Clinical characterization of men with long QT syndrome and torsades de pointes associated with hypogonadism: A review and pharmacovigilance study

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Summary

Background. – Long QT syndrome (LQTS) can cause the potentially fatal ventricular tachycardia torsades de pointes (TdP). QT interval corrected for heart rate (QTc) is shorter in men than in women, with testosterone contributing to shorten QTc. We recently described male hypogonadism as a reversible risk factor for acquired LQTS and TdP, but the clinical characteristics of such patients have not been characterized.

Aims. – To describe the clinical characteristics of men with acquired LQTS or TdP associated with hypogonadism caused by endocrine conditions or androgen deprivation therapy (ADT), and to evaluate the relationship between testosterone concentrations and electrocardiographic changes.

Methods. – We searched MEDLINE (to 04 January 2019) and the French pharmacovigilance database (to 09 August 2018) to identify male cases of acquired LQTS and TdP associated with endocrine hypogonadism or ADT; their narratives were gathered from reporting collaborators.

Results. – We identified seven cases of TdP (one fatal) with endocrine hypogonadism, abnormally long QTc and morphologically abnormal T-wave notches. After reversion of low testosterone concentrations in the surviving patients (n = 6), QTc shortened, T-wave morphology normalized and there was no TdP recurrence. Among these cases, none had mutation in the LQTS genes, three men required testosterone and three had reversible hypogonadism after resolution of a concurrent acute severe illness. We found an additional 27 reports of men with LQTS (n = 6), TdP (n = 9; 2/9 fatal) or sudden death (n = 12; 10/12 fatal) suspected to be induced or favoured by ADT (24/27 for prostate cancer). Generally, after ADT withdrawal, QTc shortened and no TdP recurred.

Conclusion. – We propose seeking for hypogonadism caused by endocrine conditions or ADT in men presenting with TdP. Caution is warranted when ADT is used in situations at risk of TdP. Testosterone may be useful to treat or prevent TdP.

Résumé

Contexte. – Le syndrome du QT long (SQTL) peut se compliquer de torsade-de-pointe (TdP) et de mort subite. L'intervalle QT corrigé sur la fréquence cardiaque (QTc) est influencé par les hormones sexuelles

et notamment raccourci par la testostérone. Nous avons récemment décrit que l'hypogonadisme masculin est un facteur de risque réversible de SQTL et de TdP.

Objectifs. – Description des caractéristiques cliniques des hommes avec un hypogonadisme endocrinien ou secondaire à un traitement anti-androgène (ADT) ayant présenté une TdP. Evaluation de la relation entre les taux de testostérone et des modifications électrocardiographiques.

Méthodes. – Analyse des bases MEDLINE et de pharmacovigilance française.

Résultats. – Des Tdp ont été identifiés chez 7 hommes hypogonadiques présentant un QTc allongé et des anomalies morphologiques de l'onde T (notches). Sur les 6 survivants, la correction de l'hypogonadisme s'est faite par administration de testostérone (n = 3) ou par résolution de son origine étiologique (n = 3). Cette correction a permis un raccourcissement du QTc, une normalisation de la morphologie de l'onde T et une absence de récidive des TdP. Aucune mutation des gènes SQTL n'a été retrouvée. La prise d'ADT a été reportée comme suspecte dans 27 autres cas de SQTL (n = 6), de TdP (n = 9 ; 2/9 décès) ou de mort subite (n = 12 ; 10/12 décès). L'arrêt de l'ADT permettait un raccourcissement du QTc et une absence de récidive des TdP.

Conclusion. – Un hypogonadisme est à rechercher chez les hommes présentant une TdP. Les ADT doivent être utilisés prudemment chez des hommes à risque de TdP. Nos données suggèrent l'utilisation de la testostérone dans la prise en charge des TdP.

KEYWORDS

Torsades de pointes;

Hypogonadism;

Long QT syndrome;

Testosterone;

Androgen deprivation therapy

Abbreviations: ADR, adverse drug reaction report; ADT, androgen deprivation therapy; aLQTS, acquired long QT syndrome; BNPV, Base Nationale de Pharmacovigilance (French pharmacovigilance

database); ICD, implantable cardioverter-defibrillator; LQTS, long QT syndrome; PVR, pharmacovigilance case report; QTc, QT interval corrected for heart rate; TdP, torsades de pointes.

Background

QT interval duration, measured on the electrocardiogram and corrected for heart rate (QTc), represents the duration of ventricular repolarization. QTc prolongation favours the potentially fatal ventricular tachycardia torsades de pointes (TdP) [1] in both the congenital form of long QT syndrome (LQTS) as well as an acquired form (aLQTS; usually drug-associated). A major mechanism for drug-associated LQTS is block of the repolarizing potassium current I_{Kr}, which, in addition to prolonging QTc, also generates morphologically distinctive low-amplitude notched T-waves on the electrocardiogram [2-5]. In healthy individuals, QTc is longer in women than in men from puberty to menopause, and women are at higher risk of aLQTS and TdP [1,6-8]. Several lines of evidence support the contention that this sex specificity is attributable to a testosterone effect that serves to shortens QTc [6,9-11]. QTc prolongation in men has been linked to hypogonadism [6,9,10], and correction of testosterone deficiency was associated with shortening of QTc [6,10,12]. However, TdP is rare, and in a very brief report we described seven cases of aLQTS/TdP in men with hypogonadism from a range of causes seen at a single centre between January 2016 and July 2017 [13]. The use of androgen deprivation therapy (ADT) in men with prostatism and prostate cancer has been associated with modest QTc lengthening (~10–20 ms), but the association with TdP and sudden death is unknown.

The objective of this study was to provide a detailed clinical characterization of patients presenting hypogonadism with aLQTS and/or TdP, by gathering information on all cases published on MEDLINE and in the French pharmacovigilance database (BNPV; Base Nationale de Pharmacovigilance) from inception of these databases until now. Furthermore, we comprehensively phenotyped our recently published case series of hypogonadism associated with TdP [13], by providing extensive serial testosterone and electrocardiogram concomitant assessment, as well as genetic data, to further evaluate the interaction between variations in testosterone concentrations and electrocardiogram changes.

Methods

The trial was registered at ClinicalTrials.gov (identifier: NCT03193138). We searched PubMed-MEDLINE (to 04 January 2019) and the BNPV (to 09 August 2018) to identify male cases of LQTS and TdP associated with hypogonadism caused by endocrine conditions or androgen deprivation therapy (ADT). In

the BNPV search, sudden deaths suspected to be induced by ADT were also collected. When cases were described insufficiently, narratives of the cases were gathered after reaching out directly to reporters, when possible. Duplicate reports were flagged and dropped.

Analysis of PubMed-MEDLINE

All articles falling under the following query were reviewed for the purpose of this study: (QT OR torsade OR torsades) AND (androgen OR testosterone OR dihydrotestosterone OR androgens OR hypogonadism OR enzalutamide OR abiraterone OR apalutamide OR castration OR flutamide OR nilutamide OR bicalutamide OR goserelin OR leuprorelin OR triptorelin OR degarelix OR abarelix OR finasteride OR dutasteride). Mechanisms of action of the different ADT drugs are represented in Fig. 1.

Analysis of the BNPV

The French pharmacovigilance system is based on a network of 31 regional centres that receive adverse drug reaction reports (ADRs), mainly from treating physicians [14]. Cases are entered into a common database administrated by the Agence Nationale de Sécurité du Médicament et des Produits de Santé, with drug causality evaluated. All cardiac ADRs related to ADT were reviewed, and aLQTS, TdP or sudden death were identified and are presented in Table 1. Cardiac ADRs were found using the Medical Dictionary for Regulatory Activities (MedDRA), searching for cardiac disorders (System Organ Class level), death and sudden death (High-Level Term) and electrocardiogram investigations (High-Level Term).

Further electrocardiogram, biological and genetic characterization of patients included in a recently published case series of TdP associated with male hypogonadism [13]

Men with aLQTS and TdP seen in the Pitié-Salpêtrière arrhythmia unit between January 2016 and July 2017 were investigated prospectively for hormonal pituitary-testicular axis function. Consent was obtained from the patients, and data were anonymized after approval of the Commission Nationale de

l'Informatique et des Libertés (n°1491960v0). QTc was calculated by Fridericia's formula [15]. In men, QTc is prolonged if > 440 ms (40–60 years), > 450 ms (60–80 years) or > 460 ms (> 80 years) [16]. Morning serum concentrations of testosterone, luteinizing-hormone and follicle-stimulating hormone were measured in the fasting state when possible, using the Modular E170® chemiluminescentimmunometric assay (Roche Diagnostics, Risch-Rotkreuz, Switzerland). Normal values for adult men were: follicle-stimulating hormone 1.5–12.4 IU/L; luteinizing hormone 1.7–8.6 IU/L; total testosterone 2.5–8.4 ng/mL; and bioavailable testosterone 1.0–3.2 ng/mL. The times between electrocardiogram and biological evaluations for each patient are summarized in Fig. 2 and Figs. A.1–A.6 Genetic screening was performed for rare variants in *KCNQ1*, *KCNH2*, *SCN5A*, plus 12 other minor genes involved in congenital LQTS [17].

Results

Case reports of men with TdP associated with endocrine hypogonadism

Seven cases of men with TdP were collected consecutively. At the time of the arrhythmic event, all patients had biochemical hypogonadism and LQTS (Fig. 2 and Figs. A.1–A.6) associated with decreased T-wave and notching (Fig. 1 and Fig. 2). Three patients had spontaneous reversal of hypogonadism after resolution of a severe critical illness, three needed testosterone supplementation and one died. After correction of testosterone concentrations, QTc shortened, T-wave maximal amplitude increased, morphology normalized and there was no further TdP. LQTS genetic screening was negative in tested surviving patients (n = 6/6).

Case report #1 (**Fig. 2** and **Fig. 3**)

This man (aged 72 years) had a history of hypertension and ischaemic cardiomyopathy and was on beta-blockers. He had been diagnosed 2 years earlier with a specific non–Langerhans-cell histiocytosis infiltrating multiple organs, associated with a *BRAF* gene mutation (Erdheim-Chester disease) [18,19]. Following this diagnosis, he developed heart failure with preserved ejection fraction, sick sinus syndrome and sexual disorders. In May 2015, he received interferon-alpha. In January 2016, the patient was transferred to the Pitié-Salpêtrière arrhythmia unit for respiratory distress and recurrent episodes of TdP, requiring six cardioversions for ventricular fibrillation after TdP. Plasma electrolytes and troponins were

normal. The first TdP episode appeared (prolonged QTc > 550 ms) before the introduction of any new drugs, while on chronic beta-blocker treatment. Interferon was withdrawn, and he received antibiotics for presumed respiratory infection. On admission to the arrhythmia unit, 7 days after his first TdP, he gave a history of no sexual activity with no erection for the past 6–8 months; clinical examination showed no heart failure signs, gynecomastia, and bilateral hypotrophic testes. Hormonal assays showed peripheral hypogonadism (Fig. 3B) and normal prostate specific antigen. Two days after admission to the arrhythmia unit, he again had a sustained TdP (Fig. 3B), with no QT-prolonging drugs or ischaemia and normal electrolytes. He received an implantable cardioverter-defibrillator (ICD). After reviewing previous electrocardiograms, we found that his QTc had increased progressively from 447 ms in 2013 to 466 ms in 2014, 565 ms in 2015 and 577 ms in January 2016 (Fig. 3A and Fig. 3C). Testosterone supplementation was introduced, hypothesizing that recent onset of sustained hypogonadism related to his histiocytosis [19] had contributed to this progressive QTc lengthening. Four days after testosterone supplementation, T-wave morphology and QTc had normalized (448 ms) (Fig. 3D). Vemurafenib, effective in cases of interferon-resisting *BRAF*-mutated Erdheim-Chester disease [20], was introduced, despite its known QT-prolonging effect [21]. Over the 18 months following vemurafenib initiation and maintenance, the favourable therapeutic response persisted. Testosterone replacement was continued, no TdP was detected on ICD telemetry and QTc remained normal (Fig. 3E and Fig. 3F). Libido increased, with the return of erections, there was regression of gynecomastia and prostate specific antigen remained normal.

Case report #2 (**Fig. 4** and **Fig. A.1**)

This man (aged 78 years) had a history of paroxysmal atrial fibrillation and ischaemic cardiomyopathy with preserved ejection fraction and was on sotalol and digoxin; QTc was 463–480 ms. He was hospitalized for severe mitral regurgitation and meningitis complicating endocarditis on 16 December 2016. He was treated with amoxicillin and gentamycin and was transferred to our hospital for valve replacement on 10 January 2017. Sotalol and digoxin were withdrawn, but 2 days after surgery he had episodes of heart block, marked QT prolongation to 520–540 ms, T-wave notches and episodes of TdP. There were no QT-prolonging drugs, abnormal electrolytes or acute ischaemia. Profound hypogonadism of mixed central and peripheral origin was diagnosed (Fig. 4). The patient was treated with temporary pacing, but 2 months

after surgery, on no antiarrhythmic therapy, his QTc was still ~500 ms; hormonal assays confirmed persistence of peripheral hypogonadism (bioavailable testosterone 0.3 ng/mL; total testosterone 0.8 ng/mL; lutenizing hormone 15.1 IU/L; follicle-stimulating hormone 27.2 IU/L). Testosterone supplementation was introduced, and QTc normalized 3 months later (Fig. 4). TdP did not recur, and prostate specific antigen remained normal at 6-month follow-up.

Case report #3 (**Fig. 4** and **Fig. A.2**)

This man (aged 75 years) had a history of pacemaker implantation for paroxysmal bradycardia-tachycardia syndrome and was being treated with amiodarone and bisoprolol; QTc was ~530 ms, ischaemic cardiomyopathy (ejection fraction 35–45%) and moderate renal insufficiency. On 07 July 2017, 12 hours after elective pacemaker replacement, he had TdP followed by a cardiac arrest. QTc was 660 ms with T-wave notching (Fig. 4), electrolytes were normal, there was no acute thrombosis on coronary angiography and hormonal assays showed undetectable testosterone concentrations. The patient had started hydroxyzine 5 days earlier for pruritus. After cardioversion, he was transiently paced (90 bpm), and amiodarone and hydroxyzine were withdrawn. Testosterone supplementation was started, and 2 weeks after testosterone initiation, QTc had shortened to < 500 ms and notching had disappeared (Fig. 4). At 2-month follow-up on testosterone supplementation, prostate specific antigen remained normal, QTc was 485 ms and TdP did not recur.

Case report #4 (**Fig. 4** and **Fig. A.3**)

This man (aged 90 years) had a history of hypertension, normal ejection fraction and borderline QTc (462 ms), cured prostate cancer, renal insufficiency and temporal arteritis; he was receiving corticosteroids. On 21 February 2016, he had multiple sustained TdP episodes requiring cardioversions; concurrent conditions included severe hypokalaemia (1.8 mmol/L), paroxysmal atrial fibrillation and pulmonary infection treated with ciprofloxacin for a week. TdP episodes did not recur after electrolyte correction, magnesium administration and withdrawal of ciprofloxacin, but QTc remained markedly prolonged (> 600 ms), and the patient was comatose. Testosterone concentrations were undetectable (Fig. 4), but within 10 days QTc returned to 480 ms as testosterone concentrations increased spontaneously, with no TdP

recurrence (Fig. 4). Testosterone supplementation was not considered because of his prostate cancer history.

Case report #5 (Fig. 4 and Fig. A.4)

This man (aged 63 years) had a history of hypertension, prostate adenoma, familial history of sudden death, normal QTc and normal ejection fraction. On 29 November 2016, he had catheter ablation of atrial fibrillation, complicated by tamponade, requiring urgent surgical intervention and the use of extracorporeal membrane oxygenation. He developed episodes of haemorrhagic and septic shock requiring transfusion, antibiotics, catecholamines, dialysis and prolonged mechanical ventilation. The patient underwent coronary stenting, and was treated with amiodarone after episodes of rapid atrial fibrillation and ventricular tachycardia. In January 2017, he developed prolonged QTc, bradycardia, normal electrolytes and multiple self-terminating TdP episodes. Testosterone concentrations were undetectable (Fig. 4). He had temporary pacing, and his clinical condition improved slowly, with normalization of testosterone concentrations and QTc in February 2017. An ICD was implanted, and he was discharged on amiodarone. In June 2017, QTc (on amiodarone) and testosterone concentrations were normal, with no TdP recurrence (Fig. 4).

Case report #6 (Fig. 4 and Fig. A.5)

This man (aged 63 years) had a history of hypertension, paroxysmal atrial fibrillation and multiple arterial aneurysms with cerebrovascular haemorrhagic strokes complicated by epilepsy and hemiplegia. QTc and ejection fraction were normal. On 15 January 2017, he had a cardiac arrest as a result of multiple TdP episodes, leading to ventricular fibrillation requiring more than 15 cardioversions. Coronary angiography did not show thrombosis, electrolytes were normal, QTc was 561 ms with T-wave notching and hormonal assays identified central hypogonadism (Fig. 4). The patient developed sepsis as a result of presumed pulmonary infection and died 4 days later.

Case report #7 (Fig. 4 and Fig. A.6)

This man (aged 72 years) had a previous history of sinus node dysfunction, with pacemaker implantation and normal QTc. During hospitalization for transient cerebral ischaemia and hypertension, he developed

prolonged QTc, notched T-waves and syncopal TdP in the absence of culprit drugs or electrolyte abnormalities. His pacemaker was upgraded to an ICD. After resolution of this acute event, QTc normalized (412 ms) and TdP did not recur. Two years later, the patient was diagnosed with endocarditis on the ICD lead. There was QTc prolongation (480 ms) with low-amplitude biphasic/notched T-waves, and he had profound central hypogonadism and normal electrolytes (Fig. A.6B). The ICD system was extracted, and he was discharged home in October 2016 on antibiotics and a LifeVest® system (Zoll Medical Corp., Pittsburgh, PA, USA) for temporary arrhythmia prevention while awaiting a new ICD. In December 2016, hormonal assays showed normalization of hypogonadism and QTc (430 ms), which persisted 6 months later, with no TdP recurrence.

Pharmacovigilance case reports of men with aLQTS, TdP and sudden death associated with ADT

Analysis of BNPV and PubMed-MEDLINE revealed 27 relevant ADR reports of men on ADT: aLQTS (*n* = 6), TdP (*n* = 9; 2/9 fatal) and sudden death (*n* = 12; 10/12 fatal). Most of these reports were from France, but three were from other countries [22-24]. Twenty-four patients (aged 59–90 years) were taking ADT for prostate cancer, two for prostate adenoma and one for androgenic alopecia (a 24-year-old with sudden death the day after starting finasteride). Details about their past medical history, ADR clinical presentation, ADT involved, time between start of ADT and onset of event, other drugs that could affect QTc and clinical evolution are presented in Table 1. All pharmacological classes of ADT were implicated: the cytochrome-P450-17 inhibitor (abiraterone); non-steroidal androgen receptor antagonists (bicalutamide, flutamide, enzalutamide); 5α-reductase inhibitors (finasteride, dutasteride); and gonadotrophin-releasing hormone receptor agonists (leuprolide, goserelin, triptorelin) and antagonists (degarelix).

Degarelix, an ADT leading to a very steep acute testosterone deficiency, was associated with two cases of TdP with no hypokalaemia (pharmacovigilance case report [PVR] #7 and PVR #8) and one case of sudden death, occurring a few hours after the third degarelix injection (PVR #16). Abiraterone, a drug known to lead to hypermineralocorticism on top of androgen deprivation, was associated with one case of aLQTS and three cases of TdP occurring in the context of hypokalaemia (PVR #1, PVR #10, PVR #11

and PVR #12) and two cases of sudden death (PVR #23 and PVR #24), occurring less than 2 months after the start of the drug. In general (Table 1), after ADT withdrawal, QTc shortened and no TdP recurred.

Discussion

This case series support the concepts that: hypogonadism is a cause of aLQTS, TdP and sudden death; correction of hypogonadism by testosterone replacement therapy can treat and/or prevent TdP; and ADT can lead to aLQTS, TdP and sudden death, particularly when patients are exposed to other risk factors. These results argue for investigating the possibility of hypogonadism when men are evaluated for aLQTS or TdP, and suggest that electrocardiogram monitoring may have a place in the surveillance of men with known hypogonadism.

Beyond sex and age, multiple correctable risk factors for aLQTS and TdP are known, including hypokalaemia, QT-prolonging drugs, bradycardia, critical illnesses and acute neurological conditions [25,26]. Our findings support the hypothesis that hypogonadism is a correctable, newly identified and easy-to-detect risk factor for TdP in men. This is particularly true when patients have suggestive sexual and non-sexual symptoms [27,28], and when prevalence of hypogonadism is expected to be high, such as in elderly men [27,28], systemic infiltrative conditions [18,19] or critical illnesses, including sepsis, cardiac surgery and cerebral events [25,29,30]. The distinction between transient hypogonadism secondary to critical illness and pre-existent hypogonadism is difficult in the acute phase, and must be based on clinical history and examination [31]. It has been shown that hypothalamic-pituitary-gonadal axis physiology is altered dramatically during critical illness and following major surgery or brain injury, leading to transient functional hypogonadism [32-34]. For these reasons, we decided to wait for a potential spontaneous normalization of pituitary function before starting treatment for patients in case reports #4 to #7 (acute sepsis, surgery or stroke). On the other hand, late-onset hypogonadism has recently been defined as a syndrome in middle-aged and elderly men reporting sexual symptoms, associated with higher cardiovascular mortality in the presence of low testosterone concentrations [35]. Late-onset hypogonadism is favoured by obesity-related metabolic and lifestyle factors, predisposing older men to the development of this syndrome [36]. Hypogonadism also appears to alter T-wave morphology beyond simple QTc lengthening. T-wave alterations identified in our cases were suggestive of I_{Kr} inhibition, with

decreased T-wave maximal amplitude and notching (Fig. 3 and Fig. 4) [2]. This is in line with preclinical studies showing that testosterone increases the repolarizing potassium currents I_{Kr} and I_{Ks}, and decreases the depolarizing L-type calcium current $I_{Ca,L}$ [6,11,37].

Testosterone supplementation may offer new therapeutic opportunities to cure or prevent aLQTS/TdP, particularly when hypogonadism is symptomatic [27,28] or irreversible, or occurs in patients carrying multiple risk factors for TdP, such as those with indications for other drugs associated with a known risk of TdP [25,29,38,39]. In fact, in our case series, most patients were severely sick, and several were taking QT-prolonging drugs, such as amiodarone, at the time of TdP event. Interestingly, in the patient in case report #1, testosterone supplementation was associated with absence of TdP recurrence, despite the introduction of vemurafenib, a QT-prolonging drug [40].

ADT is a cornerstone treatment for prostate cancer or adenoma and may be used for androgenic alopecia in younger men. There is no mention in the latest European Society of Cardiology and American Heart Association position papers on cancer treatments and cardiovascular toxicity that ADT use might lead to aLQTS, and no specific caution is recommended [21,41]. Degarelix, abarelix, apalutamide and leuprolide are the only ADT drugs considered to be associated with a possible risk of TdP, according to the reference CredibleMeds website (last accessed October 2018) used for TdP risk classification of drugs [11]. Guidelines will need to be developed to appropriately monitor and manage this risk. In fact, clinical trials evaluating ADT in men with prostate cancer have also shown consistently QTc lengthening of ~10–20ms [11,42-45]. Interestingly, all classes of ADT, even mild ADT (5α-reductase inhibitors) [46], appeared to be associated with proarrhythmic events. The risk of TdP with 5α-reductase inhibitors is particularly noteworthy because these drugs are indicated in benign conditions, including androgenic alopecia [46]. Interestingly, degarelix produces rapid onset and marked hypogonadism [47]. This marked variation in testosterone concentrations is compatible with TdP reports occurring very quickly after degarelix initiation. Abiraterone is used in association with corticosteroids, and leads more often than other ADT drugs to severe hypokalaemia – a major risk factor for TdP [48].

Conclusions

We propose seeking for hypogonadism cause by endocrine conditions or ADT in men presenting with TdP. Caution is warranted when ADT drugs are used in situations at risk of TdP. Correction of classical risk factors for TdP should be achieved in patients on ADT. Testosterone may be useful to treat or prevent TdP.

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Disclosure of interests

The authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Mechanisms of action of androgen deprivation therapy. ACTH: adrenocorticotrophic hormone; AR: androgen receptor; DHT: dihydrotestosterone; DNA: deoxyribonucleic acid; FSH: follicle-stimulating hormone; GnRH: gonadotrophin-releasing hormone receptor; LH: luteinizing hormone; PI3: phosphoinositide.

Figure 2. Schematic representation of main clinical events, risk conditions for torsades de pointes (TdP), QT interval corrected for heart rate (QTc) and bioavailable testosterone concentrations (normal ≥ 1 ng/mL) over time for the patient in case report #1. The red shading indicates abnormally low testosterone concentrations or high QTc values, and the green shading indicates values in the normal range. D: day.

Figure 3. Ten-second, 12-lead electrocardiogram (10 mm/mV, 25 mm/s) for the patient in case report #1. A. 11 months before admission for torsades de pointes (TdP). B. During an episode of TdP. C. A few hours later. D. Four days after testosterone administration. E and F. Six and 18 months after TdP, while on chronic testosterone replacement. This figure highlights how prolongation of QT interval corrected for heart rate (QTc) and notching were corrected by normalization of testosterone concentrations. Bio-T: bioavailable testosterone; FSH: follicle-stimulating hormone; HR: heart rate; LH: luteinizing hormone; Tot-T: total testosterone. Normal values for adult men: Bio-T 1.0–3.2 ng/mL; FSH 1.5–12.5 IU/L; LH 1.7–8.6 IU/L; Tot-T 2.5–8.4 ng/mL.

Figure 4. Consecutive PQRST complexes for the patients in case reports #2 to #6 during routine follow-up. A. Preceding the event. B. At the time of torsades de pointes (TdP) occurring while presenting with a stressful event and hypogonadism. C. After resolution of the acute event and reversion of hypogonadism, either after testosterone supplementation (case reports #2 and #3) or spontaneously (case reports #4 to #6). For each patient, the arrow indicates the appearance of electrocardiogram signs suggestive of I_{Kr}-blockade found in precordial leads when hypogonadism was confirmed. I_{Kr}-blockade (found in congenital long QT syndrome type 2) is characterized by prolongation of QT interval corrected for heart rate (QTc)

and, more specifically, by decreased T-wave maximal amplitude and T-wave bifid notching [2-5]. Bio-T: bioavailable testosterone; FSH: follicle-stimulating hormone; HR: heart rate; LH: luteinizing hormone; NA: not available; Tot-T: total testosterone. Normal values for adult men: Bio-T 1.0–3.2 ng/mL; FSH 1.5–12.5 IU/L; LH 1.7–8.6 IU/L; Tot-T 2.5–8.4 ng/mL.

Table 1 Details of pharmacovigilance case reports of men with acquired long QT syndrome, torsades de pointes or sudden death suspected to be induced by androgen deprivation therapy obtained from the French pharmacovigilance database (BNPV; last accessed 09 August 2018), or acquired long QT syndrome and torsades de pointes associated with androgen deprivation therapy obtained from a PubMed-MEDLINE literature review (last accessed 04 January 2019).

Patient	Medical history	Clinical presentation	ADT[a] drug involved: time to onset[b]	Intake of other treatment with suspected TdP risk[c]	Evolution
aLQTS					
77 years [49]; PVR #1	Prostate cancer; ischaemic cardiomyopathy; Alzheimer's disease	aLQTS after clozapine and aLQTS after trazodone when concomitantly on ADT (~520 ms)	Bicalutamide (po) and goserelin (sc): start date unspecified	Clozapine (PR); trazodone (CR)	No recurrence of drug-induced LQTS when clozapine and trazodone restarted after ADT withdrawal
88 years; PVR #2	Prostate cancer; renal insufficiency; AF; hypertension; diabetes; obesity; arthrosis	aLQTS (~500 ms); AF; hyperkalaemia; bradycardia; digitalis intoxication (digoxin)	Enzalutamide (po): start date unspecified	Amiodarone (KR) (chronic)	Normalization after digoxin, enzalutamide withdrawal and administration of antidigitalis immunoglobulin
59 years; PVR #3	Prostate adenoma; dyslipidaemia; esophagitis	aLQTS; kalaemia normal	Finasteride (po): start date unspecified	Cisapride (KR) (chronic, for 6 years)	Normalization after cisapride withdrawal

83 years; PVR #4	Prostate adenoma; dyslipidaemia; hypertension; renal insufficiency; hyperthyroidism; ischaemic cardiomyopathy	aLQTS (QTc 492 ms) diagnosed 4 days after procoralan introduction; previously, QTc 474 ms	Dutasteride (po): start date unspecified	Ivabradine (CR) (for 4 days)	Persistence of QTc (492 ms 1 month after ivabradine withdrawal); maintained on dutasteride
72 years; PVR #5	Prostate cancer (metastatic); gout; smoker; hypertension; renal insufficiency; aortic narrowing	aLQTS; hypocalcaemia induced by denosumab; paroxysmal AF; heart failure	Triptorelin (im): start date unspecified	None	Normalization of LQTS after calcium supplementation
71 years; PVR #6	Prostate cancer (metastatic); past smoker; hypertension; ischaemic cardiomyopathy; dyslipidaemia	aLQTS; acute renal failure; hypokalaemia (1.8 mmol/L); ventricular extrasystoles	Abiraterone (po) and leuprorelin (sc): both 10 months	None	Normalization after potassium/magnesium administration and abiraterone withdrawal
TdP					
59 years; PVR #7	Prostate cancer	SD on TdP; QTc 490 ms;	Degarelix (sc): 1.5 months	None	Survival after

	(metastatic); gout	bradycardia; normal kalaemia, angiogram and echocardiogram			appropriate cardiopulmonary resuscitation
66 years; PVR #8	Prostate cancer (metastatic); hypertension; alcoholic; smoker; pulmonary cancer; cerebral cavernoma; chronic pulmonary insufficiency	Syncopal TdP; maximal QTc 600 ms while on degarelix and alfuzosine; electrocardiogram described as normal 5 years previously; SD in family (brother)	Degarelix (sc): 10 months	Alfuzosine (PR) (for 4 months)	Resolved after introduction of nadolol and withdrawal of alfusozine; defibrillator implanted
78 years; PVR #9	Prostate cancer; diabetes; Alzheimer's disease	Syncopal TdP; prolonged QTc; bradycardia; AF	Leuprolide (im): start date unspecified	None	Death in hospital (cause: TdP)
77 years [22]; PVR #10	Prostate cancer; AF; ischaemic cardiomyopathy; left ventricular dysfunction	Syncopal TdP requiring cardioversion; prolonged QTc (650 ms); hypokalaemia (2.7 mmol/L)	Abiraterone (po): 6 months; goserelin (sc): taken chronically (start date unspecified)	None	Resolved (QTc 460 ms) after abiraterone, withdrawal, amiodarone and isoprenaline administration and

					potassium supplementation
74 years [23]; PVR #11	Prostate cancer; hypertension; diabetes; anxiety	SD on TdP (QTc 620 ms); no ischaemia; hypokalaemia (2.5 mmol/L); hypocalcaemia (4.1 mmol/L)	Abiraterone (po): 6 months	None	Resolved (QTc 440 ms) 6 days after abiraterone withdrawal and potassium supplementation
79 years; PVR #12	Prostate cancer; hypertension; ischaemic cardiomyopathy	Syncopal TdP associated with malignant hypertension; hypokalaemia (2.6 mmol/L)	Abiraterone (po): 1 month; leuprolide (sc): a few days	None	Death (cause: intractable TdP storm)
71 years [24]; PVR #13	Prostate cancer	Syncopal TdP associated with ventricular fibrillation ($QTcF^{d}$ 516 ms); electrocardiogram and QTc described as normal 1 year before ADT	Bicalutamide (po) and leuprorelin (injections): both 6 months	None	Resolved (QTc 472 ms) after introduction of beta-blockers, withdrawal of bicalutamide and leuprorelin, and rapid pacing; defibrillator implanted.

85 years; PVR #14	Prostate cancer; AF; hypothyroidism	Syncopal TdP; AF	Flutamide (po): 3 months	Citalopram (KR) (chronic)	Resolved after amiodarone introduction
80 years; PVR #15	Prostate cancer; depression; silicosis; alcoholic	TdP; prolonged QTc	Flutamide (po): start date unspecified	Tiapride (PR) (for 3 months)	Resolved after withdrawal of flutamide and tiapride
Sudden death					
67 years; PVR #16	Prostate cancer; ischaemic cardiomyopathy; psychosis	SD a few hours after third degarelix injection	Degarelix (sc): 2 months	None	Death
70 years; PVR #17	Prostate cancer; hypertension; dyspnoea	SD 15 days after goserelin injection	Goserelin (sc): 17 months	None	Death
80 years; PVR #18	Prostate cancer; AF	SD	Leuprolide (im): 2 months	None	Death
83 years; PVR #19	Prostate cancer; hypertension; diabetes; heart failure	SD	Leuprolide (im): start date unspecified	None	Death
87 years; PVR #20	Prostate cancer	SD the day after leuprolide injection	Leuprolide (im): 4 months	None	Death

80 years; PVR #21	Prostate cancer; diabetes; dyslipidaemia; Parkinson's disease	SD	Leuprolide (im): 8 months	None	Death
87 years; PVR #22	Prostate cancer	SD; hepatitis	Triptorelin (im) and flutamide (po): both 2 months	None	Death
80 years; PVR #23	Prostate cancer (metastatic); hypertension; stroke; paced atrial rhythm disease	SD; evidence of ventricular fibrillation on pacemaker monitoring	Abiraterone (po): 2 weeks; leuprolide (sc): 7 years	None	Death
85 years; PVR #24	Prostate cancer (metastatic); obesity; pulmonary embolism and hypertension; paced atrial rhythm disease; arthrosis; glaucoma; sleep apnoea syndrome;	SD; dyspnoea; weight gain (15 kg); hypokalaemia (2.6 mmol/L)	Abiraterone (po): 2 months	None	Survival after cardiopulmonary resuscitation

	proctitis				
68 years; PVR #25	Prostate cancer; ischaemic cardiomyopathy	SD	Bicalutamide (po): 2 weeks	None	Death
90 years; PVR #26	Prostate cancer; hypertension; glaucoma	SD; dyspnoea; lower limb oedema	Bicalutamide (po): 10 days	None	Death
24 years; PVR #27	Androgenic alopecia; recreational cocaine use	SD, preceded by palpitations and malaise; hypokalaemia (3.1 mmol/L); troponin normal	Finasteride (po): 1 day	None	Survival after cardiopulmonary resuscitation

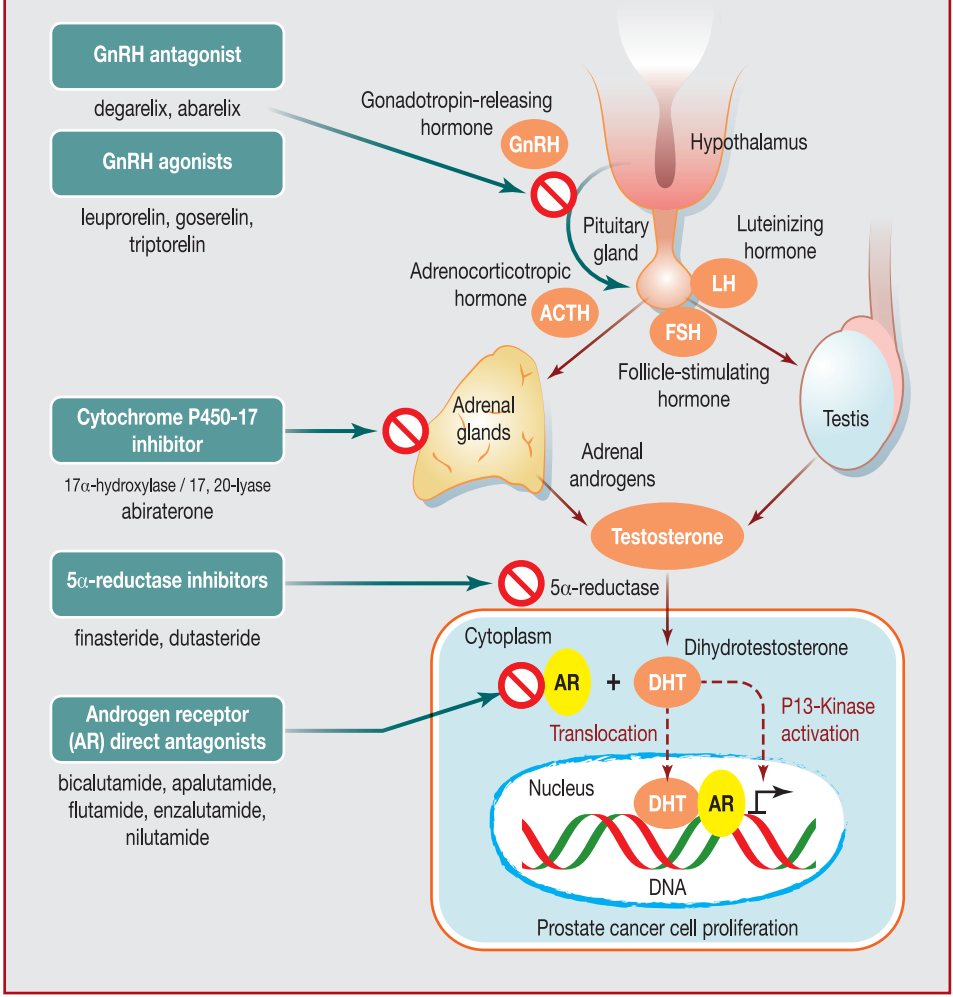
ADT: androgen deprivation therapy; AF: atrial fibrillation; aLQTS: acquired long QT syndrome; CR: conditional risk; im: intramuscularly; KR: known risk; po: orally; PR: possible risk; PVR: pharmacovigilance case report; sc: subcutaneously; SD: sudden death; TdP: torsades de pointes.

[a] Standard recommended ADT dose and treatment indications are [11]: finasteride 1 mg/day (po) for alopecia and 5 mg/day (po) for prostatism; dutasteride 0.5 mg/day (po) for prostatism; goserelin 3.6 mg/28 days or 10.8 mg/12 weeks (injectable) for prostate cancer; leuprorelin 7.5 mg/month, 22.5 mg/3 months, 30 mg/4 months or 45 mg/6 months (injectable) for prostate cancer; triptorelin 3.75 mg/4 weeks, 11.25 mg/12 weeks or 22.5 mg/24 weeks (injectable) for prostate cancer; degarelix (240 mg/28 days at first followed by 80 mg/28 days (injectable) for prostate cancer; abiraterone 1 g/day (po) in combination with gonadotropin-releasing hormone (GnRH) agonists for prostate cancer; enzalutamide 160 mg/day (po) in combination with GnRH agonists/antagonists for prostate cancer; flutamide 750 mg/day (po) in combination with GnRH agonists for prostate cancer; and bicalutamide 50 mg/day (po) in combination with GnRH agonists for prostate cancer.

[b] Time from start of ADT to onset of event.

[c] CredibleMeds [39] risk classifications (last accessed 08 October 2018). No record: no information about this drug on CredibleMeds website; not classified: this drug has been reviewed by CredibleMeds but the evidence available at this time did not result in a decision for it to be placed in any of the QT risk categories (this not an indication that this drug is free of a risk of QT prolongation or TdP, as it may not have been tested adequately for these risks in patients; TdP possible risk: these drugs can cause QT prolongation, but currently lack evidence for of a risk of TdP when taken as recommended; TdP known risk: these drugs cause QT prolongation, and are clearly associated with a known risk of TdP, even when taken as recommended; TdP conditional risk: these drugs are associated with TdP, but only under certain conditions of use (i.e. excessive dose, in patients with conditions such as hypokalaemia or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).

[d] Using Fridericia's Correction Formula.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GnRH agonists
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Gonadotropin-releasing hormone
GnRH
Hypothalamus
Pituitary gland
Luteinizing hormone
LH
Adrenocorticotropic hormone
ACTH
FSH
Follicle-stimulating hormone
Testis
Cytochrome P450-17 inhibitor
17α-hydroxylase / 17, 20-lyase
abiraterone
Adrenal glands
Adrenal androgens
Testosterone
5α-reductase inhibitors
finasteride, dutasteride
5α-reductase
Cytoplasm
Dihydrotestosterone
Androgen receptor (AR) direct antagonists
bicalutamide, apalutamide, flutamide, enzalutamide, nilutamide
AR
+
DHT
P13-Kinase activation
Translocation
Nucleus
DHT
AR
DNA
Prostate cancer cell proliferation

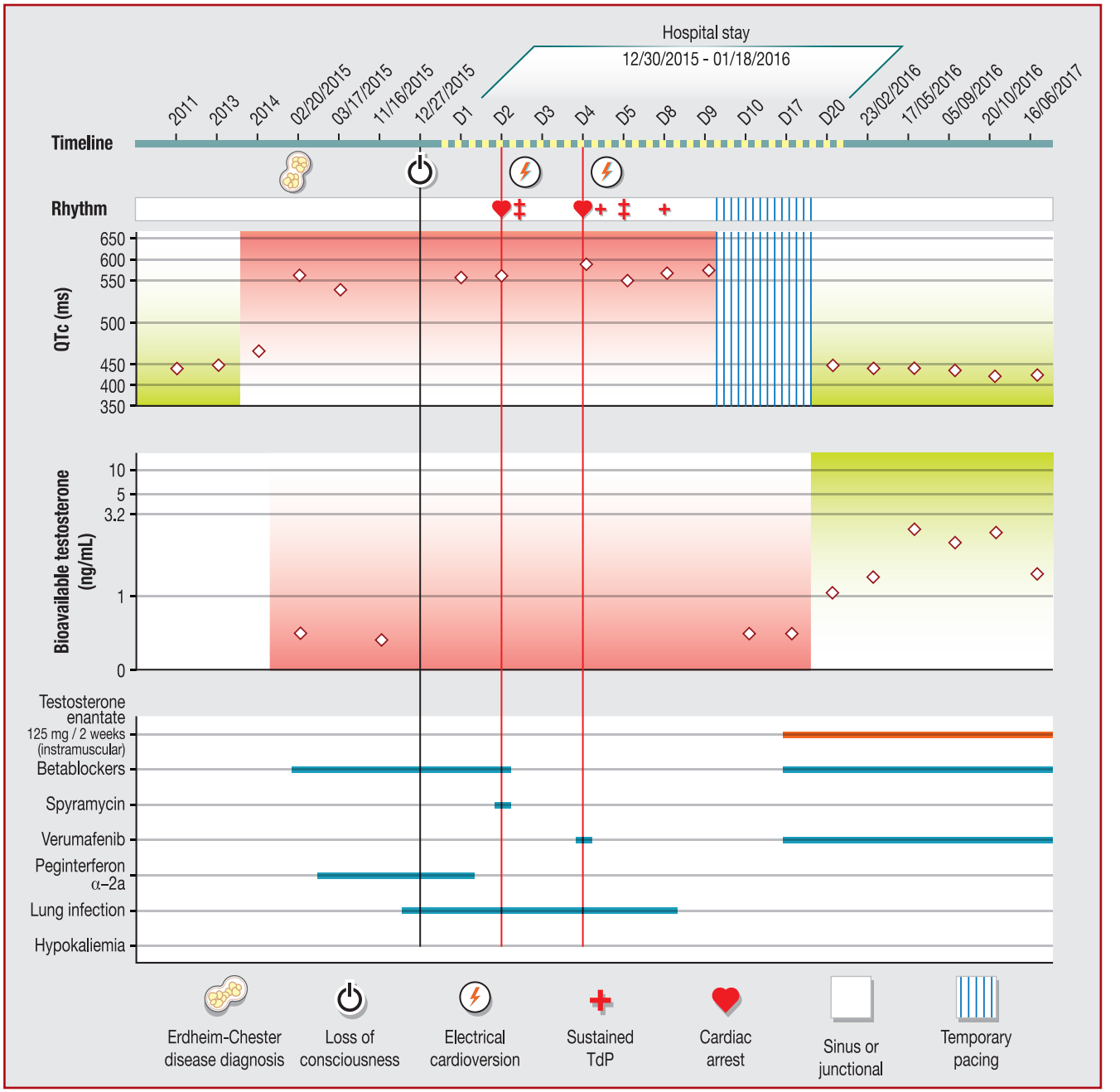
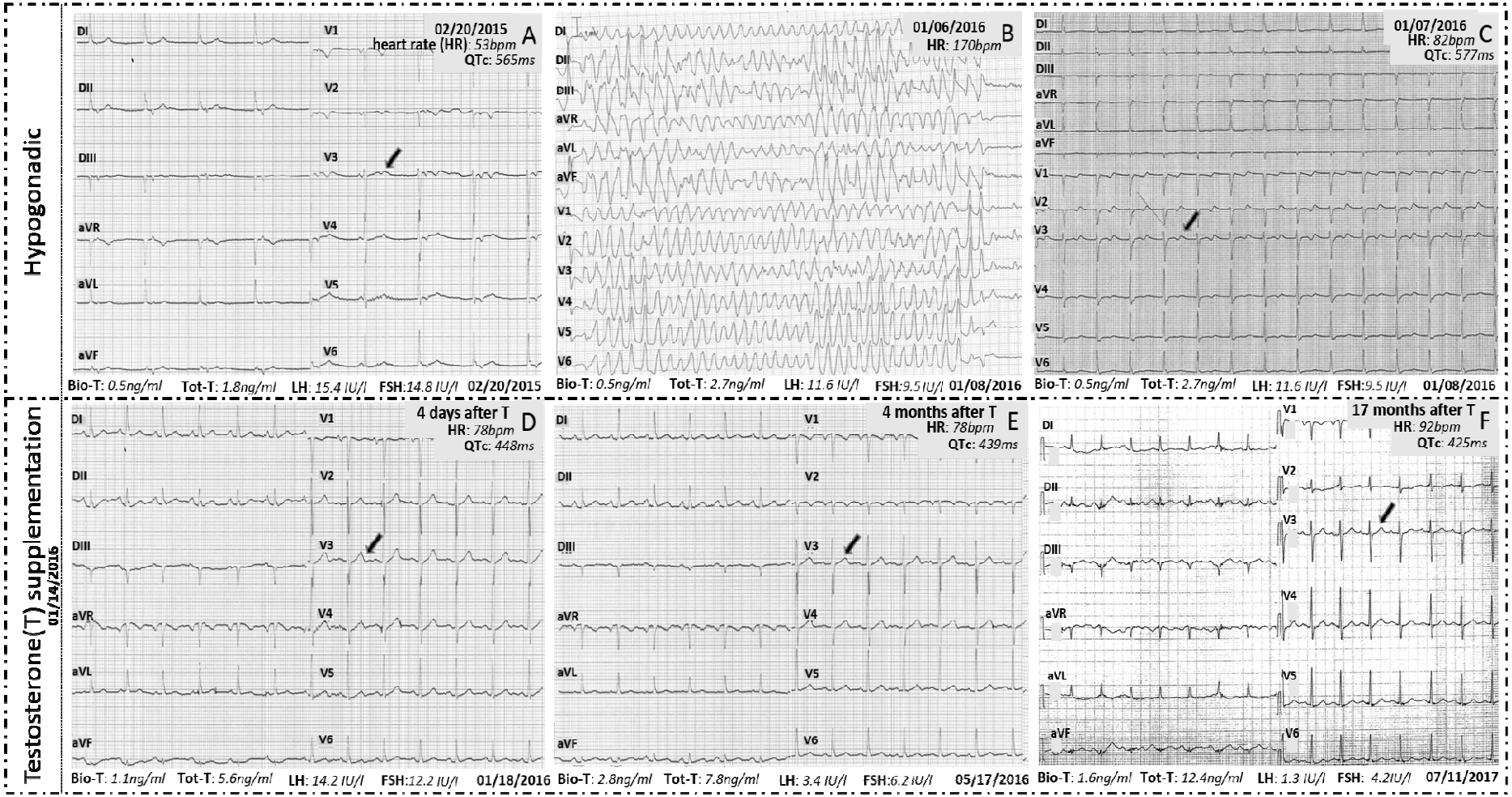
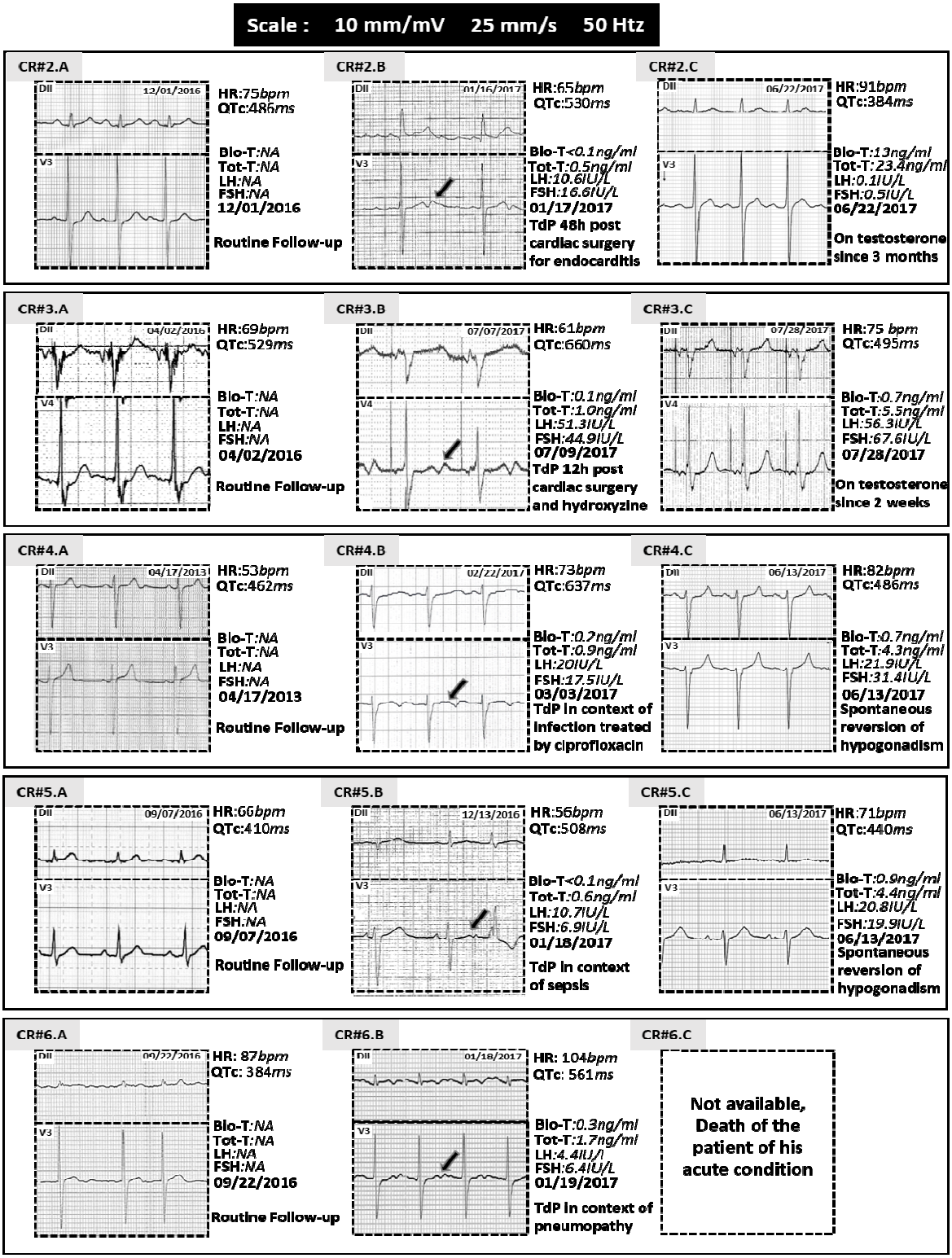

Hospital stay
12/30/2015 - 01/18/2016
2011
2013
2014
02/20/2015
03/17/2015
11/16/2015
12/27/2015
D1
D2
D3
D4
D5
D8
D9
D10
D17
D20
23/02/2016
17/05/2016
05/09/2016
20/10/2016
16/06/2017
Timeline
Rhythm
QTc (ms)
650
600
550
500
450
400
350
Bioavailable testosterone (ng/mL)
10
5
3.2
1
0
Testosterone enantate
125 mg / 2 weeks
(instramuscular)
Betablockers
Spyramycin
Verumafenib
Peginterferon α–2a
Lung infection
Hypokaliemia
Erdheim-Chester disease diagnosis
Loss of consciousness
Electrical cardioversion
Sustained TdP
Cardiac arrest
Sinus or junctional
Temporary pacing

Figure 3



Normal values for adult men were: follicle simulating hormone (**FSH**): 1.5-12.4IU/l; luteinizing hormone (**LH**): 1.7-8.6 IU/l; total-testosterone (**Tot-T**): 2.5-8.4ng/ml; bioavailable-testosterone (**Bio-T**): 1.0-3.2ng/ml

Figure 4



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