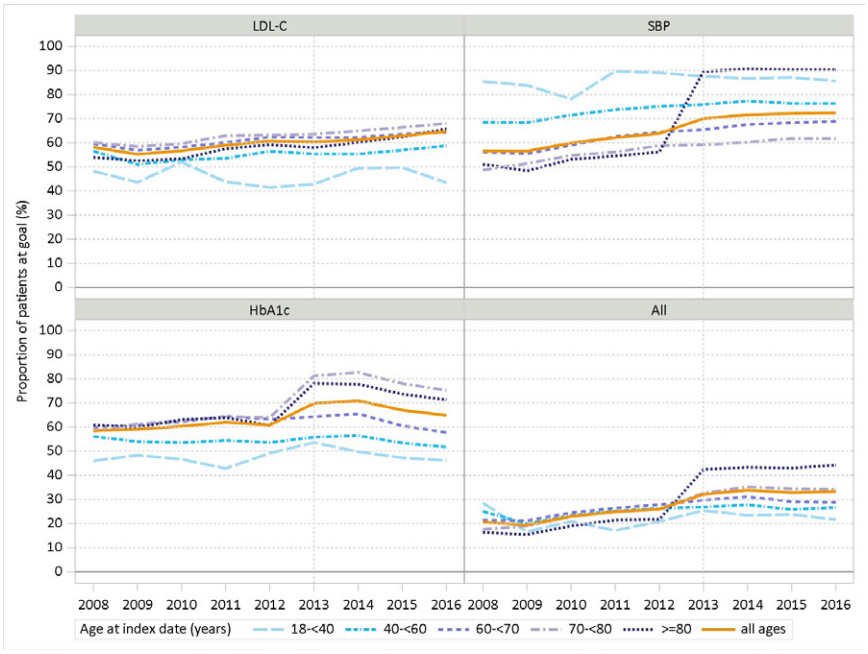


T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease

Risk factor control

Figure 4 shows proportions of patients at goal for LDL-C, SBP, HbA1c, and all risk factors combined over time,

Figure 4. *Risk factor goal attainment per age group*



LDL-C = low-density lipoprotein cholesterol; HbA1c = glycated haemoglobin; SBP = systolic blood pressure

stratified by age group. Overall LDL-C goal attainment rose from 56% in 2009 to 65% in 2016 (p for trend < .0001) (male 60% to 69%, female 50% to 60%, data not shown). Overall SBP goal attainment rose from 57% to 72% (p for trend < .0001), HbA1c goal attainment from 58% to 65% (p for trend < .0001), both similar between the sexes (data not shown). LDL-C and HbA1c goal attainment were considerably lower among the younger age groups, whereas SBP goal attainment was considerably higher. In 2009, 21% of patients attained all goals, which rose to 33% in 2016 (p for trend < .0001). The lowered HbA1c targets for patients over age 70 treated with metformin only caused HbA1c targets to rise sharply in 2013, but this had a very limited effect on combined goal attainment for the age group of 70-80 years. Raised SBP and HbA1c targets for patients over the age of 80 in 2013 caused combined goal attainment to double from 22% to 44% in this group. Combined goal attainment was about 3-4% points lower in women than in men over the entire study period (*Supplemental table 2*).

GLD use

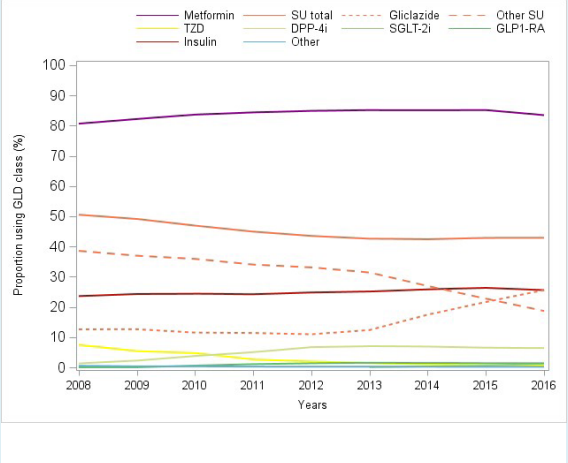
More than 80% of patients used metformin, which increased slowly over the study period (figure 5). The proportion using SUs decreased from 50% in 2008 to 43% in 2016. Between 2012 and 2016, a sharp increase in gliclazide use from about 11% to approximately 25% was observed. The proportion of insulin users was approximately 25%, showing a minimal increase over the whole study period. The proportion of patients using thiazolidinediones dropped from about 7% in 2008 to about 1% in 2012; for DPP-4 inhibitors, the proportions increased from 1% in 2008 to 7% in 2013, after which the proportion stabilised. Other GLD were used by only up to 0.5% of patients.

In total, second-line treatment after ≥ 6 months mono-metformin use was recorded for 4,159 patients during the study period (2008-2016). The proportion starting second-line therapy with SUs dropped from 96% in 2008 to 80% in 2012, then increased to 93% again in 2016 (figure 6). Within the SU class, the use of gliclazide decreased from 23% to 19% until 2012; afterwards, it increased sharply to 88% of all second-line therapy. The second most-used GLD drug class in second-line therapy was DPP-4 inhibitors, which increased until 2012 and then decreased again.

DISCUSSION

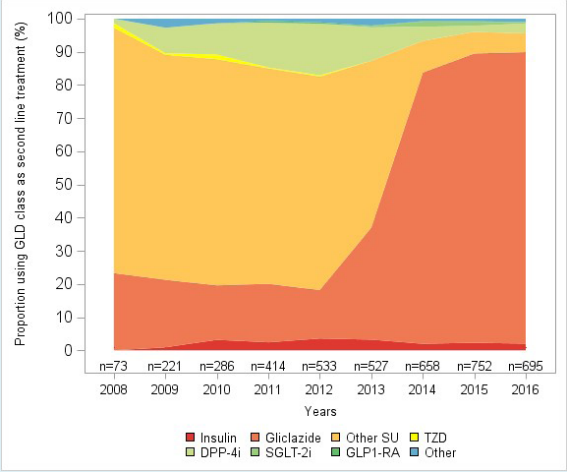
In the Netherlands, loss of life due to T2DM is considerable, averaging 3.5 years at the age of 55 compared to the general population and independent of sex. Diabetes and CVD combined, account for 5 years lost at age 55. Within the diabetes population, CVD accounts for 1.5 to 2 years lost at age 55. CVD is therefore an important driving factor behind diabetes mortality, which is why diabetes treatment guidelines aim to prevent excess mortality through prevention of CVD. Nevertheless, in our cohort of diabetes patients requiring glucose-lowering treatment, incidence rates for hospitalisations for AMI, stroke, and CHF, as well as mortality rates, increased slightly over the

Figure 5. *Proportion using GLD class*



DPP-4i = dipeptidyl peptidase 4 inhibitor; GLD = glucose-lowering drugs; GLP1-RA = glucagon like peptide 1 receptor agonist; SGLT-2i = sodium-glucose co-transporter 2 inhibitor; SU = sulfonylurea derivative; TZD = thiazolidinedione

Figure 6. *Distribution of second-line GLD class initiated after metformin monotherapy*



DPP-4i = dipeptidyl peptidase 4 inhibitor; GLD = glucose-lowering drugs; GLP1-RA = glucagon like peptide 1 receptor agonist; SGLT-2i = sodium-glucose co-transporter 2 inhibitor; SU = sulfonylurea derivative; TZD = thiazolidinedione

study period. Interestingly, this also occurred to a similar extent, in the matched diabetes-free patients, and no obvious trends could be observed in the RRs, suggesting that changes in guidelines did not yet result in reduced CVD or mortality.

Excess risk of AMI and stroke in our study were within the same range as reported by a Swedish study (69% vs. 70% for AMI; 50% vs. 57% for stroke) but excess risk of CHF was higher in our study (185% vs. 80%)[18]. This may be explained by the fact that we based incidence rates of cardiovascular events on hospitalisations only, in order to capture accurate event dates. However, with respect to CHF, there may be some detection bias: patients with T2DM may be referred to a hospital sooner than patients without CHF because GPs may be more vigilant in this population and may suspect CHF sooner. A Spanish study found that despite a 5-fold increase in hospitalisations for CHF in diabetes patients compared to non-diabetes patients, the mortality rate was actually lower,[23] which would aligns with the idea that diabetes patients are referred sooner.

In T2DM patients, incident AMI and mortality are generally reported to be higher for men, similar to our results, but excess risk of cardiovascular morbidity and mortality due to T2DM is usually higher in women compared to men, in contrast to our findings.[2,3,24] A trend of diminishing sex differences among high-income countries has been reported with respect to mortality, cardiovascular outcomes, and treatment.[18,25] Differences in treatment, higher life expectancy of diabetes-free women, as well as a greater decline in risk factors associated with diabetes in women compared to men are all thought to contribute to the sex difference in excess mortality.[2,3,24] LDL-C, SBP, and HbA1c have been shown to be important risk factors for excess mortality in diabetes: non-smokers without albuminuria and LDL-C, SBP, and HbA1c within target ranges were reported to have limited to no excess risk of mortality, AMI, or stroke, although substantial excess risk of heart failure due to T2DM remained.[2,3,26] Access to health care in Scandinavian countries is similar to the Netherlands. It is therefore interesting to note that the number of life years lost by Swedish men is similar to Dutch men and women, but Swedish women had a slightly higher excess mortality, despite declining sex differences since 2006.[18]

In our study, we found that despite modest improvements over time, goal attainment for LDL-C and HbA1c was especially poor in younger patients. Only approximately 25% of patients under the age of 60 have LDL-C, SBP, and HbA1c within target range. This is important, since the Swedish study also suggested there may be greater potential gain for young patients.[26] Results of combined risk factor control and life years lost in our study suggest much can be gained by more aggressive treat-to-target in young patients.[26]

According to our analyses, loss of life years attributable to diabetes is less than 1 year at age 80. Physicians will therefore be less inclined to treat-to-target, which is aligned with the Dutch GP guidelines stating that in elderly patients, prevention of symptomatic hyper- and hypoglycaemic events is the main focus, rather than goal attainment.[5] The raise of HbA1c and SBP targets in the 2013 revision of the guidelines are based on the same principle.[5] It also states that it is up to the GP to convince younger patients to adhere to targets, even if patients prefer not to because of the impact on life style.[5]

Use of GLD was aligned with the position of the Dutch GP guidelines: metformin, SU, and insulin were the most frequently-used medications; new drug types such as DPP-4 inhibitors, GLP1-RA, and SGLT-2 inhibitors were used by fewer than 10% of patients during the entire study period. According to the 2006 guideline, first-line oral GLD should be metformin, and second-line treatment, the addition of SU.[6] The increase in use of DPP-4 inhibitors as second-line treatment over the period 2008-2012 was probably a result of reported lower rates of hypoglycaemic events compared to SU.[27] In 2010, the Dutch GP association discouraged the use of DPP-4 inhibitors and GLP1-RA because of lack of evidence of long-term safety and efficacy.[28] In the 2013, revision of this position was confirmed, and gliclazide was introduced as preferred SU.[5] After 2013, gliclazide use increased substantially, whereas other SU use decreased substantially, and DPP-4 inhibitor use declined slowly. This pattern is especially evident in the initiation of second-line treatment after a minimum of six months metformin monotherapy as first-line treatment. In Sweden, the use of insulin increased by 30% in the period 2006-2013 to 28%, whereas the use of SU decreased by 55%.[18] Relative changes in overall SU use (-14%) and insulin use (+10%) in the Netherlands were very modest.

Even though the Dutch guidelines indicate treatment intensification usually increases treatment satisfaction, the importance of reaching a consensus with the patient is also highlighted.[5] Treatment inertia may be driven in part by reluctance of patients to initiate insulin therapy if targets are not reached with metformin or SU.[29] Basal insulin has long been the only third-line treatment option in the conservative Dutch guidelines, with high adherence.[5,6] In that respect, it is interesting to note that in the 2018 partial revision of the Dutch GP guidelines, third-line treatment options now include GLP1-RA and DPP-4 inhibitors as alternatives to basal insulin. If glycaemic control is not reached with those options, acarbose, SGLT-2 inhibitors,

pioglitazone, or repaglinide may be considered.[30] International guidelines have adopted the use of the new treatment classes as early as second-line treatment[31] and as a result, in many other European countries, their use was incorporated into diabetes type 2 care much earlier and to a greater extent over the past decade.[1,18,32]

Strengths and limitations

The data used for this study come from regular care and were not recorded for research purposes. Completeness of data and detail of information could therefore not be controlled. By matching patients on age, sex, and GP practice, it was ensured that differences in event rates between cohorts with and without T2DM were not driven by differences in recording of events by different GPs.

The study was performed in a database representative of the Dutch population and standard T2DM care in the Netherlands, combining diabetes treatment prescribed in both primary and secondary care. We limited analyses to pharmacologically-treated patients, which excludes approximately 20% of all diabetes patients. This may have led to overestimation of the cardiovascular risk for the entire T2DM population. The slightly higher HbA1c goal attainment reported in this study in comparison to a previous Dutch study covering a different part of the Netherlands, may have been caused by the inclusion of patients not using GLD, who are less severely diseased.[33] Due to transfer of data governance during the study period, coverage of hospitals in the Hospitalisation Database dropped to 85% in 2016. However, this sample of participating hospitals from which data are collected is representative of all Dutch hospitals with regard to type of hospital. Generalisability of our study to the Dutch population was therefore considered good.

The majority of HbA1c and LDL measurements were retrieved from GPs. Clinical laboratory data were used to complete those measurements for patients in secondary care (5-10% of patients), but these records were not available for all patients. This may have led to an underrepresentation of patients with poor glycaemic control and high cardiovascular risk for this subset. Furthermore, assessments of HbA1c, LDL, BMI, and BP in GP records were more frequently recorded over time, probably due to health insurance companies reimbursing GPs for the quality of record keeping when the GP is the primary treating physician in the management of T2DM, per incentives that were introduced in 2010. In general, we assume that GPs may have been more likely to record patients off target than those on target before 2010. If recording proportions increase due to the 2010 introduced incentives, this may account for more patients who are registered at target. Therefore, we may have underestimated goal attainment at the start of the study period. The risk factors albuminuria and smoking were not included in our study. The increased prevalence of comorbidities over the study period is observed in both T2DM and control cohorts; therefore, this may be attributed to increasing age and disease duration, rather than improved recording practices.

Although mortality rates in the general Dutch population are reported to decrease over time,[34] we observed a slight increase in our control cohort. The fact that we analysed an ageing subgroup of the general population might explain this difference, because younger age groups were underrepresented and therefore grouped together for standardisation. As the aim was to compare our cohorts, age standardisation can serve to compare rates with other diabetes studies, but not with general populations.

Adherence to guidelines has remained strong over the past decade, which is reflected in the conservative choices of treatment, indicating alignment with changing guidelines. During the study period, around two-thirds of patients attained goals for HbA1c, BP, and LDL-C. Despite these signs of good quality in diabetes care, only one in three reached combined goal attainment in 2016. Event rates of cardiovascular events and mortality increased over time, although the increase in T2DM patients was proportional to that in the diabetes-free population and no clear trend could be observed for RR. T2DM shortens a 55-year-old patient´s life expectancy by 3.5 years, irrespective of sex. The presence of cardiovascular complications reduces the number of life years by an additional two years at the age of 55. Trends in excess cardiovascular events and mortality due to T2DM were similar to those found in Sweden, although sex differences were absent. Poor risk factor control below the age of 60 suggests that major gains may be expected from further improving cardiovascular risk factor control in diabetes patients.

DISCLOSURES

Acknowledgements

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Conflicts of interest

Edith M. Heintjes, Eline Houben, Fernie J.A. Penning-van Beest, and Ron M.C. Herings are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies.

Wendy L. Beekman-Hendriks, Esmé Lighaam, and Susanne Cremers are employees of AstraZeneca BV, the Netherlands, working as Medical Evidence Delivery

Manager and Medical Advisors Cardiovascular, Renal & Metabolism, respectively.
Coen Stehouwer is Professor of Internal Medicine at Maastricht University Medical Centre and declares no duality of interest.

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Previous publications: Some of the study results were presented as a poster at the European Associate for the Study of Diabetes meeting held October 1st – 4th, 2018 in Berlin, Germany; and as an oral presentation at The Professional Society for Health Economics and Outcomes Research Europe 2018 Conference held November 10-14th, 2018 in Barcelona, Spain; as well as the Annual Dutch Diabetes Research Meeting 2018 held November 28-29th, 2018 in Oosterbeek, the Netherlands.

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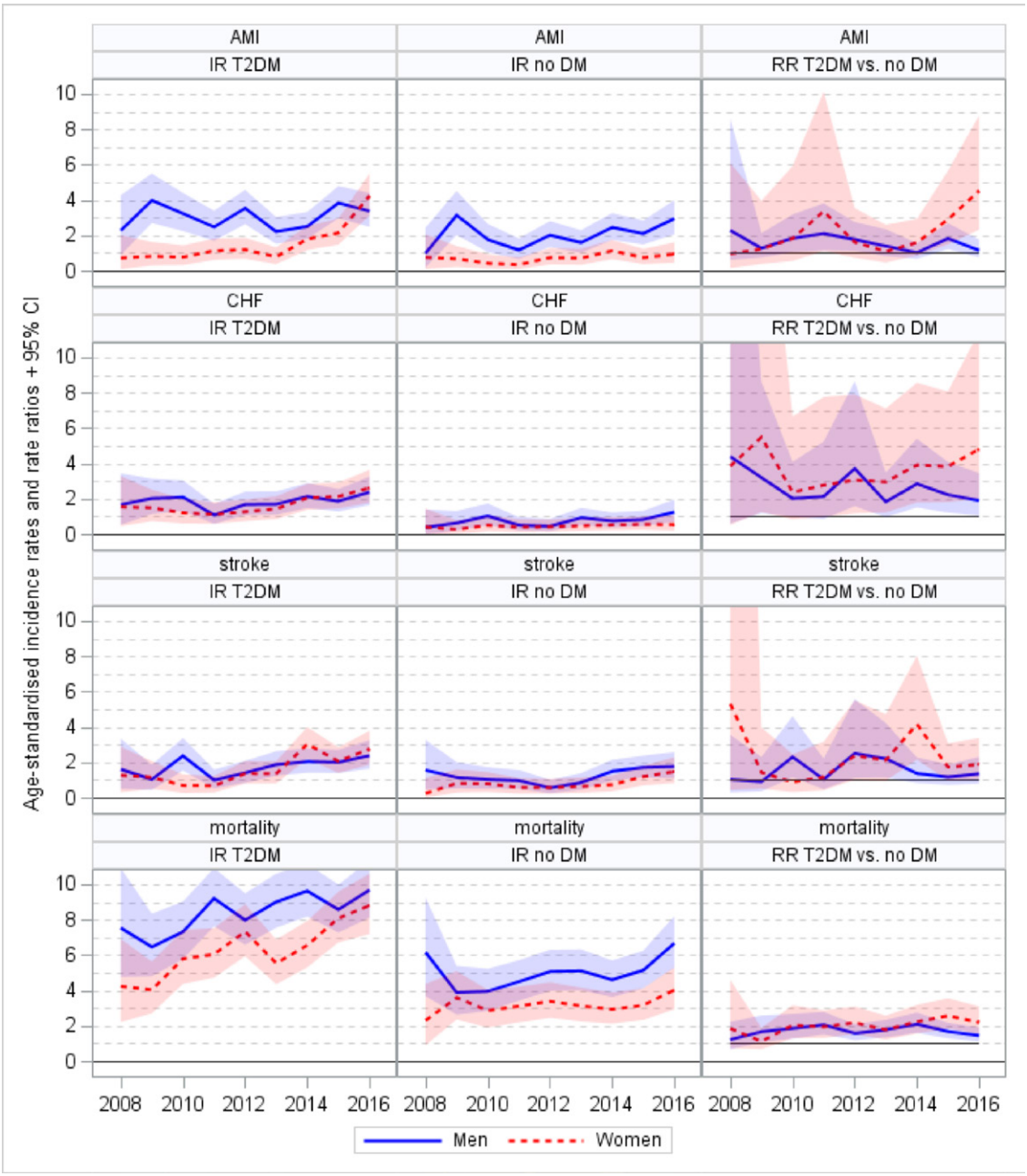
Supplemental files

Supplemental figure 1. *Sex-stratified age-standardised IR and RR of major cardiovascular events and mortality, T2DM vs. no DM*



AMI = acute myocardial infarction; CHF = congestive heart failure; CI = confidence interval; DM = diabetes mellitus, IR = incidence rates; RR = rate ratio; T2DM = type 2 diabetes mellitus

Supplemental table 1. *Characteristics of matched controls without diabetes per annual cohort*

	2008 n = 6,291	2009 n = 16,184	2010 n = 21,459	2011 n = 26,326	2012 n = 29,017	2013 n = 29,801	2014 n = 32,742	2015 n = 35,034	2016 n = 27,796	p for trend
Male sex, n (%)	3,189 (51)	8,475 (52)	11,289 (53)	13,874 (53)	15,339 (53)	15,758 (53)	17,493 (53)	18,980 (54)	15,239 (55)	<.0001
Age, mean ± SD	65 ± 11	66 ± 11	66 ± 11	67 ± 11	67 ± 11	67 ± 11	68 ± 11	68 ± 11	69 ± 11	<.0001
Morbidity[a], n (%)										
Any CVD	769 (12)	2,320 (14)	3,257 (15)	4,345 (17)	5,106 (18)	5,546 (19)	6,471 (20)	7,406 (21)	6,412 (23)	<.0001
AMI	187 (3)	555 (3)	803 (4)	1,060 (4)	1,292 (4)	1,429 (5)	1,728 (5)	1,994 (6)	1,774 (6)	<.0001
AP	339 (5)	1,023 (6)	1,469 (7)	1,918 (7)	2,332 (8)	2,495 (8)	2,879 (9)	3,178 (9)	2,730 (10)	<.0001
CHF	83 (1)	234 (1)	364 (2)	515 (2)	579 (2)	663 (2)	798 (2)	938 (3)	848 (3)	<.0001
Ischaemic stroke	265 (4)	775 (5)	960 (4)	1,271 (5)	1,408 (5)	1,464 (5)	1,682 (5)	2,023 (6)	1,747 (6)	<.0001
PAD	159 (3)	495 (3)	730 (3)	1,026 (4)	1,317 (5)	1,601 (5)	1,909 (6)	2,210 (6)	2,013 (7)	<.0001
Cancer	320 (5)	937 (6)	1,434 (7)	2,033 (8)	2,644 (9)	3,109 (10)	3,926 (12)	4,563 (13)	3,980 (14)	<.0001
Co-medication										
Antihypertensives	1,412 (22)	4,843 (30)	6,790 (32)	8,791 (33)	10,042 (35)	10,772 (36)	12,167 (37)	13,224 (38)	10,997 (40)	<.0001
Statins	696 (11)	2,373 (15)	3,363 (16)	4,551 (17)	5,444 (19)	6,140 (21)	7,183 (22)	8,086 (23)	6,952 (25)	<.0001
Platelet aggregation inhibitors	605 (10)	2,027 (13)	2,793 (13)	3,685 (14)	4,290 (15)	4,653 (16)	5,155 (16)	5,679 (16)	4,757 (17)	<.0001
BMI[b]										
Recorded, n (%)	478 (8)	1,580 (10)	2,714 (13)	4,199 (16)	5,186 (18)	6,512 (22)	8,717 (27)	10,707 (31)	9,665 (35)	<.0001
Mean kg/m2 ± SD	27 ± 4	28 ± 4	28 ± 4	28 ± 4	27 ± 4	27 ± 4	27 ± 4	27 ± 4	27 ± 4	0.1490
HbA1c[b]										
Recorded, n (%)	265 (4)	949 (6)	1,461 (7)	2,519 (10)	3,007 (10)	2,868 (10)	3,269 (10)	3,554 (10)	2,606 (9)	<.0001
Mean mmol/mol ± SD	39 ± 4	39 ± 4	40 ± 4	40 ± 6	41 ± 7	41 ± 7	41 ± 7	41 ± 7	42 ± 8	<.0001
LDL-C[b]										
Recorded, n (%)	1,318 (21)	4,280 (26)	6,164 (29)	8,443 (32)	10,093 (35)	11,083 (37)	13,300 (41)	15,393 (44)	13,421 (48)	<.0001
Mean mmol/l ± SD	3.2 ± 1.0	3.3 ± 1.0	3.2 ± 1.0	3.2 ± 1.0	3.2 ± 1.0	3.2 ± 1.0	3.1 ± 1.0	3.1 ± 1.0	2.9 ± 1.0	<.0001
Systolic BP[b]										
Recorded, n (%)	1,557 (25)	4,067 (25)	6,605 (31)	8,955 (34)	10,304 (36)	11,432 (38)	13,899 (42)	15,797 (45)	13,132 (47)	<.0001
Mean mmHg ± SD	143 ± 17	143 ± 17	142 ± 17	141 ± 17	140 ± 17	139 ± 17	139 ± 16	139 ± 16	139 ± 16	<.0001
Diastolic BP[b]										
Recorded, n (%)	1,547 (25)	3,911 (24)	6,538 (30)	8,913 (34)	10,271 (35)	11,366 (38)	13,847 (42)	15,726 (45)	13,077 (47)	<.0001
Mean mmHg ± SD	81 ± 9	81 ± 9	81 ± 9	80 ± 9	80 ± 9	79 ± 9	79 ± 9	79 ± 9	79 ± 9	<.0001

[a] Recorded in all available history; [b] Last recorded in the year prior to index date; [c] According to the GP guidelines, applicable at that time in the Netherlands and relative to known values only.
AMI = acute myocardial infarction; AP = angina pectoris; BMI = body mass index; BP = blood pressure; CVD = cerebrovascular disease; CHF = congestive heart failure; HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral artery disease

Supplemental table 2. *Risk factor goal attainment stratified by sex*

Risk factor	Sex	N	2008	2009	2010	2011	2012	2013	2014	2015	2016
LDL-C	Male	$N_{recorded}$	2,139	6,078	8,352	10,972	12,218	12,441	14,200	16,182	13,361
		$n_{at\ goal}$ (%)	1,328 (62)	3,629 (60)	5,077 (61)	6,955 (63)	7,954 (65)	8,069 (65)	9,322 (66)	10,850 (67)	9,157 (69)
	Female	$N_{recorded}$	2,107	5,523	7,424	9,724	10,815	11,068	12,354	13,723	11,062
		$n_{at\ goal}$ (%)	1,142 (54)	2,781 (50)	3,865 (52)	5,250 (54)	6,031 (56)	6,111 (55)	6,934 (56)	7,949 (58)	6,642 (60)
SBP	Male	$N_{recorded}$	1,917	5,254	8,100	10,519	11,920	12,309	14,420	16,301	13,282
		$n_{at\ goal}$ (%)	1,112 (58)	2,998 (57)	4,841 (60)	6,624 (63)	7,688 (64)	8,503 (69)	10,195 (71)	11,592 (71)	9,485 (71)
	Female	$N_{recorded}$	2,037	5,011	7,540	9,712	10,915	11,232	12,769	14,095	11,148
		$n_{at\ goal}$ (%)	1,128 (55)	2,808 (56)	4,526 (60)	5,935 (61)	6,893 (63)	7,980 (71)	9,271 (73)	10,338 (73)	8,185 (73)
HbA1c	Male	$N_{recorded}$	2,093	5,969	8,424	11,635	13,040	13,317	15,149	17,030	13,833
		$n_{at\ goal}$ (%)	1,224 (58)	3,522 (59)	5,040 (60)	7,165 (62)	7,954 (61)	9,157 (69)	10,601 (70)	11,222 (66)	8,887 (64)
	Female	$N_{recorded}$	2,128	5,524	7,687	10,402	11,641	11,783	13,165	14,431	11,412
		$n_{at\ goal}$ (%)	1,245 (59)	3,268 (59)	4,680 (61)	6,491 (62)	7,065 (61)	8,357 (71)	9,480 (72)	9,853 (68)	7,496 (66)
All combined	Male	$N_{recorded}$	1,358	4,309	6,817	9,300	10,660	11,058	12,924	14,695	11,994
		$n_{at\ goal}$ (%)	323 (24)	913 (21)	1,651 (24)	2,477 (27)	3,000 (28)	3,718 (34)	4,616 (36)	4,993 (34)	4,136 (34)
	Female	$N_{recorded}$	1,454	4,110	6,208	8,444	9,639	10,027	11,391	12,639	10,080
		$n_{at\ goal}$ (%)	256 (18)	722 (18)	1,336 (22)	1,939 (23)	2,263 (23)	3,052 (30)	3,619 (32)	3,974 (31)	3,213 (32)

HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure

ORIGINAL ARTICLE

Perspectives on the preventability of emergency department visits by older patients

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This study was presented as an oral presentation at the European Society for Emergency Medicine 2018 conference on September 10th, 2018 in Glasgow, United Kingdom.

ABSTRACT

Background: Older people increasingly demand emergency department (ED) care. ED visits have a profound impact on older patients, including high risk of adverse outcomes and loss of independency. In this study, we evaluated the opinions of patients, caregivers, general practitioners, and ED physicians on the preventability of ED visits.

Methods: Prospective, mixed-method observational and qualitative study of 200 patients aged ≥ 70 years visiting a teaching hospital ED in the Netherlands. Semi-structured interviews were performed with patients, caregivers, and general practitioners. ED physicians were provided with written surveys. Patient data were extracted to determine vulnerability.

Results: The mean age of the patients was 79.6 years; 49.5% were male. Ninety-five percent lived independently before the ED visit. Most patients reported domiciliary care (23%), a caregiver (21.5%), or both (29.5%). Patients considered 12.2% of visits potentially preventable, caregivers 9%, general practitioners 20.7%, and ED physicians 31.2%. Consensus on preventability was poor, especially among patients and professionals. While patients most frequently blamed themselves, healthcare providers predominantly mentioned lack of communication and organisational issues as contributing factors.

Conclusion: Patients and caregivers consider an ED visit preventable less frequently than professionals do. Little consensus was found among patients and healthcare providers, and the perspectives on contributing factors to a preventable visit differ between groups. To help improve geriatric emergency care, future studies should focus on why these perspectives are so different and aim to align them.

KEYWORDS

Caregiver, emergency department, geriatrics, preventability

INTRODUCTION

Background

Our population is ageing, and older people represent an increasing proportion of patients who visit the emergency department (ED).[1-5] In the Netherlands, ED visits by older patients are also increasing. This may be associated with recent changes in Dutch healthcare such as the reduction of nursing home beds, resulting in (potentially vulnerable) older people living independently at home for a longer period of time.[6]

Older patients frequently suffer from multiple conditions,[7-9] often accompanied by polypharmacy.[7] In addition, older ED patients generally have atypical clinical presentations, more serious illnesses, higher diagnostic test use, and require more staff time and overall resources when compared with younger patients. Consequently, older age is associated with a longer ED length of stay (LOS) and a higher admission rate, both of which contribute to ED crowding.[1-4] ED crowding is in turn, linked to prolonged ED LOS, reduced quality of care, impaired access, and an increased risk of adverse events. In addition, crowding is a financial burden for both patients and healthcare institutions.[10,11]

An ED visit can also have a profound impact on patients themselves; for example, more than one in three older patients experience an adverse outcome within 90 days of ED discharge.[12] Furthermore, ED admissions often lead to a decline in independency.[13,14]

Preventing certain ED visits—when possible—with active and personalised interventions in the acute care chain may be more patient-friendly and cost-effective than usual care. To achieve this, it is important to identify contributing factors that lead to 'preventable' ED visits. Unfortunately, there is no generally recognised definition of preventable ED visits. This could in part, be explained by the fact that perspectives on preventability are system-dependent and rely on how acute care is organised. Consequently, viewpoints are expected to be different between countries. Real-time perspectives of patient and healthcare workers on preventability of ED visits may provide important insights.[15-17] Therefore, we performed this prospective, observational study on the preventability of 200 ED visits by patients aged 70 years and older in a Dutch teaching hospital.

The objective of this study was to evaluate the opinions of patients, their caregivers, ED physicians (EPs), and general practitioners (GPs) on the preventability of an ED visit.

MATERIALS AND METHODS

Study design and setting

In the Netherlands, primary healthcare is well developed and accessible for patients 24 hrs a day. General practitioners (GPs) serve as gatekeepers to hospital care. During office hours, patients can consult their own GP, usually obtaining an appointment that day. After-hours primary care is provided through GP cooperatives.[10] The majority of ED patients are referred by their GP or by ambulance. Self-referrals compromise a small minority.[11] This prospective, mixed-method observational and qualitative study took place in a regional teaching hospital in the Netherlands with a yearly ED attendance of 25,000 patients in 2017; 31% of patients were ≥ 70 years of age. Data collection took place between July 24th and September 7th, 2017. The study was approved by the institutional Ethics Committee of VieCuri Medical Centre, Venlo, the Netherlands.

Patients

All patients ≥ 70 years of age who visited the ED in the study period were eligible for inclusion. Trauma-related ED visits were excluded except for visits involving a fall, because it was assumed that older people who, for example, suffer from a traffic accident, are less vulnerable. Patients were also excluded if they were not able to give written informed consent and if no legal representative was present, or if a language barrier was present. All patients gave written consent prior to the interview. Patients were included only during the time the site researcher (MV) was present. To reduce selection bias, MV worked in five random eight-hour shifts per week, both during office hours and after hours, including weekend days.

Sample size justification

To our knowledge, this was the first study to investigate the perspectives of patients and their caregivers on their ED visit, so it was not possible to conduct a power analysis. Therefore, inclusion was stopped after reaching 200 cases, which is similar to comparable studies on patient perspectives on preventability of readmissions.[15-17] Moreover, the sample size and sampling method (true random sampling) we used were shown to be the best method in a study which compared four sampling methods for observational studies in the ED. It represented the overall population for more than 95% of the samples and the probability of selection bias was low.[18]

The primary outcome was defined as if the patient, caregiver, GP, and EP considered an ED visit preventable or not. Secondary outcomes were consensus of preventability and the qualitative data derived from the interviews. Our hypothesis was that professionals would consider an ED visit preventable more often than patients and their caregivers.

Data collection

Data were collected from semi-structured interviews with the patients, their caregivers, and GPs by MV, the first author of this manuscript. The interviews were tested in a pilot patient group before we agreed on a final version. MV is a female medical master student (BSc) with two years of clinical experience. During the study period, MV was not directly involved in patient care. Interviews took place in each patient's room and lasted approximately 30 minutes (duration was not recorded). Patients and caregivers (defined as a person providing unpaid intensive and long-term care because of a personal relationship) were not separated during the interview. Before the interview commenced, participants were informed that the researcher aimed to assess their opinions about the ED visit, but they were not informed about the hypothesis of the study group. Subsequently, patients and providers were asked about the reason for the ED visit and whether they thought the ED visit could have been prevented, which was questioned in the following way: "Do you feel the current ED visit was preventable in any manner, by anyone?". Possible options were "yes", "no", or "unknown". All interviewees were asked which event(s) had led to the ED visit and what could have been done to prevent this visit. It was possible to appoint more than one event. In addition, the vulnerability of the patient was determined by a combination of questions (see Appendix A for the questionnaire). During the interview, field notes were

recorded by the interviewer. No repeat interviews took place. EPs (who were the physicians caring for the patient in the ED and included both board-certified EPs and junior physicians in different specialties) were provided with written surveys. A semi-structured interview was held with the GP by telephone. If the patient's personal GP was not available, the locum GP was consulted. Subsequently, the answers were clustered into categories (open coding followed by axial coding; see Appendix B) by MV and an EP (author DB). In cases of disagreement, an internist (author FS) was consulted. No feedback was provided to participants on the findings.

Apart from the interviews, a structured medical record review was performed in which information was collected regarding vulnerability, comorbidity, and medication. We defined polypharmacy as the concomitant use of five or more drugs.[19] Different scores (such as the Charlson Comorbidity Index [CACI][20] and the Acutely Presenting Older Patient [APOP] score)[21] were calculated, combining information from the interviews and the medical record. Office hours were defined as weekdays between 08.00 hrs and 16.59 hrs. Out-of-office hours were weekdays between 17.00 hrs and 07.59 hrs and during the weekend.

Statistical analysis

Baseline characteristics were presented as the number and percentage for categorical variables and as mean and standard deviation (SD) for continuous variables (in case of a non-normal distribution, we presented median [range]). For analysis of preventability in subgroups (triage category, way of referral, cognitive decline, etc.), we used the Pearson's chi-square and Fisher's exact test for dichotomous and categorical data. The Mann-Whitney U test was used for continuous variables. Differences were considered statistically significant at a p -value of less than 0.05. Cohen's kappa (κ) was used to measure agreement of preventability assessments (options "yes", "no", and "unknown") separately for each pair of four interviewed groups. We defined kappa values between 0.00 and 0.20 as slight agreement, between 0.21 and 0.40 as fair agreement, between 0.41 and 0.60 as moderate agreement, between 0.61 and 0.80 as substantial agreement, and between 0.81 and 1.00 as almost perfect or perfect agreement.[22] Statistical analysis was performed in IBM Statistics SPSS V.22.0.

RESULTS

Patient characteristics

During the study period, 372 eligible patients aged ≥ 70 years visited the ED during the time MV was present, of whom 200 were included (inclusion rate of 53.8%).

Table 1. *Baseline characteristics*

Patient characteristics (n = 200)	Number (%)
Age, median	79.0 (73-85)
Gender	
Male	99 (49.5)
Female	101 (50.5)
Presenting time	
Office hours	158 (79.0)
After hours	42 (21.0)
Arrival	
By ambulance	26 (13.0)
Referred by GP	
By ambulance	96 (48.0)
Own transport	47 (23.5)
Referred by specialist	24 (12.0)
Other	7 (3.5)
Speciality±	
Internal medicine	53 (26.5)
Surgery	52 (26.0)
Neurology	26 (13.0)
Pulmonary medicine	23 (11.5)
Orthopaedics	18 (9.0)
Gastroenterology	17 (8.5)
Urology	11 (5.5)
Length of stay (min), mean	184.6 (SD: 75.1)
CACI score, mean (19)	5.4 (SD: 1.96)
APOP score, median (20)	
Risk of functional decline	28.0% (range 17-45)
Mortality risk	7.0% (range 3-14)
Official diagnosis cognitive impairment*	7 (3.5)
Polypharmacy	
Yes	139 (69.5)
Medication-related visit	24 (8.0)
Fall-related visit	48 (24.0)
Fall in last 6 months#	
Yes	99 (49.5)
Living situation	
Independent	190 (95.0)
Nursing home	10 (5.0)
Care at home	
None	52 (26.0)
Domiciliary care	46 (23.0)
Caregiver	43 (21.5)
Both	59 (29.5)
Discharge disposition	
Home	88 (44.0)
Admission	110 (55.0)
General ward	102 (92.7)
High care unit	8 (7.3)
Other institution	2 (1.0)

GP = general practitioner; CACI = Charlson Age-Comorbidity Index; APOP = Acutely Presenting Older Patient (risk of functional decline or mortality in three months); SD = standard deviation
*Diagnosed by geriatrician. # Including the present ED visit. ± Patients could not be registered for the specialty emergency medicine.

The reasons for exclusion (n = 172) were trauma-related (n = 81; 47%), participation refusal (n = 31; 18%), no possibility of obtaining informed consent (n = 31; 18%), language barrier (n = 19; 11%), and other (i.e., too ill or nonresponsive; n = 10; 6%). In the study period, 456 eligible patients were missed because the site researcher (SR) was not present. The median age of participants was 79.0 years (range 73-85 years), 50.5% were female, and 79% presented during office hours. Most (95%) lived independently before the ED visit. Twenty-three percent of patients reported domiciliary care, 21.5% a caregiver, and 29.5% both. A large proportion (69.5%) used five or more drugs at the time of the ED visit. The mean CACI score was 5.4 (SD: 1.96), and the median risks of functional decline and mortality according to the APOP score were 28.0% (range 16-45) and 7.0% (range 3-14), respectively. Patient characteristics are summarised in table 1.

The primary ED diagnoses for each visit were clustered into major clinical categories (table 2). Injury and poisoning were the most common diagnoses (25.0%); of these, 50.0% were categorised as a fracture, 24.0% as cerebral concussion, and 26.0% involved other injuries (e.g., wounds, contusions). Nonspecific diagnoses, relating to "symptoms, signs, and ill-defined conditions", represented 20.5% of diagnoses and usually referred to general symptoms, such as malaise and fatigue (29.3%), syncope (17.1%), abdominal pain (12.2%), and unspecified fever (12.2%). Diagnoses related to the circulatory, digestive, and respiratory system accounted for 11.0%, 11.0%, and 9.5% of diagnoses, respectively.

Table 2. *Primary ED diagnoses for older adults, major clinical categories**

Disease/disorder category	%	n
Injury and poisoning	25.0	50
Symptoms, signs, and ill-defined conditions	20.5	41
Diseases of the circulatory system	11.0	22
Diseases of the digestive system	11.0	22
Diseases of the respiratory system	9.5	19
Diseases of the genitourinary system	4.5	9
Endocrine, nutritional, and metabolic diseases	3.5	7
Diseases of the blood	3.0	6
External causes of morbidity and mortality	3.0	6
Diseases of the nervous system	2.5	5
Diseases of the musculoskeletal system and connective tissue	2.5	5
Infectious and parasitic diseases	2.5	5
Neoplasms	0.5	1

*Derived from: World Health Organization. (2004). ICD-10: international statistical classification of diseases and related health problems: 10th revision, 2nd ed. World Health Organization.
ED = emergency department

Table 3. *Preventability according to the interviewed groups*

Group	Answer	Number (%)	95%-confidence interval
Patients (n = 188)	Yes	23 (12.2)	7.5-16.8
	No	123 (65.4)	58.6-72.1
	Don't know	43 (22.3)	16.4-28.3
Caregivers (n = 100)	Yes	9 (9.0)	3.4-14.6
	No	63 (63.0)	53.5-72.5
	Don't know	28 (28.0)	19.2-36.8
General practitioners (n = 174)	Yes	36 (20.7)	14.7-26.7
	No	109 (62.6)	55.4-69.8
	Don't know	29 (16.7)	13.9-19.5
ED physicians (n = 199)	Yes	62 (31.2)	24.8-37.6
	No	127 (63.8)	57.1-70.5
	Don't know	10 (5.0)	3.5-6.5

ED = emergency department

Preventability

Patients regarded 12.2% of ED visits preventable, caregivers 9%, GPs 20.7%, and EPs 31.2%. The assessment per interviewed group is listed in table 3. EPs were more likely to consider visits preventable during office hours than during after-hours (34.4% [54 of 157] vs 19.0% [8 of 42]; p = 0.001). The experience of the EPs was also relevant to their judgment: board-certified EPs considered the visits preventable significantly more often than did junior doctors (45.8% vs 26.5%; p = 0.033). Subgroup analyses for triage category, referral by a locum GP, polypharmacy, APOP score, CACI score, cognitive decline, living situation, and medical specialty showed no significant differences. Also, no difference was found between patients who were admitted and discharged from the ED.

Consensus on preventability of ED visit (κ)

Table 4 shows Cohen's kappa for the consensus on the opinions among the interviewed groups. None of the

Table 4. *Consensus on preventability of ED visit*

Consensus among interviewed groups	Kappa (κ)
Patient – caregiver	0.299
Patient – GP	0.013
Patient – ED physician	0.084
Caregiver – GP	0.032
Caregiver – ED physician	0.109
GP – ED physician	0.255

GP = general practitioner; ED = emergency department

kappas were satisfactory; they were all below κ = 0.3. The poorest agreement was found between patient and GP and between caregiver and GP, with κ = 0.013 and κ = 0.032, respectively. The highest kappa was found for patient and caregiver and for GP and EP, with a rate of κ = 0.299 and κ = 0.255, respectively.

Patients' and providers' perceptions

Qualitative data derived from interviews with patients, caregivers, GPs, and EPs revealed different perspectives between the groups. Participants who answered "yes" or "unknown" on the question about the preventability of an ED visit were included in this analysis. For all interviewees, it was possible to sum up multiple causes. The patients who answered "yes" or "don't know" (n = 65) most frequently blamed themselves for the visit, saying they should have called for help earlier or should have been more careful to prevent themselves from falling (17/65). Other frequently mentioned causes by patients were related to hospital care (i.e., early discharge and better follow-up [13/65]) or primary care (i.e., fall prevention, other/earlier intervention [10/65]). Caregivers (n = 37) frequently mentioned that the ED visit could have been prevented if the GP had acted earlier (10/37), if hospital doctors had communicated better with the patient during an earlier admission (6/37), or if they had not discharged the patient too early (5/37). GPs (n = 65) often wanted to refer a patient to a specialist but could not obtain an appointment that met their expectations in terms of timeframe, thus ultimately sending the patient to the ED (19/65). Also, GPs mentioned patient-related factors, such as avoiding care (9/65) or calling the ambulance instead of the GP (5/65). EPs (n = 72) most often mentioned aspects of GP care as a contributing factor, stating that the GP could have visited the patient earlier (5/72), could have treated the patient him/herself (9/72), or would not have referred the patient to the ED after a more thorough discussion with the patient and his/her family (4/72). EPs thought better communication between GPs and specialists could have prevented some visits as well (12/72).

DISCUSSION

The purpose of this present study was to assess the opinions of the patient, caregiver, GP, and EP on the preventability of an ED visit. Patients considered 12.2% of their ED visits preventable. Caregivers, GPs, and EPs regarded ED visits as preventable (9.0%, 20.7%, and 31.2%, respectively). Patients and caregivers, and GPs and EPs had the highest consensus, but their kappa measurements were still very poor. Although patients most frequently blamed themselves, healthcare providers predominantly mentioned lack of communication and organisational issues as contributing factors to preventable ED visits in older patients.

ED patient profiles

To our knowledge, this is the first study to assess the preventability of ED visits by using perspectives of patients and their providers. However, it is not the first study to define the older population in the ED. Median age, gender distribution, and reasons for ED visits are comparable with previous studies.[5,21,23] In our cohort, 24% of ED visits were fall-related, and almost half of our patients (49.5%) experienced a fall in the six months prior to their visit, which confirms findings of previous studies.[1,2,24] In addition, the polypharmacy rate was in agreement with earlier studies in older ED patients.[1,7] Both the mean CACI score of 5.4 (which means the estimated relative mortality risk in our group was higher than 6.38% [CI: 3.07-13.2]) and the high median risks of functional decline and of mortality measured by the APOP score show the high degree of vulnerability in our study population.[20,21] Despite being vulnerable, almost all patients lived independently (95%).

Preventability

Nearly all previous studies on patients' perspectives on preventability assessed readmissions.[15,16,25,26] One study did investigate the preventability of ED visits, but that study's objective was to understand the patient's perspective on the circumstances that led to the ED visit, not the preventability of the visit. It did not include all stakeholders and questioned patients retrospectively.[27] A recent British study estimated that 19.4% of ED attendances could be avoided, based on a survey filled in by senior consultants within the ED. According to their analysis, ED visits of patients older than 65 years (5%) were less likely to be deemed avoidable than those in patients younger than 16 years (34.9%) or adults aged 16 to 64 years (18.5%).

However, the researchers' method of determining this was completely different from that in our study. We also believe that some of the items in the checklist used to define appropriate ED visits are not exclusively linked to appropriateness, such as arrival by ambulance or overnight stay in a facility. Older people are sometimes admitted for nonmedical reasons, which does not directly mean the ED visit was appropriate.[28]

In our study, EPs considered 31.2% of ED visits preventable, which means they believed that these patients could have been managed effectively by other health service providers. If one in three ED visits by older patients can be diverted or prevented, this would benefit both patients and EDs. The high percentage of preventability attributed by EPs is probably due to their knowledge about alternatives to hospital care. This hypothesis is strengthened by the fact that EPs were more likely to consider ED visits preventable during office hours than during after-hours (34.4% vs 19.0%). However, hindsight bias might have played a role in the EPs' judgment of preventability: in cases of negative diagnostic testing, the post-test probability of regarding an ED visit preventable is much higher than the pre-test probability (which is applicable to GPs). This may be the reason why GPs considered ED visits less-often preventable than their hospital colleagues, even though some of the GPs also knew the ED visit outcome when they were interviewed. Only 1:8 patients and 1:10 caregivers thought their visit was preventable. Poor consensus was found among the different groups. Patients and caregivers agreed most often, probably because of their similar perspectives. The same applies to the perspectives of GPs and EPs, who likely have similar professional views. Little agreement was found between patients and GPs and in particular, between caregivers and GPs. This confirms previous studies on the preventability of readmissions, which also show little consensus among patients and professionals.[25] Ideally, patients and providers speak the same language, resulting in better agreement between patients and providers toward their expectations of emergency care. It would be interesting to investigate whether better communication and/or shared decision making improves consensus and lowers utilisation of emergency care services.

Limitations

This study has several limitations. First, the SR was not present 24 hours per day. To reduce selection bias, the SR was scheduled in random shifts. This 'true random sampling' method has been shown to represent the overall population for more than 95% of the samples and it has a low probability of selection bias.[18] To assess generalisability, we compared our study population with all eligible patients who visited the ED in the same study period. Almost all patient characteristics were comparable, except for the presenting time; the study's patients presented more frequently during office hours (79.0% vs 31.7%). Only few previous studies described the time of ED presentation and showed that most older people presented during weekdays (71.9%),[5] especially in the morning and late afternoon.[2] Second, education level and possible cognitive impairment were not measured systematically. These could have been influencing factors in the selection of participants. Third, the number of respondents varied between groups, with the smallest numbers in the caregiver and GP group. Half of the patients did not have a caregiver, and 13% of the GPs refused to participate in the study. Fourth, this was a single-site study, which reduces the generalisability of our findings to other hospitals or countries. Fifth, we included only Dutch-speaking patients, which could be a limitation because of the increasing multicultural aspect of our society. Sixth, trauma-related visits (except for those involving a fall) were excluded as it was assumed that these patients are generally less vulnerable. The exclusion of non-fall related injuries may have caused some bias as not all older patients who, for example, drive a car are fit, and some accidents might have been preventable. This would be an interesting topic for future research. In addition, for the qualitative part of the study, we did not assess whether saturation was reached. However, because of the extensive sample size of 200 patients the probability of data saturation is high. During the interview, no audio or visual recording was used to collect data. Instead, the input was collected by field notes and subsequently categorised. The results of the qualitative part of our study should therefore be interpreted with caution. Finally, patients and caregivers were not separated during the interview and could have influenced each other's answers. However, the low kappa measurement shows great nonconformity between the groups.

To be improve upon our findings, future studies should be multi-centre, with a better balance of patients who present during office hours and after hours. There should also be more focus on the reasons for the disparity between the perspectives of all stakeholders, which, for example, can be assessed through focus group research. Finally, it should be investigated whether better communication and/or shared decision making improves consensus among patients and providers and subsequently lowers ED visits.

CONCLUSIONS

In this study, patients and caregivers consider an ED visit preventable less frequently than professionals, who consider a visit preventable in almost one-third of all visits. Little consensus is found among professionals and

patients or their caregivers, and all groups have different perspectives on the contributing factors of a preventable visit. To our knowledge, this is the first study to provide insight into the preventability of ED visits in the elderly according to patients, their caregivers, GPs, and EPs. To help improve geriatric ED care, future studies should focus on the differences between the opinions of patients and providers and how to align those involved in care.

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APPENDIX A

An overview of the questions asked to determine the vulnerability of older patients visiting the emergency department.
How many different types of medication do you think you use?
Did you experience a fall during the last six months? If yes, how many times?
Have you been admitted to a hospital during the last six months?
How is your current living situation? (Living independently or in a facility; if living independently, differentiating between living alone or together, and with or without domiciliary care)
Do you need help bathing or showering?
Do you need help getting dressed?
Do you need help regularly around the house or with cooking meals?
Can you tell me which year and month it is now?

APPENDIX B

Identified causes of contributing factors for possible preventable ED visits (if the question on preventability was answered by "yes" or "don't know"; n = 65)

Group	Main category	Subcategory
Patient	Patient-related (17)	Should have asked for help earlier (8)
		Fall caused by own fault (5)
		Other (2)
	GP-related (10)	GP should have acted earlier/differently (9)
		GP should not have referred (1)
	Healthcare professional-related (13)	Premature discharge (6)
		Nonspecific: 'something should have been done' (3)
		Other (4)
EP	Patient-related (6)	N/A
	GP-related (25)	Earlier or more frequent home visits (5)
		More detailed history or examination needed (5)
		GP should have treated the patient differently (9)
		Better explanation or counseling could have prevented ED visit (4)
		Incorrect referral (2)
	Healthcare professional-related (26)	Incorrect or unnecessary ambulance referral (5)
		Communication errors (14)
		Other (7)
	Healthcare organisation-related (20)	Earlier outpatient appointment (13)
		Expansion of domiciliary care or admission to a nursing home (6)
		Other (1)
	Medication-related (4)	N/A
	Other (2)	N/A
GP	Patient-related (17)	Care avoider (9)
		Called ambulance instead of GP (5)
		Other (3)
	GP-related (9)	Should have treated differently (3)
		Incorrect referral (5)
		Better communication(1)
	Healthcare professional-related (4)	Premature discharge (2)
		Incorrect or unnecessary ambulance referral (2)
	Healthcare organisation-related (21)	Earlier outpatient appointment (19)
		Unclear or incorrect agreements between hospital specialist and their patients (2)
	Other (2)	N/A
Caregiver	Patient-related (3)	Should have asked for help sooner (2)
		Other (1)
	GP-related (10)	GP should have acted earlier (10)
	Healthcare professional-related (13)	Premature discharge (5)
		Specialist should have acted differently (6)
		Other (2)
	Healthcare organisation-related (4)	More domiciliary care (3)
		Earlier outpatient appointment (1)
	Medication-related (1)	N/A

ED = emergency department; GP = general practitioner; N/A = not applicable.

CASE REPORT

Exceptional response of brain metastases to short course nivolumab while on high-dose steroids

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ABSTRACT

In this manuscript, we describe a patient with an exceptional response of brain metastases from lung cancer to short course nivolumab while on high-dose steroids. This case shows that immunotherapy can cause delayed and enduring responses even in patients with poor predictive parameters for treatment success, such as low programmed death ligand-1 (PDL1) expression and long-term treatment with high-dose corticosteroids. Secondly, it underscores the importance of follow up after the administration of immunotherapy, even in cases with a deemed poor prognosis and few received cycles of immunotherapy.

KEY WORDS

Brain metastases, immunotherapy, NSCLC, poor predictive factors

INTRODUCTION

Non-small cell lung cancer (NSCLC) is a prevalent disease in the Netherlands, with over 10,000 new patients each year. In the past years, immunotherapy treatment with PDL1 inhibitors has become the standard of care for the majority of patients. Immunotherapy can result in both unusual responses and unusual toxicity. This has a major impact on patients as well as their treating physicians who must manage this new phenomenon. In this paper, we describe an unusual response to immunotherapy with poor predictive factors and also propose a better follow up for these patients.

What was known on this topic?
Immunotherapy is a new pillar in the treatment of advanced non-small cell lung cancer with, in some patients, impressive results. Patient selection is suboptimal at this moment. PDL1 expression is currently the most widely used predictive factor, but has a relatively poor sensitivity and specificity. The use of high-dose steroids is considered a strong contraindication for immunotherapy.

What does this add?
This case report adds that an exceptional response to immunotherapy is possible, even in patients with poor prognostic factors such as low PDL1 status and steroid use. In addition, radiographic and/or clinical progression is not always true tumour progression, but can also be pseudoprogression, with a favourable prognosis. Finally, in patients treated with immunotherapy, careful follow up is very important, even in patients with an estimated poor prognosis. Unusual responses or toxicity may still occur and may require attention of the physician. Comedication for preventing steroid side effects should be started despite a poor estimated prognosis.

CASE REPORT

In January 2017, 62-year-old healthy man was diagnosed with a symptomatic cerebral lesion of 5 cm in the left parietal lobe. His medical history only consisted of Graves' disease with current hypothyroidism, stable on levothyroxine. He was a former smoker, who quit 28 years ago, after 15 pack years.

Further examination revealed a small tumour in the right upper lobe with a probable hilar lymph node metastasis and normal pulmonary function tests. Endobronchial ultrasound was negative. The patient was staged as T1cN0M1b NSCLC, oligometastatic. In February, he underwent a craniotomy. Pathological examination revealed a thyroid transcription factor 1-positive lung adenocarcinoma. Sequencing revealed wild type epidermal growth factor receptor (EGFR), KRAS, BRAF and ERB2. Anaplastic lymphoma kinase and ROS1 immunohistochemistry were negative. The completeness of the resection was doubtful; hence the patient was treated with additional stereotactic radiotherapy to his brain, 3 x 8 Gy.

After a quick recovery, he subsequently underwent a lobectomy of the right upper lobe. Pathological evaluation revealed a completely resected lung adenocarcinoma (3 cm), with a nodal metastasis on level 10R. Final staging was pT1cN1M1b. Thereafter, he underwent four cycles with adjuvant chemotherapy (carboplatin/pemetrexed), uneventfully.

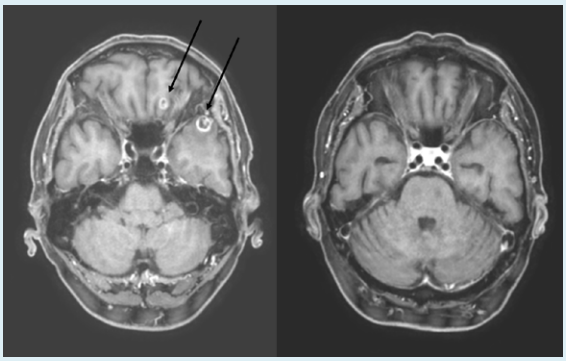
In July 2017, he was doing well with a good quality of life. Thoracic computed tomography (CT) and magnetic resonance imaging (MRI) of his brain showed no tumour growth or new lesions. However, in April 2018, at a routine follow-up MRI of his brain, six new brain metastases were observed. He was subsequently treated with whole brain radiotherapy, 10 x 3 Gy. He was still in excellent health, with an Eastern Cooperative Oncology Group 0 performance status. He was treated for a short time with dexamethasone. A CT of the thorax and abdomen showed no signs of an extracranial recurrence.

Further treatment options were discussed. PDL1 testing on the lobectomy specimen revealed a PDL1 score of < 1% (Roche SP263 assay on a Ventana Benchmark Ultra). Apart from best supportive care, the treatment guidelines propose second-line chemotherapy or immunotherapy monotherapy. The PDL1 score is a mediocrely predictive marker for a patient's response to immunotherapy.[1] Our patient declined chemotherapy. Despite the low PDL1 score, we decided to start nivolumab immunotherapy in June 2018. After just two cycles of immunotherapy, he was admitted to the hospital with lethargy, nausea, and vomiting. Repeated MRI of his brain showed progressive disease, with increased leptomeningeal mass. A lumbar puncture was not performed.

Based on clinical and radiological deterioration, we defined the patient as having progressive disease. Nivolumab was stopped and dexamethasone was started at a dose of 2 mg b.i.d. After the start of dexamethasone, he quickly recovered and became asymptomatic. Further treatment options were considered. He again was not interested in treatment with docetaxel chemotherapy.

Because of the progressive cerebral and leptomeningeal progression, the prognosis was deemed as very poor.

Figure 1. *MRI of the brain after two cycles of nivolumab, showing two cerebral metastases in the left frontal and temporal lobe (left). MRI of the brain 10 months after termination of nivolumab and on steroid treatment shows complete response of these lesions (right)*



For symptomatic relief, the dexamethasone was continued. The patient was discharged with best supportive care and no further appointments in the hospital were made. His general practitioner took over his care.

Ten months later, the patient was admitted to the hospital with abdominal and lower back pain. In general, he was doing well. He had gained 25 kg, and was still working almost full-time in his office. A CT scan revealed no metastases were observed in the thorax or abdomen. His abdominal pain was explained by constipation, probably caused by the morphine given as treatment for lumbar backpain. The CT scan also showed several osteoporotic vertebral fractures. Because of his very stable clinical situation, an MRI of his brain was repeated (figure 1), and his cerebral and leptomeningeal metastases had either disappeared or decreased in size.

We concluded that the patient had experienced a delayed, near-complete response after just two doses of immunotherapy, despite a PDL1 score < 1% and continuous administration of 4 mg dexamethasone daily. The dexamethasone had caused Cushing's syndrome, with severe weight gain, full moon face, and osteoporosis. Because of the estimated poor prognosis at progression (considered weeks), no osteoporosis prophylaxis and cotrimoxazol prophylaxis was started, neither was follow up of possible hyperglycaemia. He already used a proton pump inhibitor.

The patient was treated with additional laxatives, osteoporosis prophylaxis, and an orthopaedic lumbar support for pain relief, in addition to pain medication. The dexamethasone dosage was reduced and will be stopped after tapering. Further follow up with MRI is planned.

DISCUSSION

Nivolumab is one of the immunotherapy options in the second-line treatment of metastasised NSCLC, with a median overall survival of 12.2 months and 19% response rate.[1] This effect is however, much stronger in patients with a high PDL1 expression compared to patients with low PDL1 expression. Patients with brain metastases could also potentially benefit from immunotherapy, as immunotherapy may cross the blood-brain barrier. In untreated brain metastases of NSCLC, pembrolizumab showed a 44% response rate in the brain in patients selected for PDL1 expression.[2] Brain metastases may only decrease but may also show pseudoprogression after nivolumab and ipilimumab.[3] Pseudoprogression is an increase in tumour size after start of immunotherapy, not caused by tumour growth but by a temporary inflammatory reaction of the tumour to immunotherapy. Pseudoprogression can be symptomatic, especially in the brain. In this case, we believe that the symptoms of our patient could be explained by pseudoprogression.

Of further note, it is known that the use of high-dose steroids has a poor impact on outcome.[4] Patients receiving corticosteroids or its equivalent of > 10 mg daily for indications such as dyspnea or brain metastases had a decreased progression-free survival and overall survival. Interestingly, patients receiving corticosteroids for treatment of immune-related adverse events did not have a poorer treatment efficacy compared to patients not receiving corticosteroids.[5]

Altogether, we present a case of a patient with an exceptional and delayed cerebral response to two doses of nivolumab while on high-dose steroids. This case shows that immunotherapy can cause delayed and enduring responses even in patients with poor predictive parameters for treatment success, such as low PDL1 expression and long-term treatment with high dose corticosteroids. Of note, clinical and/or radiological pseudoprogression may also occur, causing a temporary deterioration, as in this patient.

This case also underscores the importance of follow up after the administration of immunotherapy, even in cases with a deemed poor prognosis and few received cycles of immunotherapy. This is equally important for the monitoring of side effects, which can evolve several months after the termination of immunotherapy.[5] We believe that with a follow up, we may have prevented the development of steroid side effects, and that in hindsight, better prophylaxis and follow up for steroid side effect should have been started.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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CASE REPORT

Acute calcium channel blocker withdrawal-induced cardiac arrest

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KEY WORDS

Angina pectoris, calcium channel blockers, denervation, humans, nitrates

ABSTRACT

Acute withdrawal of calcium channel blockers can lead to the so-called calcium channel blocker withdrawal phenomenon, in particular, when high dosages are used. In the case presented, inadequate drug substitution led to this phenomenon which resulted in a serious course of events. Careful monitoring the process of drug substitution with respect to equal therapeutic dosages is therefore a necessity, especially in vulnerable patients.

INTRODUCTION

Vasospastic angina (VA), also known as Prinzmetal angina, is a less common form of angina in which spams of the coronary arteries cause typical anginal symptoms along with ST-segment deviation. Long lasting VA may result in myocardial ischaemia, potentially leading to life-threatening ventricular arrhythmias. Calcium channel blockers (CCBs) and nitrates are the most frequently used drugs that may, in high dosages, provide symptom relieve in 30-80% of these patients.[1] In order to further improve symptom relief, novel invasive treatment options such as renal denervation (RDN) are currently being studied.[2,3] Here, we present a case with refractory VA undergoing RDN. It is our aim to create awareness for the potential lethal consequences of inadvertent changes in chronic medical treatment in vulnerable patients with VA.

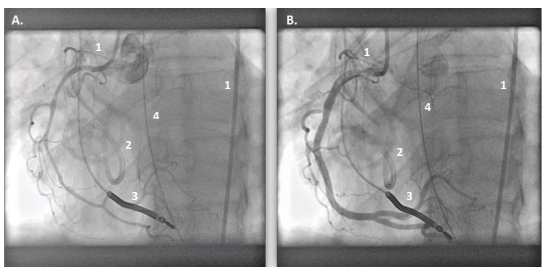
What was known on this topic?
Patients with vasospastic angina are frequently treated with high-dose calcium channel blockers. Acute withdrawal of calcium channel blockers in these patients can lead to coronary spasm.

What does this add?
For patients with vasospastic angina, withdrawal of calcium channel blockers (CCBs) can lead to a severe course of events with a high risk of mortality. Drug substitution in these patients should be monitored very carefully with respect to dose equivalence of CCBs to prevent symptoms of withdrawal.

CASE DESCRIPTION

A 46-year-old woman with refractory VA with confirmed spasm of the right coronary artery (RCA) and recurrent

Figure 1. *Angiography of the right coronary artery, which shows extensive coronary vasospasm before (A) and after (B) administration of intracoronary nitroglycerine. 1. Angiography catheter; 2. Cord lying on the patient; 3. Implantable Cardioverter Defibrillator (ICD)-lead; 4. Enteral feeding tube*



ventricular tachycardia leading to implantable cardioverter defibrillator (ICD) shocks, was referred to undergo renal denervation (RDN). In order to control the VA episodes, she used verapamil with controlled release (CR) (total daily dose (TDD) 480 mg), isosorbide mononitrate CR (TDD 120 mg), and perindopril (TDD 2 mg).

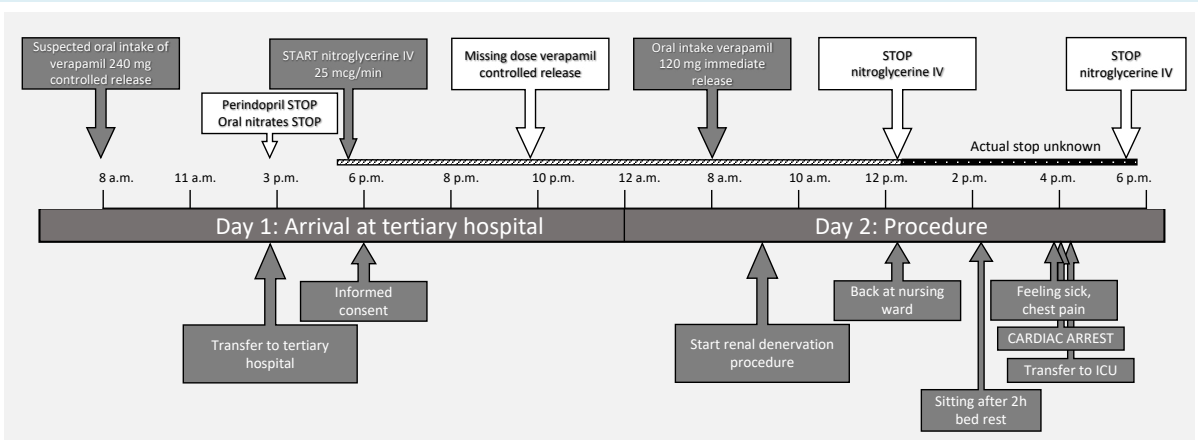
At arrival, perindopril was stopped and isosorbide mononitrate was switched to nitroglycerine intravenously (1.5 mg/hour) to better control potential fluctuations in blood pressure during the procedure. Verapamil was switched from CR to normal release tablets (120 mg 4 times/day) because verapamil CR tablets were not available. The next morning, the patient successfully underwent bilateral RDN using the Symplicity Spyral multi-electrode catheter. Five hours post procedure, she was feeling ill with recurrence of chest pain, severe perspiration, and vomiting. The electrocardiogram showed bradycardia followed by ventricular pacing. Soon after, the patient experienced a cardiac arrest with pulseless electrical activity (PEA). Recirculation was successfully restored after three blocks of cardiopulmonary resuscitation and epinephrine. At the Intensive Cardiac Care Unit, she needed resuscitation two more times due to PEA preceded by a third-degree AV block and ST elevation in the inferior leads. Severe biventricular dysfunction was present on the echocardiograph. Subsequently, extracorporeal membrane oxygenation (ECMO) was started to ensure circulation. During this procedure, coronary angiography was performed which confirmed extensive coronary vasospasm of the RCA that resolved after intracoronary nitroglycerine (figure 1). After a few days, the ECMO could be removed and the patient gradually recovered. Approximately a half-year after the procedure, she had fewer complaints of chest pain, but was still in need of ICD shocks and high-dose verapamil and isosorbide mononitrate.

DISCUSSION

The differential diagnosis of this unexpected cardiac arrest included CCB poisoning due to the clinical presentation of severe cardiogenic shock. However, when critically reviewing her medication charts, it became clear that from the moment she arrived at the hospital up until the first cardiac arrest, that the patient had received only one dose of direct release CCB in a dose of 120 mg in the morning; the afternoon dose was not given, probably because the patient was away for the procedure and somnolent afterwards. CCB poisoning was therefore not plausible. An association with the RDN was considered, but in light of the pathophysiological mechanism, this seemed unlikely.[2]

However, the abrupt switch of high-dose verapamil with controlled release (240 mg twice daily) to direct release 120 mg, which she received only once, could lead to the so-called CCB withdrawal phenomenon (figure 2).[4] This phenomenon is characterised by clinical symptoms similar to CCB poisoning, including nausea, vomiting, and cardiogenic shock. The mechanism behind this CCB withdrawal phenomenon is largely unknown, but a commonly adapted theory is that CCB use results in a depletion of calcium in the smooth muscle cells (SMCs).[5-7] Because of this, the calcium gradient between extracellular and intracellular calcium of SMCs is high and calcium will follow this gradient towards the inside of the SMCs. Upon abrupt withdrawal of CCBs, a burst

Figure 2. *Timeline of events. Upper part of the graph shows the administration of medication over time and the lower part, the events around the renal denervation procedure*



of calcium will enter the cell and cause depolarisation of the cell wall, resulting in prolonged contraction of the SMC and ultimately lead to coronary vasospasm. Patients with VA are more prone to experiencing vasospasm by CCB withdrawal.[8-10] Experimental evidence would further elucidate the pathophysiology of this phenomenon. In addition, it is known that low-dose nitrates, which cause venous vasodilation, are insufficient to prevent coronary spams due to the required arterial vasodilation. Termination early after the procedure, as could have been the case, would certainly have contributed to the course of events. Independent of the exact stop of nitroglycerine, so before or after the event, the patient's records show that both the CCB as nitrate therapy were sub-therapeutic at the time of cardiac arrest (figure 2).[4]

CONCLUSION

This case demonstrates that acute withdrawal of CCBs can have severe consequences, especially in patients with VA, who can be considered high-risk patients. This can result from drug substitutions, which are sometimes inevitable, for example, due to local limited availability of drugs, and in this case, drug substitution led to inadequate therapy of critical medication for a patient with VA. In addition, treatment of this syndrome is difficult, as an arterial spasm is always confirmed after the occurrence of symptoms. ECMO therapy, while lifesaving, may not be available in most hospitals, which means that prevention of CCB withdrawal syndrome is essential. This case highlights the need to carefully monitor the process of drug substitution with respect to equal therapeutic dosages to prevent unintentional changes in essential medication.

DISCLOSURES

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PHOTO QUIZ

'Swollen legs' after self-limiting diarrhoea

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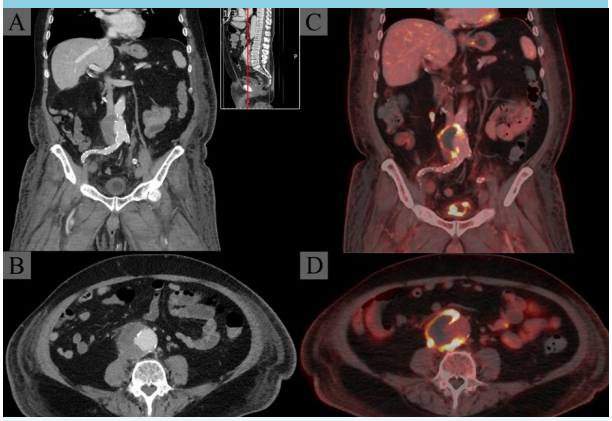
Figure 1. *Frontal (A) and transverse (B) images obtained during CT scan; frontal (C) and transverse (D) images obtained during FDG-PET/CT scan showing an abnormality compressing the inferior vena cava, with increased FDG uptake*



FDG-PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography

CASE REPORT

A 75-year-old male was referred to our emergency room because of dyspnoea, hypotension, and a swollen leg. His medical history included type 2 diabetes mellitus, stroke, hypertension, and colon cancer two years prior, treated with laparoscopic resection and adjuvant chemotherapy. The patient complained of progressive fatigue over the last few weeks followed by swelling of the left leg, which occurred one day prior to his visit, with progressive dyspnoea afterwards. His blood pressure was 70/50 mmHg, heart rate 115 bpm, temperature 36.2°C, respiratory rate 32 breaths per minute, and peripheral oxygen saturation 95%. Palpation of the abdomen was painful, but there was no abdominal rigidity. The left lower leg was swollen and erythematous but not noticeably warmer than the right leg. Laboratory testing showed high inflammatory markers (C-reactive protein 193 mg/l, leucocyte count 24.4 × 10^9/l). Ultrasound of the left leg revealed deep vein thrombosis. Therefore, a pulmonary embolism was suspected, which was confirmed on computed tomography (CT) imaging.

Low molecular weight heparin therapy was initiated in conjunction with ceftriaxone because concomitant sepsis was presumed. Blood pressure improved with intravenous fluid administration; therefore, we concluded that hypotension was mainly caused by sepsis and not obstructive shock secondary to the pulmonary embolism. Hence, no thrombolysis was initiated. Within several days the dyspnoea abated, blood pressure normalised, and heart and respiratory rates improved. Surprisingly, blood cultures (which were taken at admission because of the high inflammatory markers) became positive for *Salmonella enterica* subsp. *enterica* serotype Enteritidis, sensitive for ceftriaxone and ciprofloxacin. When asked, the patient mentioned that he had severe, self-limiting diarrhoea six weeks prior to current admission. A few days later, the contralateral right leg also became swollen, raising the suspicion of compression of the inferior vena cava. Indeed, further imaging demonstrated compression of the inferior vena cava by a fluorodeoxyglucose (FDG)-positron emission tomography (PET)-positive abnormality (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 345 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 344)

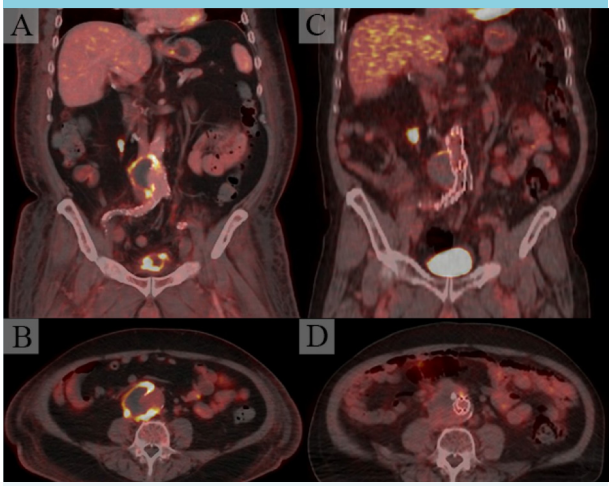
'SWOLLEN LEGS' AFTER SELF-LIMITING DIARRHOEA

DIAGNOSIS

In our patient, we diagnosed a *Salmonella*-infected aortic aneurysm which compressed the adjacent inferior vena cava, causing bilateral deep venous thrombosis and secondary pulmonary embolism. These series of events occurred after, and most likely because of, a seemingly self-limiting gastroenteritis.

This patient was infected by *Salmonella enterica*, a non-typhoidal *Salmonella* (NTS) species, which consist of strains other than *S. Typhi* and *S. Paratyphi*. *Salmonella enterica* accounts for the majority of salmonella infections in humans, and predominately occurs from contact with animals or ingestion of contaminated animal products such as milk, poultry, and eggs.[1,2] NTS infection is a commonly diagnosed illness, affecting millions annually. In patients with NTS enteritis, there is about a 6% chance of developing NTS bacteraemia,[2] which can cause possible lethal complications such as septic shock, meningitis, endocarditis, bone/joint infections, and vascular infections.[1,2] Salmonella has the ability to invade the normal arterial intima. However, this risk is increased in the presence of atherosclerosis, leading to infectious aneurysms. The incidence of developing vascular infections in patients over the age of 50 years during NTS bacteraemia is estimated to be as high as 25%, especially with underlying atherosclerosis or vascular prosthesis. The mortality rate in vascular NTS infections is high: up to 90% with antibiotic treatment alone, and around 40% when combined with surgery.[3]

Figure 2. *Frontal (A, C) and transverse (B, D) images obtained during FDG-PET/CT scan showing normalisation of activity comparing before (A, B) and after treatment, six months later (C, D)*



FDG-PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography

Therefore, treatment of NTS-infected aneurysms consists of a combination of antibiotic therapy and surgery. Complete surgical removal of the infected tissue after sufficient pre-operative antibiotic therapy is preferred. However, due to the high perioperative risks of open aortic surgery,[4] this is not always possible. In such cases, less invasive endovascular repair could be considered to avoid rupture of the aneurysm; however, as the infected tissue remains in situ, this will inevitably lead to a chronic infection, including infection of the vascular prosthesis itself. Endovascular repair needs to be followed by very long term (sometimes lifelong) antibiotic therapy to prevent other complications.

Despite antibiotic therapy with ceftriaxone and ciprofloxacin, the aneurysm diameter in our patient increased from 57 to 71 mm over a period of one month. Open surgery with resection of the mycotic aneurysm to remove infected tissue and prevent rupture was considered, but regarded too risky because of a recent pulmonary embolism, current active infection, and previous abdominal surgery. Therefore, the patient underwent endovascular aorta repair (EVAR) surgery to prevent rupture. Because the infected tissue could not be removed, antibiotic therapy with ciprofloxacin was continued. After eight months of follow-up, the previous symptoms vanished, and erythrocyte sedimentation rate (ESR) decreased from 97 to 31 mm/hour. C-reactive protein decreased from 266 to 10 mg/l. PET-CT showed normalisation of FDG-uptake (figure 2). Cessation of antibiotics will be considered in the near future.

Complications due to NTS infection can be difficult to diagnose, especially when there is no current gastrointestinal symptom or recent diagnosis of NTS infection, as in our patient. Awareness of this rare but severe complication of a relatively common gastro-intestinal infection is essential to establish early diagnosis and treatment of affected patients.

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PHOTO QUIZ

Skin lesions in a diabetic patient

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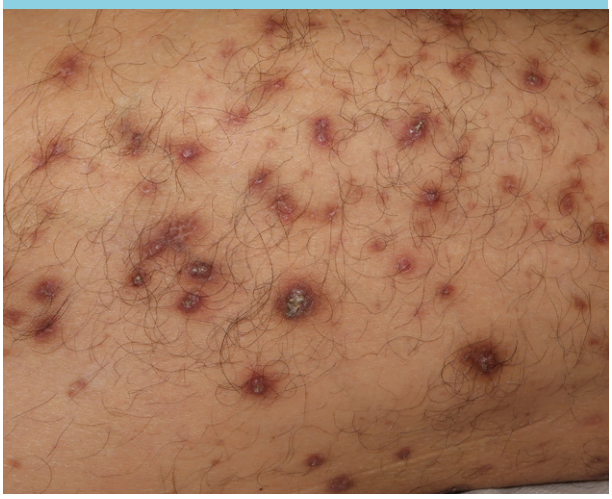
Figure 1. *Papules and nodules located on the anterior and lateral aspects of both thighs with central keratotic plugs*



CASE REPORT

A 65-year-old man with a 10-year history of type II diabetes mellitus (DM), hypertension, and chronic renal failure (glomerular filtration rate of 36 ml/min/1.73 m^2) presented with a 3-month history of mildly pruritic erythematous papules and nodules located on the anterior and lateral aspects of both thighs, some of them with a linear arrangement. Central keratotic plugs were evident within the lesions and were easily removed with gentle manipulation (figure 1). A skin biopsy was performed, and histopathological examination with haematoxylin and eosin staining demonstrated dilated follicular infundibula filled with keratinous and cellular debris. The follicular epithelium was disrupted in at least one area and the adjacent dermis showed degenerative changes. A moderate perivascular inflammatory infiltrate was present.

WHAT IS YOUR DIAGNOSIS?

See page 347 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 346)

SKIN LESIONS IN A DIABETIC PATIENT

DIAGNOSIS

Clinical and histopathological findings were consistent with the diagnosis of acquired perforating dermatosis (APD). Topical treatment with topical tretinoin 0.5% cream was commenced and a prompt review with the nephrology team was arranged.

Perforating diseases are defined by the transepidermal elimination of materials from the dermis, including elastic fibres, collagen, and keratin. APD characteristically presents in adulthood in association with systemic disease, most notably DM and chronic renal disease. Pathogenesis remains uncertain but a possible relationship to mild superficial trauma (e.g., chronic rubbing or scratching) has been suggested and is supported by the frequent linear arrangement of lesions (Koebner phenomenon) and the improvement of lesions with antipruritic treatments.[1-3] Clinically, lesions most commonly present as mildly erythematous hyperkeratotic or crateriform papules and nodules with a predilection for the follicular unit.[4] They are usually pruritic and favour the extensor surface of the legs, the upper extremities, and the trunk.[2,4] Regarding taxonomy, whether APD can be classified as an acquired form of one of the classical perforating dermatoses (reactive perforating collagenosis, elastosis perforans serpiginosa, perforating folliculitis, or Kyrle's disease) or as a variant remains controversial.[2] In addition, the terms 'acquired reactive perforating dermatosis' and 'Kyrle's disease' are often used interchangeably in the literature as a synonym of subtype of APD.[1,3] Histological findings are variable and may include epidermal invagination, dilated or cystic follicles, basophilic necrotic debris and ortho or parakeratotic plugs, inflammatory infiltrate, and altered collagen or elastic fibres in the superficial dermis.[1,4]

Differential diagnoses include other disorders characterised by nodules or papules with keratotic plug or crusts, such as prurigo nodularis and prurigo simplex, folliculitis, and multiple dermatofibromas or keratoacanthomas.

Regarding treatment, general measures include avoiding ongoing trauma and addressing pruritus. Special consideration should be given to identifying and treating any coexisting underlying disease. Topical and intralesional corticosteroids and oral antibiotics have shown inconsistent results. The beneficial effects of topical and systemic retinoids, oral allopurinol, and narrow band UVB and UVA phototherapy have been described in several case reports and case series. Combination treatment, rather than monotherapy, appears to result in more favourable outcomes.[3]

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